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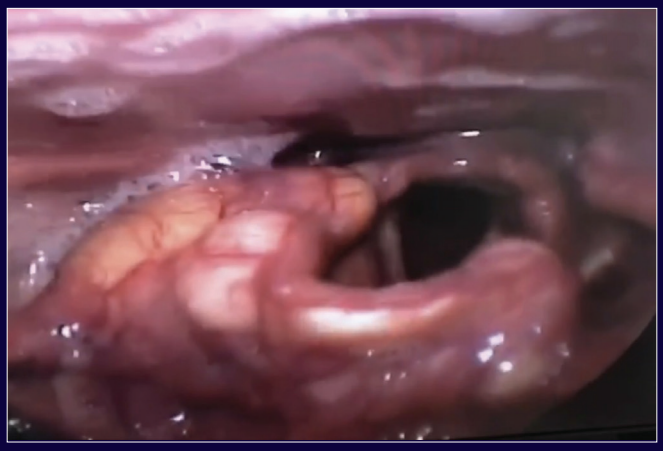

Multiple Dermoid Cysts in the Epiglottis Presenting with Dysphonia and Dysphagia: A Rare Case Page 173-6

Original Investigations

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Owner and Responsible Manager on behalf of the Turkish Otorhinolaryngology Head and Neck Surgery Society / Türk Kulak Burun Boğaz ve Baş Boyun Cerrahisi Derneği adına Sahibi ve Sorumlu Yazı İşleri Müdürü: Özgür YİĞİT • Publication Type: Yerel süreli / Local periodical • Basım yeri / Printed at: Matsis Matbaa Hizmetleri San. ve Tic.Ltd.Şti, Tevfikbey Mah., Dr. Ali Demir Cad. No: 5, 34290 Sefaköy, Turkey (+90-212-624 21 11) • Basım tarihi / Printing Date: Eylül 2020 / September 2020 • Türk Kulak Burun Boğaz ve Baş Boyun Cerrahisi Derneği tarafından yayımlanmaktadır. Published by Turkish Otorhinolaryngology Head and Neck Surgery Society, Çobançeşme Sanayi Cad. No: 11 Nish İstanbul A Blok D: 8 Yenibosna, İstanbul, Turkey (+90 212 233 11 26)

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Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

Aims and Scope

The Turkish Archives of Otorhinolaryngology (Turk Arch Otorhinolaryngol) is the scientific, peer-reviewed, open-access journal of the Turkish Otorhinolaryngology-Head and Neck Surgery Society since 2001. The journal comprises four issues as March, June, September and December in a volume, and it is published quarterly every year. The journal's publication language is English.

The aim of the journal is to publish qualified original clinical, experimental and basic researches on ear, nose, throat, head and neck diseases and surgery, reviews that contain sufficient amount of source data conveying the experiences of experts in a particular field, case reports, video articles and original images of rare clinical pictures which would shed light on the clinical practice and which were not previously published, letters from the readers and experts concerning the published studies, articles about general practice and subject of the journal with historical content, memories of scientific significance, educative and catechetical manuscripts about medical deontology and publication ethics.

The target audience of the journal includes academic members, specialists, residents and other relevant health care professionals in the field of ear, nose, throat, and head and neck disorders and surgery.

The editorial and publication processes of the journal are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

Turkish Archives of Otorhinolaryngology is indexed in **PubMed, PubMed Central, Web of Science (Emerging Sources Citation Index), ULAKBIM TR Index, EBSCO, GALE, CINAHL, J-Gate** and **ProQuest.**

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Open Access Policy

This journal provides immediate open access to its content on the principle that making research freely available to the public supports a greater global exchange of knowledge.

The Turkish Archives of Otorhinolaryngology's Open Access Policy is based on the rules of Budapest Open Access Initiative (BOAI). By "open access" to [peer-reviewed research literature], we mean its free availability on the public internet, permitting any users to read, download, copy, distribute, print, search, or link to the full texts of these articles, crawl them for indexing, pass them as data to software. The only constraint on reproduction and distribution, and the only role for copyright in this domain, should be to give authors control over the integrity of their work and the right to be properly acknowledged and cited.

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Our journal's Abstracting/Indexing services store essential information about articles. In addition, some of our journals' Abstracting/Indexing services archive metadata about the article and electronic versions of the articles.In this way, copies of articles are presented to the scientific

community through these systems as an alternative to journals. This journal's archive has been backed up by PubMed Central (PMC) as from 2015 publications.

Author Self-Archiving Policy

Authors are permitted and encouraged to post their articles on personal and institutional websites after publication (while providing full bibliographic details and a link to the original publication).

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Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

Instructions to Authors

CONTEXT

The Turkish Archives of Otorhinolaryngology (Turk Arch Otorhinolaryngol) is a scientific, open access periodical published by independent, unbiased, and double-blinded peer-review principles. The journal is the official publication of the Turkish Otorhinolaryngology Head and Neck Surgery Society, and published quarterly in March, June, September and December. The publication language of the journal is English.

The aim of the journal is to publish qualified original clinical, experimental and basic research on ear, nose, throat, head and neck diseases and surgery, reviews that contain a sufficient amount of source data conveying the experiences of experts in a particular field, case reports and original images of rare clinical pictures which would shed light on the clinical practice and which were not previously published, letters from the readers and experts concerning the published studies, articles about general practice and subject of the journal with historical content, memories of scientific significance, educative and catechetical manuscripts about medical deontology and publication ethics.

EDITORIAL AND PUBLICATION PROCESS

The editorial and publication process of the Turkish Archives of Otorhinolaryngology are shaped in accordance with the guidelines of the International Committee of Medical Journal Editors (ICMJE), World Association of Medical Editors (WAME), Council of Science Editors (CSE), Committee on Publication Ethics (COPE), European Association of Science Editors (EASE), and National Information Standards Organization (NISO). The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

Originality, high scientific quality, and citation potential are the most important criteria for a manuscript to be accepted for publication. Manuscripts submitted for evaluation should not have been previously presented or already published in an electronic or printed medium. The journal should be informed of manuscripts that have been submitted to another journal for evaluation and rejected for publication. The submission of previous reviewer reports will expedite the evaluation process. Manuscripts presented in a meeting should be submitted with detailed information on the organization, including the name, date, and location of the organization.

PEER REVIEW PROCESS

Manuscripts submitted to the Turkish Archives of Otorhinolaryngology will go through a double-blind peer-review process. Each submission will be reviewed by at least two external, independent peer reviewers who are experts in their fields in order to ensure an unbiased evaluation process. The editorial board will invite an external and independent editor to manage the evaluation processes of manuscripts submitted by editors or by the editorial board members of the journal. The Editor in Chief is the final authority in the decision-making process for all submissions. For more detailed information, please read Ethical Policy page of the Journal.

Preprint

The Turkish Archives of Otorhinolaryngology does not consider preprint publications as prior publications. In other words, authors are allowed to present and discuss their findings on a non-commercial preprint server before submission to a journal.

Authors must provide the journal with the preprint server deposition of their article accompanying its DOI during initial submission. If the article is published in the Turkish Archives of Otorhinolaryngology, it is the responsibility of the authors to update the archived preprint and link it to the published version of the article.

AUTHORSHIP

Each person listed as an author should fulfil the authorship criteria recommended by the International Committee of Medical Journal Editors. The ICMJE recommends that authorship is based on the following four criteria:

Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND

Drafting the work or revising it critically for important intellectual content; AND

Final approval of the version to be published; AND

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. Also, the authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged in the title page of the manuscript.

Author Affiliations

Authors are expected to state the institutions which they affiliated in the time of the study. Their current affiliation can be added to the article as the corresponding address. Change of affiliation requests will not be implemented after submission. The Turkish Archives of Otorhinolaryngology requires corresponding authors to submit a signed and scanned version of the Authorship Contribution Form during the initial submission process to act appropriately on authorship rights and to prevent ghost or honorary authorship. If the editorial board suspects a case of "gift authorship", the submission will be rejected without further review. As part of the submission of the manuscript, the corresponding author should also send a short statement declaring that he/she accepts to undertake all the responsibility for authorship during the submission and review stages of the manuscript.

Instructions to Authors

Change of Authorship

The Turkish Archives of Otorhinolaryngology reviews the authorship according to the author's declaration in the Title Page; thus, it is the authors' responsibility to send the final order of the complete author names. Requests in the change of authorship (e.g. removal/addition of the authors, change in the order etc.) after submission are subject to editorial approval. Editorial Board will investigate these kind of cases and act following COPE flowcharts.

Change of authorship requests should be submitted to the Editorial Office with an official letter stating the change's reasons. The letter must be signed by all authors and include their approval on the change in authorship. If the request is approved by the Editorial Board, authors need to submit a new Copyright Agreement Form according to the final order list.

DECLARATION OF INTEREST

The Turkish Archives of Otorhinolaryngology requires and encourages the authors and the individuals involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to potential bias or a conflict of interest. Any financial grants or other support received for a submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the ICMJE Potential Conflict of Interest Disclosure Form should be filled in and submitted by all contributing authors. The journal's Editorial Board resolves cases of a potential conflict of interest of the editors, authors, or reviewers within the scope of COPE and ICMJE guidelines.

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The Editorial Board of the journal handles all appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office regarding their appeals and complaints. The Editor in Chief is the final authority in the decision-making process for all appeals and complaints.

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Open access is an approach that supports interdisciplinary development and encourages collaboration between different disciplines. Therefore, the Turkish Archives of Otorhinolaryngology contributes to the scientific publishing literature by providing more access to its articles and a more transparent review process.

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Statements or opinions expressed in the manuscripts published in the Turkish Archives of Otorhinolaryngology reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility regarding the published content rests with the authors.

SUBMISSION REQUIREMENTS

• Cover Letter,

• ICMJE Conflict of Interest Statement Form for all contributing authors,

• A separate title page (Title Page should be submitted with all manuscripts and should include the title of the manuscript, name(s), affiliation(s), major degree(s) and ORCID ID of the author(s). The name, address, telephone (including the mobile phone number) and fax numbers and e-mail address of the corresponding author should be clearly listed. Grant information and other sources of support should also be included. Individuals who contributed to the preparation of the manuscript but did not fulfil the authorship criteria should also be acknowledged on the title page),

• Abstract divided into appropriate sections,

• Keywords (For indexing purposes, a list of 4–8 keywords in English is essential),

• Article divided into appropriate sections,

• List of references styled according to "journal requirements",

• A blinded main text (Please exclude all information that may indicate an individual or institution from the main document to ensure a blinded review process),

• The Copyright Agreement and Acknowledgement of Authorship Form (Please submit a wet-signed and scanned copy of the Copyright Transfer Form with your submission),

• Upload your title page and forms in the system to the Potential Conflict of Interest category to ensure a blinded review process,

• Figures (Figures should be submitted as standalone images through the submission system in .JPG or .TIFF format),

• Ethics Committee Approval Statement (with decision/file no, date and name of the institution, for original articles),

MANUSCRIPT PREPARATION

The manuscripts should be prepared in accordance with ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. Authors are required to

The presentation of the article types must be designed in accordance with trial reporting guidelines:

Human research: Helsinki Declaration as revised in 2013

Instructions to Authors

Systematic reviews and meta-analyses: PRISMA guidelines

Case reports: the CARE case report guidelines

Clinical trials: CONSORT

Animal studies: ARRIVE and Guide for the Care and Use of Laboratory Animals

Diagnostic accuracy: STARD Guidelines

Non-randomized public behaviour: TREND

Manuscripts can only be submitted through the journal's online manuscript submission and evaluation system, available at www.turkarchotolaryngol.net. Manuscripts submitted via any other medium and submissions by anyone other than one of the authors will not be evaluated.

Manuscripts submitted to the journal will first go through a technical evaluation process where the editorial office staff will ensure that the manuscript has been prepared and submitted in accordance with the journal's guidelines. Submissions that do not conform to the journal's guidelines will be returned to the submitting author with technical correction requests.

Authors are required to submit the following:

Copyright Agreement and Acknowledgement of Authorship Form

ICMJE Potential Conflict of Interest Disclosure Form (should be filled in by all contributing authors) during the initial submission. These forms are available for download at turkarchotolaryngol.net.

Preparation of the Manuscript

Title page: A separate title page should be submitted with all submissions, and this page should include:

The full title of the manuscript, as well as a short title (running head) of no more than 50 characters,

Name(s), affiliations, highest academic degree(s), and ORCID IDs of the author(s),

Grant information and detailed information on the other sources of support,

Name, address, telephone (including the mobile phone number), and e-mail address of the corresponding author,

Acknowledgement of the individuals who contributed to the preparation of the manuscript but who do not fulfil the authorship criteria.

Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

Keywords: Each submission must be accompanied by a minimum of four to a maximum of eight keywords for subject indexing at the end of the abstract. The keywords should be listed in full without abbreviations. The keywords should be selected from the National Library of Medicine, Medical Subject Headings database.

Main Points: All submissions except letters to the editor and clinical images should be accompanied by 3 to 5 "main points" which should emphasize the most noteworthy results of the study and underline the principle message that is addressed to the reader. This section should be structured as itemized to give a general overview of the article. Since "Main Points" target the experts and specialists of the field, each item should be written as plain and straightforward as possible.

Manuscript Types

Original Articles: This is the most essential type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Methods section, and the statistical software that was used during the process must be specified.

Units should be prepared in accordance with the International System of Units (SI).

Clinical Trials

Turkish Archives of Otorhinolaryngology adopts the ICMJE's clinical trial registration policy, which requires that clinical trials must be registered in a publicly accessible registry that is a primary register of the WHO International Trials Registry Platform (ICTRP) or in ClinicalTrials.gov.

Instructions for the clinical trials are listed below:

A clinical trial registry is only required for the prospective research projects that study the relationship between a health-related intervention and an outcome by assigning people.

To have their manuscript evaluated in the journal, the author should register their research to a public registry at or before the time of first patient enrollment.

Based on most up to date ICMJE recommendations, the Turkish Archives of Otorhinolaryngology accepts public registries that include a minimum acceptable 24-item trial registration dataset.

Authors are required to state a data sharing plan for the clinical trial registration. Please see details under "Data Sharing" section.

For further details, please check ICMJE Clinical Trial Policy.

Data Sharing

As of 1 January 2019, a data-sharing statement is required for the registration of clinical trials. Authors are required to provide a data

sharing statement for the articles that reports the results of a clinical trial. The data sharing statement should indicate the items below according to the ICMJE data sharing policy:

Whether individual de-identified participant data will be shared

What data, in particular, will be shared

Whether additional, related documents will be available

When the data will be available, and for how long

By what access criteria will be shared

Authors are recommended to check the ICMJE data sharing examples at http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html

While submitting a clinical trial to Turkish Archives of Otorhinolaryngology:

Authors are required to make registration to a publicly accessible registry according to ICMJE recommendations and the instructions above.

The name of the registry and the registration number should be provided in the Title Page during the initial submission.

Data sharing statement should also be stated on the Title Page even the authors do not plan to share it.

The clinical trial and data sharing policy of the journal will be valid for the articles submitted from 1 January 2021.

Editorial Comments: Editorial comments aim to provide a brief critical commentary by reviewers with expertise or with a high reputation in the topic of the research article published in the journal. Authors are selected and invited by the journal to provide such comments. Abstract, Keywords, Tables, Figures, Images, and other media are not included.

Review / Systematic Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. While submitting your Review, please confirm that your manuscript is a systematic review and include a statement that researchers have followed the PRISMA guidelines.

Please check Table 1 for the limitations for Review / Systematic Review Articles.

Video Article: Videos should be up to 30 minutes in duration. The video must include audio narration explaining the procedure. All text and audio in the video must be in English. Audio must include narration in clear, grammatically correct English. Videos must be clear, in focus, and without excessive camera movement. Radiographs and other material must not contain any patient-identifiable information. Limited number of slides incorporated into video may be included to provide details of patient history, clinical and laboratory findings.

Video articles should include:

1) Copyright Transfer and Author Declaration Statement Form: This form must indicate that "Patients' Informed Consent Statement" is obtained.

2) Title Page

3) **Summary:** Summary should point out critical steps in the surgery up to 500 words. This part was published as an abstract to summarize the significance of the video and surgical techniques. The author(s) may add references if it is required.

5) **Video:** Please upload your video to turkarchotolaryngol.net using online submission system. Accepted video formats are Windows Media Video (WMV), AVI, or MPEG (MPG, MPEG, MP4). High-Definition (HD) video is preferred.

6) "Acknowledgements From" should be uploaded separately.

Preparing video content

In order to provide reviewers with a convenient method of accessing video content online, we have restricted video file types to mp, webM and Ogg format. This allows reviewers to view video content easily from all modern browser types without the inconvenience of downloading plug-ins and video players.

Mp4 is the most common online video format, and there are many converters available that will convert other file types to Mp4.

We can recommend using this free online converter to create a suitable mp4 file.

Video file size is limited to 50 Mbytes, and we suggest reducing file size for quicker upload times using this service Compress Mp4.

Please check Table 1 for the limitations for Video Article.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Letters to the Editor: This type of manuscript discusses important parts, overlooked aspects, or lacking parts of a previously published article. Articles on subjects within the scope of the journal that might attract the readers' attention, particularly educative cases, may also be submitted in the form of a "Letter to the Editor." Readers can also present their comments on the published manuscripts in the form of a "Letter to the Editor." Abstract, Keywords, Tables, Figures, Images, and other media should not be included. The text should be unstructured. The manuscript that is being commented on must be properly cited within this manuscript.

Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

Instructions to Authors

Clinical Image: These type of submissions should present a striking image that may challenge and inform readers and contribute to their education. Submissions can include high-quality clinical images, radiology results or surgical images. Please check Table 1 for the limitations for Clinical Images.

Please note that there are author limitations for some article types. Authors should provide a reason for the manuscripts that exceed author limitations. The exception of the articles that are above the author limits is subject to Editorial decision.

Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables. Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text). Tables should be created using the "insert table" command of the word processing software, and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labelled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures, too, should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in the USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)."

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

Both in-text citations and references must be prepared according to the Vancouver style.

While citing publications, preference should be given to the latest, most up-to-date publications. Authors are responsible for the accuracy of references. If an ahead-of-print publication is cited, the DOI number should be provided. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed, followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Turkish Archives of Otorhinolaryngology does not acknowledge citations to preprints since preprints yet have not passed the reviewers' evaluation process and verified by experts in the field.

Journal Article: Erkul E, Cekin İE, Kurt O, Gungor A, Babayigit MA. Evaluation of patients with unilateral endoscopic sinus surgery. Turk Arch Otorhinolaryngol 2012; 50: 41-5.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach

Table 1. Limitations for each manuscript type

Type of manuscript	Author limit	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	N/A	3500	250 (Structured)	30	6	5 or total of 10 images
Review Article	4	5000	250	50	6	10 or total of 15 images
Systematic Review	N/A	5000	250 (Structured)	50	2	10 or total of 15 images
Video Article	N/A	1500	250 (Structured)	106	2	2
Case Report	6	1000	200	10	No tables	4 or total of 8 images
Letter to the Editor	3	500	No abstract	5	No tables	No media
Clinical Images	3	500	No abstract	5	No tables	3 or total of 7 images

SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the complete drug reference. 34th ed. London: Pharmaceutical Press; 2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme; 2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92.

Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. pp.1561-5.

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Instructions to Authors

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Turkish Archives of Otorhinolaryngology
Türk Otorinolarengoloji Arşivi

Contents

The Journey of a Manuscript Submitted to the Turkish Archives of Otorhinolaryngology: From Receipt to Decision

Editorial

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The most important considerations for an author when submitting an article to a journal are the journal's impact factor, the indexes in which the journal is listed, whether or not there is a publication charge, and of course, the speed of its evaluation process (1-3).

To understand the speed and the results of a journal's evaluation process, it is necessary to know and understand the background work done by the journal's editorial team (4). From an editorial standpoint, the objective, timely, and high-quality evaluation of a manuscript is the work of a large network that begins with the author and involves the editor, the associate editors, and the reviewers (5).

As the editorial board of the Turkish Archives of Otorhinolaryngology (TAO), we would like to share with authors, reviewers, and readers the editorial work we do in the background and give some details about the peer-review process.

Between 2015-2019, 646 manuscripts were submitted to TAO. When the manuscripts are analyzed according to their subspecialties, 176 (27.24%) were about rhinology-facial plastic surgery and sleep disorders, 169 (26.16%) about head and neck surgery, 156 (24.15%) about otology, 74 (11.46%) about pediatric otorhinolaryngology, 26 (4.02%) about laryngology, and 45 (6.97%) were classified as other.

In the initial editorial review of the 646 manuscripts, the editorial board had rejected 265, and 381 were assigned to reviewers for the peer review process. A total of 2,122 reviewers were assigned to 381 manuscripts (5.57 per manuscript). Table 1 shows the responses of the reviewers to invitations.

Reviewers evaluated 381 manuscripts, of which 154 were rejected after the initial review, 196 were returned for major revision, 20 were returned for minor revision, and 11 were accepted for

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Table 1. Response and completion rates of assigned reviewers

	Number of reviewers assigned by the editor	Reviewers who accepted	Reviewers who completed the review on time	Reviewers who declined	Reviewers who did not respond	Reviewers who accepted to review but did not complete it in time
Numbers	2122	1254	1123	137	731	131
%	100	59.095	52.922	6.46	34.449	6.173
/Per paper	5.57	3.291	2.9948	0.359	1.919	0.344

publication as-is. After all revisions, 207 manuscripts were accepted for publication.

The first step of a paper is pre-editorial evaluation. If the manuscript is found to be written in line with the guidelines of TAO, then it is sent to the Editor. After editorial evaluation, the editor either rejects the manuscript or sends it to one of the associate editors. The associate editors also evaluating the manuscript, can either directly reject or send it to the reviewers according to the subject of the manuscript and the field of expertise of the reviewer.

In 2015 to 2019, the pre-editorial time after submission of a manuscript to the journal was 18.0±45.29 days, and the time to appointment of an associate editors was 1.5±3.01 days after editorial evaluation. Thus, it can be seen that the pre-editorial period brought about an average time loss of 18.5 days for the authors. Pre-editorial time was mostly associated with the manuscript's inconsistency with the TAO's writing and uploading guidelines or with carelessly written content. Accordingly, authors can shorten the evaluation process by 18 days by ensuring that the manuscript is prepared according to the guidelines of the journal and uploaded correctly.

The associate editor then selects two to four reviewers and assigns the manuscript for review. The average response time of the reviewers who had accepted the review was 2.98±2.58 days and their average review time was 5.81±3.93 days. Once invitations to review are sent to candidate reviewers, the associate editors allows a response time. When the evaluation period of the reviewers who did not respond is accepted as 21 days, the average evaluation time of the reviewers who completed the review was 13.46±4.38 days. The total mean evaluation time for a manuscript after submission was 55.88±65.38 days. The time from submission to the final decision was 37.38±48.19 days. The appointment of the reviewers is critical in the manuscript evaluation process. The editorial team expects each candidate reviewer to respond to their invitation, whether positive or negative. Reviewers who do not respond to the invitation, and particularly those who do not review the manuscript despite having agreed to do so, cause the journal's editorial service to be lengthened and delayed. The response and review completion data of the assigned reviewers are detailed in Table 1.

It can be seen that the most important issue in the manuscript evaluation time in terms of reviewers is the reviewers who do not respond. Those who accept or decline the review assignment have no impact on the duration of the review time.

To determine the features of completed reviews, we evaluated the character and word counts of each reviewer report. The average word count was 101.705±88.033, and the average character count was 610.997±515.796. The average word count for accepted papers, major revisions, minor revisions and rejected papers were different. The reviewers wrote shorter reports on the articles they accepted, and longer reports on the articles they rejected or for which they suggested major revision (Table 2).

For the purposes of this study, we also developed a scoring system for monitoring the progress of the manuscripts. In this respect, we calculated a decision score for each paper. According to this scoring system, each reviewer's decision was scored as

- Accept = 3 points,
- Minor revision = 2 points,
- Major revision = 1 point,
- Reject = 0 point,

then the total score was divided by the number of reviewers. To put it briefly, decision score of manuscript = total of scores from all reviewers / total number of reviewers. This scoring system was used both for first evaluations and for revisions.

In the first decision, the totally mean decision score was 1.371±0.756. The decision score for accepted manuscripts was 2.538±0.598. It was 2.075±0.574, 1.641±0.569 and 0.844±0.616 for minor revisions, major revisions, and rejected manuscripts, respectively. The manuscripts requiring minor revision increased their decision score after revision from 2.075±0.574 to 2.342±0.543. Those requiring major revision increased their decision score after revision from 1.641±0.569 to 2.176±0.622. The overall decision score

Table 2. Decision scores of submitted manuscripts

	First decision	After revision
Accepted	2.538±0.598	-
Requiring minor revision	2.075±0.574	2.342±0.543
Requiring major revision	1.641±0.569	2.176±0.622
Rejected	0.844±0.616	-
Total	1.371±0.756	-

for manuscripts requiring both minor and major revisions increased from 1.685±0.576 to 2.172±0.614 after revision.

To sum up, the editorial process can be shortened with more attention paid to certain points. Particularly, it is critical that authors should prepare their manuscripts in accordance with the instructions to authors guidelines, the editors should act fast and unbiased, and finally, reviewers should provide timely, sufficient and reliable evaluations.

All contributors of the journal are responsible for shortening the evaluation process. While it is very important for the authors to prepare their manuscripts in accordance with the journal's writing guidelines, it is crucial that reviewers promptly respond to invitations and complete evaluations within the given timeframe once they accept the invitation. Editors and associate editors, on the other hand, can shorten the evaluation processes by prioritizing those reviewers who provide positive and fast response to invitations.

We hope that all stakeholders of the journal, including members of editorial board, authors, reviewers, and readers will benefit from this paper aimed to present a detailed account of TAO's review processes.

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Investigation of Toll-like Receptor-2, -3 and -4 Gene Expressions in Larynx Squamous Cell Carcinoma

Original Investigation

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Abstract

Objective: Despite all the recent advancements, larynx cancer has shown no improvement in survival rates. The aim of this study was to investigate the expressions of toll-like receptor (TLR)-*2, -3,* and *-4* genes, and determine any relationships with the histopathologic characteristics of the disease.

Methods: This retrospective study included 50 subjects who underwent total or partial laryngectomy with an open surgical method for larynx squamous cell carcinoma. Measurements of TLRs-2, -3, and -4 expression values were taken with quantitative real time-polymerase chain reaction in normal tissue and tumor tissue samples of the patients.

Results: Evaluations were made of TLR-2, -3, and -4 mRNA expressions according to $2^{-\Delta\Delta CT}$ calculations in 50 subjects with larynx cancer. When the tumor tissue was compared with the healthy tissue from the same subjects, reductions were determined in TLR expression in 86%, 84%, and 82%, respectively. This reduction in each gene expression was statistically significant ($p<0.001$). No statistically significant correlation was determined between the change in TLR-2, -3, and -4 expression and the histopathologic characteristics of the disease.

Conclusion: The data obtained in this study demonstrated that TLR-2, -3, and -4 expressions were reduced in larynx squamous cell cancer. The results of further studies targeting these genes would be useful in the diagnosis and treatment of the disease.

Keywords: Larynx cancer, toll-like receptors, gene expression, squamous cell carcinoma, tumor microenvironment

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Introduction

Laryngeal cancers are the second most common malignancy of all head and neck sites and the 5-year survival rate has been reported as 67%. The majority (95%) of these cancers are squamous cell carcinomas (SCCs) (1). Despite all the advancements in healthcare, significant improvement could not be achieved in the survival rates in the past 50 years. Although environmental carcinogens (tobacco, alcohol) contribute significantly to the development of larynx SCC, it is

thought that partial inadequacy of the natural immune response to the tumor could lead to the progression of the disease.

Significant risk factors that reduce survival in laryngeal cancers are the local invasion status (e.g., lymphatic invasion, vascular invasion, perineural invasion, cartilage invasion), spread to surrounding tissues, and local and/or distant metastasis. Tumor development and invasion of surrounding tissues occur as a result of complex events in which several mechanisms interact such as apoptosis inhibition in the tumor micro surroundings, angiogenesis, and proliferation activation (2).

Toll-like receptors (TLRs) are a class of receptors expressed from the epithelial and endothelial cells of the human immune system cells. Ten human TLRs, each of which recognizes a certain microbial component, have been identified (3). The function of each TLR is extremely complex and varied and affected by several factors. Various TLRs play different roles in carcinogenesis (2). The main role of TLRs in tumor formation is still not fully known. They may be related to cancer progression or inhibition. Improvement of the inflammatory process with TLRs plays a key role in the processes that both increase tumor progression and induce anti-tumor reactions. Just as TLRs can prevent apoptosis, they have also been reported to have pro-apoptotic activity through a series of mechanisms (4).

This study aimed to obtain insight about how the *TLR-2, -3* and *-4* genes play a role in laryngeal cancer carcinogenesis and to evaluate the relationship between the expression level of these genes and tumor histopathological features.

Methods

Ethical Considerations

The İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty Ethics Committee approved the study, and the study was conducted in line with the Declaration of Helsinki. All patients and volunteers provided their written informed consent. Approval for the study was granted by the Clinical Research Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty (decision date: 15.11.2017, decision no: 93777809-604.01.01-429320).

Patients

This retrospective study evaluated 50 subjects with confirmed laryngeal SCC. Tumor tissues and adjacent non-cancerous laryngeal mucosal tissues of patients who underwent total or partial laryngectomy between 2016 and 2018 at the Otolaryngology and Head and Neck Surgery Department of the İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty were analyzed. Non-cancerous tissue samples were taken by incisional biopsy from the intact laryngeal tissue farthest from the tumor. Subjects who had received preoperative chemotherapy and/or radiotherapy were excluded from the study. All of the samples were human papilloma virus-negative. Inclusion criteria were first time diagnosed laryngeal SCC patients over 18 years of age. Clinical and histopathological features of all subjects' tumors were recorded. Localization, stage, grade, and invasion characteristics (lymphatic invasion, vascular invasion, perineural invasion, cartilage invasion) of the tumors were determined according to the histopathology reports. Grade and stage of the tumors were defined according to the guidelines published by the 2017 American Joint Committee on Cancer (5).

RNA Isolation and cDNA Synthesis

To quantitate mRNA expression of *TLR-2, -3,* and *-4* genes, total RNA was extracted from the tumor and adjacent non-cancerous laryngeal mucosal tissues using the PureLink RNA Mini Kit (Life Technology, NY, USA) according to the kit protocol. Following RNA isolation, RNA measurements were taken with Nano Drop ND1000 (Thermo Fisher Scientific, USA). A total of 200 ng isolated RNA was reverse-transcripted using the Revert Aid First Strand cDNA Synthesis kit (Thermo Fisher Scientific, Inc.) according to the manufacturer's protocol.

Quantitative Real Time-polymerase Chain Reaction (qRT-PCR) Analyses

The mRNA expression levels of TLR-2, -3 and -4 were quantified by qRT-PCR using the Light Cycler 480 II device. qRT-PCR was performed using 200 ng cDNA, PowerUp™ SYBR™ Green Master Mix (Thermo Fisher Scientific, USA) and 10μ M forward and reverse primers. The glucose-6-phosphate dehydrogenase (*G6PD*) gene was used as a housekeeping gene for normalization of mRNA levels of target genes. The sequences of the primers are presented in Table 1. qPCR reactions were performed at least three times. PCR cycling conditions were as follows: 95 °C for 15 min, followed by 40 cycles at 95 °C for 15 sec, 61 °C for 30 sec and 72 °C for 30 sec, and a final 10 sec at 50 °C. Quantitative RT-PCR data of mRNA levels were calculated using the comparative CT method (also known as the $2^{-\Delta\Delta CT}$ method) (6). Expression levels were evaluated according to the assumptions that the $2^{-\Delta\Delta CT}$ value was between 0.9 and 1.1, greater than 1.1 and smaller than 0.9. Values between 0.9 and 1.1 were considered as unchanged, i.e., meaning there was no difference at gene expression level between the tumor and the normal tissue of the patient. Values greater than 1.1 were considered as increased, and values smaller than 0.9 were considered as decreased.

Statistical Analysis

Data obtained in the study were analyzed statistically using IBM SPSS version 21.0 software. Descriptive statistics of numerical variables were expressed as mean ± standard

deviation, minimum and maximum values, and categorical variables were expressed as number (n) and percentage (%). For the statistical evaluation of the data obtained, first the normality test was performed. In the comparisons of tumor tissue and normal tissue, data not showing normal distribution were assessed using the Wilcoxon signed-rank test. Spearman's rho correlation test was used in the comparisons of TLR-2, -3, and -4 gene expressions with each other, and the chi-square test was used in the comparison of clinicopathologic data. A value of $p<0.05$ was accepted as statistically significant.

Results

The study was carried out with 50 subjects with laryngeal SCC. Of the 50 subjects, 47 were male and 3 were female with a mean age of 60.56±9.67 (range, 34–84) years; 12 consumed alcohol and 45 smoked. Early-stage tumor (T1, T2) was determined in six subjects and advanced stage (T3, T4) in 44 subjects. There was blood vessel invasion in 25 (50%), lymphatic invasion in 43 (86%), perineural invasion in 22 (44%), and thyroid cartilage invasion in 22 (44%) subjects.

Table 1. Primer series of *TLR-2*, *-3*, and *-4* genes

Gene	Primer series (5'→3')
TLR-2	Forward primer: 5'-GGTGTCGGAATGTCACAGGACA-3'
	Reverse primer: 5'-GCATCATAGCAGATGTTCCTGCT-3'
TLR-3	Forward primer: 5'-TGGAGCCAGAATTGTGCCAGA-3'
	Reverse primer: 5'-GGATTGAGTTGGACATGAGATGGA-3'
TLR-4	Forward primer: 5'-TGCGTGGAGGTGGTTCTTAAT-3'
	Reverse primer: 5'-AAGCTATAGCTGGCTAAATGCCTG-3'
G6PD	Forward primer: 5'-ATGCCTTCCATCAGTCGGATACA-3'
	Reverse primer: 5'-ATAGCCCACGATGAAGGTGTTTTC-3'

TLR: Toll-like receptor, G6PD: Glucose-6-phosphate dehydrogenase

The TLR-2, -3, and -4 gene expression levels were analyzed in the tumor and adjacent non-cancerous laryngeal tissue samples taken from the 50 subjects by normalizing with G6PD housekeeping gene. Except for one subject, TLR-2, -3, and -4 mRNA expressions were determined in all tumor and adjacent non-cancerous laryngeal tissue samples. In one subject, TLR-2 mRNA was not determined in the non-cancerous tissue so the data of that subject were not included in the evaluation.

In this study with 50 subjects, CT values of target gene (TLR-2, -3 or -4) were normalized with CT values of internal control *G6PD* gene. After normalization, as described by Schmittgen and Livak (6), expression of all target genes were presented as fold change ($2^{-\Delta\Delta CT}$). All fold change rates for TLR-2, -3, and -4 are shown in Table 2 (0.07, 0.04 and 0.04, respectively). In the tumor tissue samples, TLR-2 gene expression level was determined to have decreased in 86% (42/49), TLR-3 in 84% (42/50), and TLR-4 in 82% (41/50) compared to the non-cancerous tissue samples. The expression levels of TLR-2, -3, and -4 genes in tumor tissues were lower than those of the non-cancerous tissues and these decreases were determined to be statistically significant ($p<0.001$) (Figure 1). On the other hand, no statistically significant correlations were found between any of the histopathological parameters and TLR-2, -3 and -4 gene expression levels (Table 3).

Discussion

TLRs are found in immune system cells, and they recognize the surface proteins of micro-organisms (7). TLRs also have a role in the control of the immune system, tissue homeostasis, and the regulation of cell death (8). Depending on the intracellular localization, type, amount, and presence of ligands, TLRs have a two-way effect in cancer development, either by supporting the tumor or by promoting an anti-tumor response (7).

qRT-PCR is a widely applied technique that provides quantitative analyses of gene expression. Experimental comparison between normal and abnormal tissues can be made with the qRT-PCR technique. Wide dynamic range, remarkable sensitivity and sequence specificity are

Table 2. Expression levels of *TLR-2*, *-3*, and *-4* genes in laryngeal tissues of 50 patients

		CT Mean ± SD	G6PD CT Mean ± SD	ΔCT Mean ± SD	ΔΔCT Mean ± SD	$2^{-\Delta\Delta CT}$	*p-value
TLR 2	Tumor	25.96±1.7	24.20±2.29	1.76±2.25	3.82±3.51	0.07	<0.001
	Normal	26,56±1.57	28.76±2.53	-2.03±2.44	0	1	
TLR 3	Tumor	27.41±1.84	24.20±2.29	3.21±2.6	4.71±5.02	0.04	<0.001
	Normal	27.26±3.47	28.76±2.53	-1.50±4.45	0	1	
TLR 4	Tumor	32.01±2.76	24.20±2.29	7.81±2.9	4.83±4.28	0.04	<0.001
	Normal	31.74±2.27	28.76±2.53	2.98±3.01	0	1	

SD: Standard deviation, TLR: Toll-like receptor, CT: Threshold cycle, *Statistical analysis was tested with the paired sample t-test

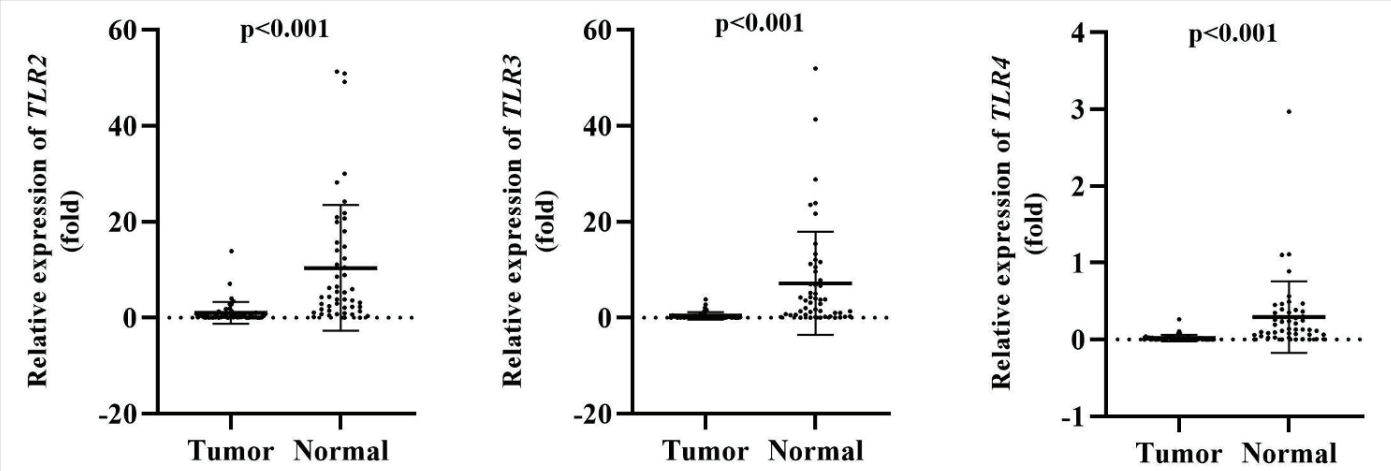

Figure 1. Relative expression graph of *TLR-2*, *-3*, and *-4* genes in tumor tissue compared to normal tissue

Table 3. Relationships of histopathological parameters with TLR-2, 3, and 4 gene expressions

Clinical and pathological parameters		TLR-2 expression				TLR-3 expression				TLR-4 expression			
		Increased	Decreased	Unchanged	*p-value	Increased	Decreased	Unchanged	*p-value	Increased	Decreased	Unchanged	*p-value
Tumor localization	Glottic	2 (4.1)	13 (26.5)	1 (2)	0.494	2 (4)	15 (30)	0 (0)	0.353	3 (6)	13 (26)	1 (2)	0.666
	Transglottic	3 (6.1)	13 (26.5)	0 (0)		4 (8)	12 (24)	0 (0)		3 (6)	13 (26)	0 (0)	
	Supraglottic	1 (2)	16 (32.7)	0 (0)		1 (2)	15 (30)	1 (2)		2 (4)	15 (30)	0 (0)	
Stage	T1	0 (0)	1 (2)	0 (0)	0.968	0 (0)	1 (2)	0 (0)	0.956	0 (0)	1 (2)	0 (0)	0.935
	T2	0 (0)	5 (10.2)	0 (0)		0 (0)	5 (10)	0 (0)		0 (0)	5 (10)	0 (0)	
	T3	1 (2)	6 (12.2)	0 (0)		1 (2)	6 (12)	0 (0)		1 (2)	6 (12)	0 (0)	
	T4	5 (10.2)	30 (61.2)	1 (2)		6 (12)	30 (60)	1 (2)		7 (14)	29 (58)	1 (2)	
Grade	Grade 1	0 (0)	1 (2)	0 (0)	0.885	0 (0)	1 (2)	0 (0)	0.713	0 (0)	1 (2)	0 (0)	0.874
	Grade 2	4 (8.2)	23 (46.9)	1 (2)		5 (10)	24 (48)	0 (0)		4 (8)	24 (48)	1 (2)	
	Grade 3	2 (4.1)	18 (36.7)	0 (0)		2 (4)	17 (34)	1 (2)		4 (8)	16 (32)	0 (0)	
Blood vessel invasion	Present	4 (8.2)	20 (40.8)	1 (2)	0.418	4 (8)	20 (40)	1 (2)	0.538	5 (10)	19 (38)	1 (2)	0.423
	Absent	2 (4.1)	22 (44.9)	0 (0)		3 (6)	22 (44)	0 (0)		3 (6)	22 (44)	0 (0)	
Lymphatic invasion	Present	4 (8.2)	37 (75.5)	1 (2)	0.343	5 (10)	37 (74)	1 (2)	0.461	6 (12)	36 (72)	1 (2)	0.583
	Absent	2 (4.1)	5 (10.2)	0 (0)		2 (4)	5 (10)	0 (0)		2 (4)	5 (10)	0 (0)	
Perineural invasion	Present	3 (6.1)	17 (34.7)	1 (2)	0.459	3 (6)	18 (36)	1 (2)	0.522	4 (8)	17 (34)	1 (2)	0.473
	Absent	3 (6.1)	25 (51)	0 (0)		4 (8)	24 (48)	0 (0)		4 (8)	24 (48)	0 (0)	
Cartilage invasion	Present	2 (4.1)	18 (36.7)	1 (2)	0.459	2 (4)	20 (40)	0 (0)	0.431	3 (6)	18 (36)	1 (2)	0.494
	Absent	4 (8.2)	24 (49)	0 (0)		5 (10)	22 (44)	1 (2)		5 (10)	23 (46)	0 (0)	

TLR: Toll-like receptor, *Statistical analyses were done with the chi-square test

the most important advantages of this technique over other techniques (9). The test is based on measuring the increase in fluorescent signal corresponding to the amount of DNA produced during each PCR cycle. A single PCR reaction is characterized by the PCR cycle in which fluorescence first rises above threshold background levels (threshold cycle, CT). Therefore, the higher the mRNA concentration of the target gene, the lower the CT value. If a comparison is

to be made between two tissues, the relative mRNA levels are calculated using the comparative $2^{-\Delta\Delta CT}$ method and valued as the gene expression level ratio between the two tissues (6). *G6PD* gene mRNA levels are used as controls for normalization.

There are a few reference studies that have examined TLR family members in head and neck cancers, especially in laryngeal cancer (10-17). With the inclusion of 50 subjects with laryngeal cancer, this study is one of the most extensive in the literature. The results of this study showed that TLR-2, -3, and -4 mRNA expressions were present in both the cancer tissues and the healthy tissues of the same subjects. Moreover, TLR-2, -3, and -4 mRNA expressions in the tumor tissues were statistically significantly lower than in healthy tissues. These results have both similar and conflicting points with those of previous studies that have investigated the TLR-2, -3, and -4 levels in patients with head and neck cancer (10-17).

TLR-3, which is a member of the TLR family with intracellular location, has the predominant characteristic of being tumor-suppressing. In a previous study, TLR-3 activation has been shown to initiate anti-tumor immunity involved in dendritic cell maturation, natural killer (NK) cell activation, and type I interferon signaling. Administration of Poly(I:C) (TLR-3 analogue) increases tumor infiltration of NK cells, leading to NK-dependent tumor regression (18). In some cancers, including endometrial cancer and acute lymphoblastic leukemia, the absence of TLR-3 has been observed to cause tumor growth (19). Chew et al. (20) determined a positive relationship between TLR-3 expression in liver cancer and patient survival rates. In another study by Salaun et al. (21), it was shown that apoptosis in the breast cancer cell line could be directly started by TLR-3. A study conducted on head and neck cancer cell lines in 2010 reported that TLR-3 was the cause of direct apoptosis (10). In another study by Luo et al. (17), TLR-3 activation was shown to inhibit tumor growth in oral SCC in a xenograft mouse model.

In the literature only a study by Pries et al. (11) reported in 2008 that c-MYC oncoprotein expression was reduced when TLR-3 expression was reduced with siRNA, and therefore, suggested that TLR-3 had an effect on tumor cell proliferation. In our study, a significant reduction of 84% was determined in TLR-3 mRNA expression in the tumor tissues of the subjects with laryngeal cancer compared to healthy tissues ($p<0.001$). The results of our study are consistent with those of the other studies in the literature, except for the above-referred one. We concluded that *TLR-3* gene showed a tumor suppressor characteristic at the mRNA level in larynx cancer.

A review of the studies conducted on TLR-2 and -4, which unlike TLR-3 are located on the cell surface, showed an organ-specific contribution with a tumor-suppressing effect in some cancers and with an oncogenic effect in some. TLR-4 has been determined to have a tumor-supportive role in colon and liver cancers, and by contrast, to prevent cancer development in some cancers such as lung and breast (22-25). In a 2009 study by Szczepanski et al. (12), TLR-4 expression was shown to be increased in head and neck cancers. The higher expression has been found especially in tongue cancers compared with larynx and other oral cavity cancer tissues. In a study by Mäkinen et al. (13) who investigated the tongue cancer cell cultures and the tissues of six patients with tongue cancer, TLR-4 expression was found higher in tumor cells, and higher expression was determined in the nuclei in healthy tissues and the cytoplasm in cancerous tissues. Mäkinen et al. (14) conducted another study on 30 patients with primary, recurrent, or metastatic tongue cancer. In primary tumors, the nucleus localization of TLR-4 was found to be higher than recurrent and metastatic tumors. Although there are few studies in the literature supporting the tumor suppressor effect of TLR-4, unlike other TLRs, TLR-4 activation is regulated by MyD88 as well as toll/interleukin-1 receptor-domain-containing adapter-inducing interferon-β (TRIF). This stimulation induces the activation of antigen presenting cells, mainly contributing to the increase in T-cell proliferation (26). In addition, it is known that lipid A, the biologically active part of lipopolysaccharides, binds to TLR-4 and promotes the inhibition of tumor growth (27). In our study, TLR-4 expression was seen to be reduced in 82% of the cancer tissues ($p<0.001$). When compared to the other studies in the literature, it was seen that the previous studies had been conducted with peripheral blood samples taken from subjects or with different methods in cell cultures. Therefore, it would not be correct to make direct comparisons.

TLR-2, which is another cell surface TLR family member, may promote or suppress tumors, just like TLR-4. Tumor-supportive characteristics of TLR-2 are seen in lung cancer (28). Wang et al. (15) reported that TLR-2 mRNA expression was higher in tumor tissues in 22 patients with laryngeal cancer. In the study by Mäkinen et al. (13), increased expression of TLR-2 and -4 in tongue cancer was seen to be positively correlated with deeper tumor invasion. In contrast to these findings, Park et al. (16) found that TLR-2 expression did not affect oral squamous carcinoma cell invasion. Moreover, TLR2 deficiency leads to increased cell proliferation and reduced apoptosis during colitis-associated cancer development (29). In another study, researchers found that a TLR-2 variant with a deletion in the promoter region increased the risk of hepatocellular carcinoma in patients with chronic hepatitis C (30). In our study, TLR-2 expression was reduced in 85.7% of the 50 subjects with laryngeal carcinoma ($p<0.001$). This result demonstrated the tumor-suppressing characteristic of TLR-2 in laryngeal cancer.

As a result of the studies, it has been seen that TLR-3 had predominant anti-tumor activity (10, 17-21). This, however, does not apply to TLR-2 and -4. Depending on the tumor type, these two receptors sometimes indicate pro-tumorigenic effects, and sometimes the opposite effect. In different studies this reciprocal effect has been seen even in the same tumor type (13, 16). Although the authors have put forward various theories about these outcomes the reason has not been fully revealed. According to the literature data, TLRs may show reciprocal effects depending on the cell type. The most plausible theories related to this are quantitative differences in the expression of various TLRs on tumor cells and inflammatory cells, mutating or polymorphism of TLRs on tumor cells. The results of our study support the literature for the anti-tumor activity of TLR-3 in laryngeal carcinoma, and new data and discussion have been put forward for TLR-2 and -4.

The limitations of our study were that it was retrospective and the expression level in the tissue was not taken into account when evaluating gene expression levels with qRT-PCR. Non-cancerous tissue samples were obtained from the laryngeal tissue in the furthest region from the cancerous tissue, constituting the control group. Another limitation was that the control group was not obtained from subjects with intact larynx. While a significant decrease in gene expressions has been detected, prospective studies are needed to investigate its expression at the protein stage in tissue.

Conclusion

Despite the recent advancements, laryngeal cancer is one of the diseases with a rarely falling 5-year survival rate. Recent studies have shifted to research on the role of cellular immunity, in particular, and on the tumor micro-environment. In the current study, we examined TLR-2, -3, and -4 from the TLR family in subjects with laryngeal cancer as these have been determined to play a role in cancer progression in several types of tumors such as those in the oral cavity, the colon, the prostate, the breasts, the skin, and the lungs. TLR-2, -3 and -4 mRNA expressions were determined to be significantly low in larynx cancer tissue samples compared to the healthy surrounding tissues. There are clues and signs that TLR-2, -3 and -4 assume a tumor suppressor role in laryngeal cancer. With the future development of agents directed at these receptors, it can be considered that tumor behavior, resistance, and sensitivity to medical interventions and cancer progression could be changed.

Ethics Committee Approval: Approval for the study was granted by the Clinical Research Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty (decision date: 15.11.2017, decision no: 93777809-604.01.01-429320).

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Authorship Contributions

Surgical and Medical Practices: Ç.E., H.C.İ., A.Ç., E.D.G., E.K., Concept: Ç.E., H.C.İ., A.Ç., Design: Ç.E., H.C.İ., A.Ç., Data Collection and/or Processing: Ç.E., H.C.İ., A.Ç., E.D.G., E.K., Analysis and/or Interpretation: Ç.E., H.C.İ., A.Ç., E.D.G., E.K., Literature Search: Ç.E., H.C.İ., A.Ç., Writing: Ç.E., H.C.İ., A.Ç.

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Main Points

- Depending on the intracellular localization, type, amount, and presence of ligands, TLRs have a two-way effect in cancer development either by supporting the tumor or by promoting an anti-tumor response.
- We found TLR-2, 3, and 4 expressions decreased in larynx squamous cell carcinoma tissues compared to normal tissues.
- Decrease in TLR-2, 3 and 4 may contribute to the progression of laryngeal cancer.
- In particular, therapies targeting the TLR-3 gene may be used in the treatment of laryngeal cancer in the future.

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Objective Evaluation of Smell and Taste Senses in COVID-19 Patients

Original Investigation

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Abstract

Objective: The severe acute respiratory syndrome-coronavirus-2 pandemic is one of the largest of the recent times and can cause many symptoms including smell and taste disorders. In the literature, smell disorders caused by coronavirus disease-2019 (COVID-19) have been reported within a wide range from 3.2% to 98.3%. A small number of these studies demonstrated smell and taste disorders through objective tests. Our aim in this study was to determine the prevalence of smell and taste disorders in hospitalized patients due to COVID-19 infection.

Methods: The study was carried out with 100 patients who were positive for real-time polymerase chain reaction and treated at the Kayseri City Hospital, and 100 healthcare worker relatives. We used the Connecticut Chemosensory Clinical Research Center test to evaluate the sense of smell. Sense of taste was evaluated using four different standardized bottles of preparations, and the results were scored according to the patients' statements.

Results: Patient (Group 1) and control (Group 2) groups were compared for age, gender, smell and taste disorders. There were 39 women and 61 men in the patient group, and 40 women and 60 men in the control group. Mean age was 50.2±1.37 (range 21–70) years in Group 1 and 47.6±1.25 (range 18–70) years in Group 2, and there was no significant difference between the two groups. While the rate of smell disorder was 80% in Group 1, we found this rate as 35% in Group 2. Taste disturbance was identified in 38 patients, of whom 16 had mild hypogeusia, 17 had moderate hypogeusia, four had severe hypogeusia, and one patient had ageusia. We found that taste disorder was 38% in Group 1 and 3% in Group 2.

Conclusion: Smell and taste dysfunctions are very common symptoms in COVID-19 patients. The results obtained using objective test methods are higher than the rates obtained from patient statements.

Keywords: COVID-19, anosmia, olfactory dysfunction, taste disorders

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Introduction

The World Health Organization named the disease, which was first seen in Wuhan, China in the last months of 2019 and thought to be a type of viral pneumonia, as coronavirus disease-2019 (COVID-19). Since it appeared, the disease was shown

to cause many symptoms such as fever, fatigue, cough, sputum, muscle pain, anorexia and shortness of breath, and more information was obtained on these symptoms overtime (1).

Another symptom seen in COVID-19 patients is smell and taste disorders, and its frequency was thought to be relatively low at the onset of the pandemic (2). In many later studies, however, these rates were shown to be much higher. Since the beginning of the pandemic, many studies were conducted to assess the senses of smell and taste in COVID-19 patients; while a small portion of these studies involved objective tests, most were observational studies. Since there are many variables such as the method of the studies, the tests used, and the regions where the studies were conducted, the prevalence of smell disorder in these studies varies between 3.2% and 98.3% (3). In this study, we aimed to assess the senses of smell and taste in COVID-19 patients with the Connecticut Chemosensory Clinical Research Center (CCCRC) test and comparative to a control group.

Methods

The study protocol was approved by the Kayseri City Hospital Ethics Committee (decision no: 196, date: 27.10.2020). Informed consent was obtained from all participants. The study was carried out with 100 patients who were positive for real-time polymerase chain reaction (RT-PCR) and were treated at the Kayseri City Hospital's pandemic departments between 1-21 November 2021. The control group was chosen from among the relatives of the hospital's healthcare workers.

Inclusion criteria were determined as patients aged 18–70 years, with a positive nasopharyngeal swab sample for COVID-19, and without neurological or psychiatric diseases. Those who had a history of smell and taste loss, sinonasal and cranial surgery, head trauma, allergic rhinitis, and chronic sinusitis and those who had been previously infected with COVID-19 or could not cooperate with the test in structions were excluded.

Age, sex, smell test and taste test results were recorded for all participants. All participants were first told how to do the test. The mean duration of symptoms of patients who reported loss of smell was 8.8 days (3–27 days). The tests were carried out by the same two otolaryngologists, taking all personal protective measures. No physical examinations were performed on the individuals in the study groups.

The CCCRC test described by Cain in 1988 was used to assess sense of smell. The CCCRC test includes the butanol threshold test and the smell identification test.

In the butanol threshold test, participants were asked to smell the contents of 8 bottles. Seven of the bottles contained butanol concentrations at different ratios (the strongest butanol concentration contained 4% butanol in deionized water and the concentration was diluted at a ratio of 1:3 for each subsequent bottle), and marked from one to seven. One bottle (bottle 0) was filled with water. The outer appearance of all bottles was the same.

Participants were asked to close a nostril with their finger, the apparatus was placed at the tip of the bottle and placed under the open nostril. Apparatus changed for each patient. The participants were asked to identify which bottle had smell, starting with the lowest concentration (bottle 7), with one bottle of water in each trial. In cases where the participant could not discriminate between water and smell, a more concentrated bottle was used. When a participant correctly identified the concentration four times in a row, the score was recorded as the threshold value. The same procedure was repeated for the other nostril and the value was recorded. The threshold value of butanol was calculated by taking the mean of the threshold values for the right and left nostrils.

The smell identification test used common odorants familiar to the Turkish population (4). One of these was Vicks®, VapoRub™ (Eczacıbaşı, Turkey) which was thought to evaluate trigeminal nerve function and was not taken into account in scoring. Other odorants presented to the participants included peanut butter, soap, coffee, chocolate, cinnamon, mothballs, and baby powder. Participants were asked to identify the odorants placed in opaque jars by closing their eyes and using one nostril. After each procedure, the participants were given a form containing a total of 20 scents along with distracting odorants and asked to choose from these (Table 1). Each odorant was presented to the participants twice. Calculation was made over seven points in total. The same procedure was repeated for the other nostril, and the smell identification score was calculated by taking the mean of the two sides. The mean of the butanol threshold and odorant identification test scores was calculated. The value found was recorded as anosmia between 0 and 1.75, severe hyposmia between 2 and 3.75, moderate hyposmia between 4 and 4.75, mild hyposmia between 5 and 5.75 and normosmia between 6 and 7 (Table 2).

Table 1. Smell identification test

Ammonia	Coffee
Peanut butter	Tobacco
Baby powder	Garlic
Black pepper	Ketchup
Burnt paper	Pine (turpentine) oil
Rubber	Vicks
Chocolate	Naphthalene
Fish	Grape jam
Cinnamon	Onion
Soap	Wood shavings

To evaluate the sense of taste, four different standardized bottles were prepared. They were prepared by adding 30 g of refined sugar in 1 L of distilled water to obtain a sweet solution, 30 g of table salt in 1 L of distilled water to obtain a saline solution, and 90 mL of lemon juice in1 L of distilled water to obtain a sour solution. For the bitter solution, hydroxychloroquine dissolved in water was used. The solutions were prepared as spray formulations and sprayed on the dorsal part of the tongue. Participants were asked to identify one of these four flavors and the results were recorded as correct or incorrect. They were asked to rinse their mouth with distilled water and the test paused for 30 seconds between two applications. The flavors were presented to the participants in random order. However, the bitter taste was applied last in order not to suppress other tastes. The patient's taste scores ranging from 0 to 4 were classified as: normal (score 4), mild hypogeusia (score 3), moderate hypogeusia (score 2), severe hypogeusia (score 1), and ageusia (score 0).

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 22 (IBM Corp.; Armonk, NY, USA). The normality of the data distribution was analyzed using the Kolmogorov-Smirnov test. Data were expressed as mean ± standard deviation. The Independent sample t-test was used for parametrically distributed data, and the Mann–Whitney U test was used for nonparametrically distributed data. A p-value of <0.05 was considered statistically significant.

Table 2. CCCRC test mean scoring system

Score	Clinical diagnosis
0–1.75	Anosmia
2–3.75	Severe hyposmia
4–4.75	Moderate hyposmia
5–5.75	Mild hyposmia
6–7	Normosmia

CCCRC: Connecticut Chemosensory Clinical Research Center

Table 3. Characteristics and test results of the patient and control groups

	Group 1	Group 2	p-value
Age	50.2±1.37	47.6±1.25	0.157
Sex	39 F 61 M	40 F 60 M	0.885
BTT	4.93±0.13	5.88±0.09	0.001
SID	4.31±0.19	5.84±0.09	0.001
CCCRC	3.42±1.16	4.55±0.68	0.001
Gustatory test	3.34+0.96	3.97+0.17	0.001

BTT: Butanol threshold test, SID: Smell identification test, CCCRC: Connecticut Chemosensory Clinical Research Center, F: Female, M: Male

Results

The patient (Group 1) and the control (Group 2) groups were compared for age, gender, smell and taste scores (Table 3). There were 39 women and 61 men in Group 1, and 40 women and 60 men in Group 2. Mean age was 50.2±1.37 (range, 21–70) years in Group 1 and 47.6±1.25 (range, 18–70) years in Group 2. There was no statistically significant difference between the two groups in terms of age and gender. Additionally in Group 1, loss of smell was observed in 30 of the 39 female patients and in 50 of the 61 male patients, and no statistically significant association was found between loss of smell and gender (p=0.539).

The mean score of the butanol threshold test done to assess smell functions was 4.93±0.13 in Group 1, and 5.88±0.09 in Group 2. The mean score of the smell identification test was 4.31±0.19 in Group 1 and 5.84±0.09 in Group 2. As stated above, the mean CCCRC scoring system calculated based on butanol threshold test and smell identification tests were found 3.42±1.16 for Group 1 and 4.55±0.68 for Group 2. All these olfactory function evaluation test results were statistically significant between the two groups (p<0.001).

While 80 patients in the patient group (Group 1) had smell disorder, this number was 35 in the control group (Group 2). In Group 1, 6 patients had anosmia, 17 had severe hyposmia, 26 had moderate hyposmia, 31 had mild hyposmia, and 20 patients had normosmia (Table 4). The number of patients subjectively reporting smell disorder in Group 1 was 30. Objectively, smell disturbance was detected in 29 of these. Fifty-one of the 70 patients who did not report any loss of smell were found to have loss with the CCCRC test.

As a result of the test performed to evaluate the sense of taste, 38 participants in Group 1 and three participants in Group 2 were found to have taste disturbances. The mean scores of the taste tests were 3.34±0.96 in Group 1 and 3.97±0.17 in Group 2, and the difference was statistically significant (p<0.001). Of the 38 patients with taste disturbance, 16 had mild hypogeusia, 17 had moderate hypogeusia, for had severe hypogeusia, and one patient had ageusia (Table 5). Taste dysfunction was most common for salty (27 patients) and sour (six patients) tastes. While 35 of 80 patients with smell disorder had taste loss, 45 patients had no taste disorder.

Table 4. CCCRC test results

Clinical diagnosis	Group 1 (n)	Group 2 (n)
Anosmia	6	0
Severe hyposmia	17	1
Moderate hyposmia	26	8
Mild hyposmia	31	26
Normosmia	20	65

CCCRC: Connecticut Chemosensory Clinical Research Center

Table 5. Gustatory function results

Score	Clinical diagnosis	Group 1 (n)	Group 2 (n)
0	Ageusia	1	0
1	Severe hypogeusia	4	0
2	Moderate hypogeusia	17	0
3	Mild hypogeusia	16	3
4	Normal	62	97

Discussion

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is one of the largest infectious diseases in history, affecting millions of people worldwide for more than two years. Many symptoms caused by the virus were reported over time. Although smell and taste disorders were thought to be less common in the early stages of the pandemic, they were shown to be more common in subsequent studies (1, 2).

Viral infections are the most common etiological cause of olfactory dysfunction with a rate of 30–40% (5). Although many clinicians attribute postviral olfactory dysfunction to inflammatory irritation in the nasal mucosa and rhinorrhea, its etiopathogenesis is not clearly understood. Some studies have shown that viral infections caused olfactory dysfunction through the olfactory neuroepithelium and the central nervous system (6-7). Previous studies showed coronavirus to be a member of the virus family that causes anosmia and reported that this effect could not be explained solely by rhinorrhea and inflammatory causes (8). In a previous animal study, it was argued that the brain was the main target organ for coronaviruses through the SARS-CoV receptor (human angiotensin-converting enzyme 2) and that it entered the brain mainly through the olfactory bulb (9).

Smell dysfunction is a very important symptom seen in patients infected with SARS-CoV-2. The fact that the smell disorder can be seen with other symptoms and its emergence as the first symptom has increased attention in this direction (10). In a multi-center European study based on a questionnaire, they reported the loss of smell as 85.6% and reported that the first symptom was smell disorder in 11.8% of the cases (11). Most of the studies examining the relationship between COVID-19 and the sense of smell are subjective studies in the form of questionnaires or retrospective anamnesis, and there are a few objective studies. Agyeman et al. (3) in a systematic review and meta-analysis where they examined 24 studies, of which five included objective methods, they determined the smell dysfunction rate as 41%, the taste dysfunction rate as 38%, and stated that the smell dysfunction rates were higher in studies using objective methods. Borsetto et al. (12) in their systematic examinations involving 3,563 patients, found the rate of smell and taste dysfunction as 47%, and they reported that smell disturbance emerged as the first symptom in 20% of the cases. In our study, we used the CCCRC test, which was previously performed and thought to be more suitable for the Turkish population (4). We found the smell dysfunction rate to be 80% and that six of these patients had anosmia, 17 of them had severe hyposmia, 26 of them had moderate hyposmia, and 31 of them had mild hyposmia. In our study, the rate of olfactory disorders in Group 2 (controls) was 30%. Veyseller et al. (4) investigated the rate of smell disorders in the healthy Turkish population using the CCCRC test and found this rate as 19.4%. In a study investigating the smell disorder in COVID-19 patients, the authors reported the rate of smell disorders as 18% in their control group (13). That olfactory disorders are seen in otherwise healthy individuals at certain rates has been revealed by a number of studies and relatively similar rates were found in our study.

It is thought that the cause of taste disorders in COVID-19 patients is the dysfunction of taste receptors or the spread of infection to the cranial nerves responsible for transmitting the sense of taste (14). In a study by Hintschich et al. (15) they investigated taste disorders in COVID-19 patients using the Taste Strip test and found the rate as 28%. In another study which used Burghart taste strips to evaluate the sense of taste, the authors found the rate of taste impairment as 25% and reported that this loss was mostly in sour and salty tastes (16). We found the rate of taste dysfunction as 38%. Of our 38 patients with taste disturbance, 16 had mild hypogeusia, 17 had moderate hypogeusia, four had severe hypogeusia, and one patient had ageusia. Consistent with other studies, we found the most significant loss of taste in salty (27%) and sour (6%) tastes.

In their respective studies with objective tests, Vaira et al. (17) found the rate of smell dysfunction as 73% with the CCCRC test, and Gözen et al. (18) found a rate of 83% by with the Sniffin' Sticks test. Moein et al. (13) found this rate as 98% with the University of Pennsylvania Smell Identification test method. In a study using quick smell identification test to investigate smell disorder, the prevalence of olfactory disorder was found as 16.3% (19).

In some studies conducted to evaluate the sense of smell, objective tests were compared with self-reports. Lechien et al. (20) assessed 86 patients who reported smell loss with the Sniffin' Sticks test and found smell dysfunction in only 62% of these patients. In another study, although 61% of the participants self-reported loss of smell, this rate was found to be 83% with the psychophysical test. Gözen et al. (18) found the rate of olfactory dysfunction as 52.5% with a questionnaire, while this rate was found as 83% with a psychophysical test. In our study, we did not use a special questionnaire for smell assessment in order not to prolong the contact time with the patient. Participants were asked whether or not they had loss of smell. Out of our 30 patients who self-reported to have loss of smell, dysfunction was

identified in 29, whereas 51 of the 70 patients who did not report any loss of smell were identified to have smell loss with the CCCRC test. The differences between the mentioned studies may be due to the use of questionnaires to assess the loss, the degree to which patients care about loss of smell, and viral or ethnic differences.

The relationship between the symptoms of smell loss and the prognosis of the disease have also been the subject of studies. Yan et al. (21) reported that patients with olfactory dysfunction needed hospitalization ten times less than the patients without loss of smell. Aziz et al. (22) reviewed 51 studies in a meta-analysis they conducted and reported that smell dysfunction was shown as a positive prognostic factor in all seven studies examining the relationship between smell and prognosis, but they reported that these results were limited. Since we conducted our study on hospitalized patients with mild-to-moderate COVID-19, we could not have the opportunity to examine the effect of smell dysfunction on prognosis. Another study reported that loss of smell were associated with better prognosis (23). Although, basing on the current knowledge, there is a general belief that olfactory dysfunction is a positive prognostic factor, new studies are needed on this subject.

There are some limitations in the presented study. First, we did not utilize any questionnaires to assess the loss of smell and taste. Also, any association between olfactory dysfunction and the severity of the disease could not be established since the presented study did not include the patients with more severe symptoms. In addition, since we did not perform RT-PCR testing on healthy volunteers, it is possible that there were COVID-19 positive individuals in the control group.

Conclusion

Smell and taste dysfunction is a very common symptom in COVID-19 patients. In the presented study, 80% of our COVID-19 patients had smell dysfunction, whereas 35% had taste dysfunction. In the control group, these rates were 35% and 3%, respectively. Of the 70 patients who did not report any loss of smell, 51 were found to have loss with the CCCRC test. The results obtained using objective test methods are higher than the rates obtained from patient statements. More detailed studies are needed to assess the senses of smell and taste in COVID-19 patients.

Ethics Committee Approval: The study protocol was approved by the Kayseri City Hospital Ethics Committee (decision no: 196, date: 27.10.2020).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.K., S.A., Concept: A.K., S.A., M.Y., İ.Ö., Design: A.K., S.A., M.Y., İ.Ö., Data Collection and/or Processing: A.K., S.A., İ.Ç., Analysis and/or Interpretation: A.K., S.A., İ.Ç., Literature Search: A.K., S.A., İ.Ç., Writing: A.K., S.A., M.Y., İ.Ö., İ.Ç.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Main Points

- Smell and taste dysfunction is a very common symptom in COVID-19 patients.
- The results obtained using objective test methods are higher than the rates obtained from patient statements.
- 80% of COVID-19 patients had smell dysfunction, whereas 35% had taste dysfunction.

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From Diagnosis to Treatment of Human Otoacariasis: Demographic and Clinical Characteristics of Patients

Original Investigation

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Abstract

Objective: Otoacariasis is the presence of ticks and mites in the ear canals of humans or animals, and particularly common in rural areas. This study aimed to present the clinical characteristics of patients that presented with ticks in their ear canal.

Methods: The study was conducted with a total of 425 patients with 527 ticks in their ear canal at the Muş Malazgirt State Hospital Ear-Nose-Throat Clinic between June 2019 and June 2020. The removed ticks were examined at the parasitology laboratory of Van Yüzüncü Yıl University.

Results: Of the 425 cases included in the study, 72% (n=306) were female and 28% (n=119) were male (mean age 40±20, minimum-maximum: 4 months–81 years). A total of 527 ticks were removed in the one-year period. Three-hundred-and-fifty-one patients had adult or nymph ticks, and 74 patients had a larval form of the tick. Of the patients with adult or nymph tick, foreign body sensation was the dominant symptom in 68.7% (n=242), whereas pain was the dominant symptom in 62% (n=46) of those with larval tick. In the comparison between groups, foreign body sensation was statistically significantly higher in the adult tick group, and pain was higher in the larval tick group (p<0.001). There were no systemic diseases related to the ticks in any of the cases.

Conclusion: Ticks in the ear is endemic in Eastern Anatolia and poses a public health problem. Tick infestations could be minimized with various precautions and educating the general public on preventive methods. Our study is the largest series in the literature on cases with ear ticks.

Keywords: Ticks, external auditory canal, foreign bodies, otobius megnini, patient education, public health

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Introduction

Ticks are major ectoparasites of animals and humans. They are mandatory blood-sucking arthropods and are found across the world, especially in tropical and subtropical regions. There are more than 900 tick species worldwide. Ticks can transmit a variety of pathogenic microorganisms, including protozoa, rickettsiae, spirochetes, and viruses, and also cause irritation, toxic reactions, and allergies (1).

Otoacariasis involves the presence of ticks and mites in the ear canal of humans or animals, and is highly common in rural areas (2). Ixodid ticks (hard ticks) comprise 80% of all ticks, with the remainder being argasid ticks (soft ticks). Otobius ticks belong to the argasid tick family and can be parasitic in both animals and humans (3). Soft ticks (Argasidae) live near hosts, and in the parasitic stage, they only feed on the host for a short time and then leave.

Larvae and nymphs of the soft tick Otobius megnini (O. megnini) parasitize the external ear canal of many animals and occasionally humans (4). From its center of origin in Southwestern North America, O. megnini has spread to a vast geographic region, including Turkey (5). A typical soft tick life cycle involves four developmental stages: egg, larva, nymph, and adult (male/female). The duration of the life cycle can extend from several weeks to many years, depending on host availability (6). O. megnini has adapted to complete its life cycle on a single host, upon which the larvae and nymphs feed for several days to months (7). Fully engorged nymphs detach after a long parasitic phase and molt on the ground to become non-feeding adults, which are nonparasitic. O. megnini has a long parasitic period and short nonparasitic period. It has a single gonotrophic cycle; hence, females die soon after oviposition (4). O. megnini displays seasonal dynamics, with a high larval activity during warmer and dryer months (8).

In this study, we present the clinical characteristics of patients with ticks in their ear canals. And we aimed to show the possible difficulties and the coping methods that may be used in otoacariasis.

Methods

The patients diagnosed with a tick in the external auditory canal in the Otolaryngology Department or Emergency Department of Muş Malazgirt State Hospital between June 2019 and June 2020 were included in the study. The ticks in the external auditory canal of all patients included in the study were removed by two otolaryngology physicians with the same intervention. Adult or nymph ticks were removed by holding their legs or abdomen with alligator forceps. In cases where the leg of the tick is seen more prominently, it is easier to remove by holding its leg; but it isn't easier to remove the tick when the leg of the tick is relatively hidden, or the abdomen is more prominent. Sometimes ticks are so engorged with blood that they fully block the external ear canal. In such case, the only way to remove the tick is by pulling the abdomen with alligator forceps. In the larval form of ticks, legs have not yet formed, and in fact, there is no complete tick appearance, and the larval forms appear as pink or red colored, round millimetric soft tissues attached to the external ear canal. Larval forms can be removed by alligator forceps or with a curette. If the larval form is hidden behind the only protrusion in the external ear canal, it is not possible to remove it with straight alligator forceps, in this case it can be removed more easily with a curette. Patients who did not come for follow-up after tick removal and patients whose interventions were performed by emergency physicians were not included in the study. The study was approved by the Muş Provincial Health Directorate and Muş Malazgirt State Hospital Chief Physician on 18.02.2021, and the protocol number is 35465298-799. Informed consent was not received because of retrospective design of the study.

Agriculture and livestock are the main livelihoods in our district. The land area of the district is 1527 km^2; population 51,323; elevation 1530 m; mean annual rainfall 468 mm; mean annual temperature 7.1 °C; and mean relative humidity 59%.

The patients' age, gender, complaints, complaint duration, physical examination findings, need for local therapy after tick removal, side of the ear from which the tick/s was/were removed, type of tick (larva or nymph/adult), number of removed tick/s and follow-up (at least two weeks) were recorded.

The ticks were removed with alligator forceps or an ear curette with the same intervention in all patients. Endoscopy was used during the physical examination of the patients' ears and during tick removal in all patients to detect small nymphal ticks and larvae. The ear canal and tympanic membrane of all patients were examined with endoscopy once again after tick removal.

The ticks removed from the patients' external auditory canals were preserved in 70% alcohol solution and taken to the Parasitology Laboratory of Van Yüzüncü Yıl University for taxonomic classification. All removed ticks were examined under a stereomicroscope (Leica MZ16, Leica Microsystems, Switzerland). The taxonomic findings given by Walker et al. (9) were used for morphological identification.

All patients were asked for any systemic symptoms for a possible infectious disease and were followed-up for two weeks for any systemic symptoms or signs; however, we could not provide any tests for infectious diseases due to the inadequate conditions of our hospital.

Statistical Analysis

Statistical analyses were performed using SPSS software version 23 (IBM SPSS® Statistics 23.0, Armonk, N.Y., USA). The proportions were presented using tables of frequencies and percentages. The chi-square test or Fisher's Exact test was used to compare these proportions in different groups. A p-value of less than 0.05 was considered to demonstrate a statistically significant result.

Results

The study included a total of 425 patients, 306 females (72%) and 119 males (28%). The mean age of the patients was 40 years with a standard deviation of 20 years. The youngest patient was 4 months old and the eldest was 81 years old. A total of 527 ticks were removed from the external auditory canals of these 425 patients. Three-hundred-and-fifty-one patients had adult or nymph ticks in their ear canal, and a total of 413 ticks were removed from the ear canals of these patients; 74 patients had a larval form of the tick, and a total of 114 larval forms were removed from these patients' ear canals. The causative agent of otoacariasis in all of our patients was the soft tick O. megnini. The main symptom of the patients at admission was foreign body sensation in the ear in 256 patients (60%), pain in 75 patients (18%), itching in 53 patients (12.5%), aural fullness and hearing loss in 26 patients (6%), and restlessness and ear pulling in 15 patients (3.5%) (Table 1).

The patients were analyzed according to their complaint duration. At admission, complaints had existed for one week in 113 patients (26.6%), for two weeks in 110 patients (25.9%), for three weeks in 101 patients (23.7%), for four weeks in 70 patients (16.5%), and for more than one month in 31 patients (7.3%) (Table 1).

The ticks were in the right ear in 205 patients (48.2%), in the left ear in 190 patients (44.7%), and in both ears in 30 patients (7.1%).

During endoscopic examination, there were no pathological findings with the ear canal in 371 patients (87.3%). Fifty-four patients (12.7%) had signs of external otitis, such as hyperemia and edema of the external ear canal, and ear drops containing antibiotic and steroid were given to these 54 patients. None of the patients in the study required systemic therapy.

Removed ticks were in the nymph or adult form in 351 patients (82.6%) and in the larval form in 74 patients (17.4%) (Table 1).

When patients with nymph or adult forms of the tick were distributed according to the seasons, 191 patients (54.4%) were admitted to the hospital in summer, 67 patients (19.1%) in spring, 66 patients (18.8%) in autumn, and 27 patients (7.7%) in winter. When patients with a larval form of the tick were distributed according to the seasons, 60 patients (81.1%) were admitted to the hospital in summer, 13 patients (17.6%) in autumn, one patient (1.4%) in spring. No patients with a larval form were admitted in the winter season (p≤0.001) (Figure 1).

More than half of the patients (238 out of 425) were females between the ages of 19–65 years. Compared to men, the incidence of ticks in females in this age group was quite high, and the difference was statistically significant (p≤0.001). There was no statistically significant difference between females and males in the 0–18-year age group or in the 66 years and over group (Table 2).

Patients were analyzed according to major complaints. In patients with adult or nymph ticks, foreign body sensation was the major complaint in 241 patients (68.7%). In patients with larval ticks, pain was the major complaint in 46 patients (62%). Clinico-demographic characteristics of the patients are shown in Table 1.

Patients were analyzed according to the number of ticks removed. Whereas a single adult tick was detected in 301 of 351 patients (85.8%), two or more adult ticks were found in 50 patients (14.2%). A single larval tick was detected in 47 of 74 patients (63.5%), whereas two or more larval ticks were found in 27 patients (36.5%).

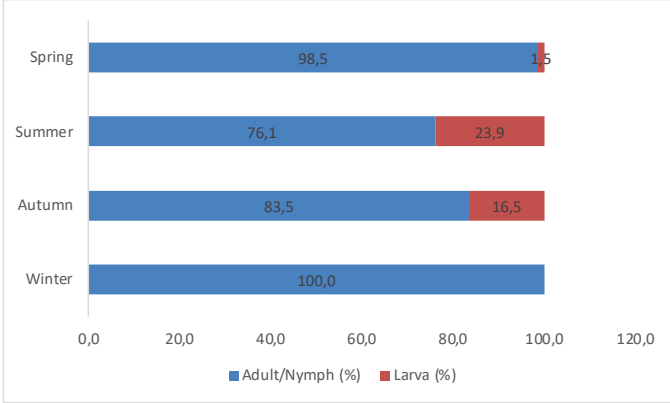

Figure 1. Distribution of adult/nymph and larva ticks by seasons

Table 1. Clinico-demographic characteristic of the patients

Adult or nymph (n)		Tick stage		p-value
		Larva (n)		
Sex	Male	100 (28.5%)	19 (25.7%)	0.624
	Female	251 (71.5%)	55 (74.3%)	
Season	Winter	27 (7.7%)	0	0.007
	Spring	67 (19.1%)	1 (1.4%)	≤0.001
	Summer	191 (54.4%)	60 (81.1%)	≤0.001
	Autumn	66 (18.8%)	13 (17.6%)	0.804
Patient's major complaint	Pain	29 (8.3%)	46 (62.2%)	≥0.001
	Moving body	241 (68.7%)	15 (20.3%)	≥0.001
	Aural fullness or hearing loss	25 (7.1%)	1 (1.4%)	0.063
	Itching	41 (11.7%)	12 (16.2%)	0.283
	Ear pulling	15 (4.3%)	0	0.085
Duration of complaint	One week	67 (19.1%)	46 (62.2%)	≤0.001
	Two weeks	91 (25.9%)	19 (25.7%)	
	More than 2 weeks	193 (55.0%)	9 (12.2%)	

n: Number of patients

Table 2. Distribution of ticks in men and women by age group

Age groups (years)	Sex		p-value
	Male (n)	Female (n)	
0–18	41 (34.5%)	41 (13.4%)	>0.05
19–65	69 (58%)	238 (77.8%)	≤0.001
66 and over	9 (7.6%)	27 (8.8%)	>0.05

n: Number of patients

External ear canal and tympanic membrane examinations were performed in all patients during and after tick removal. There were only two types of complications: otitis externa and tympanic membrane perforation. External otitis was detected in 54 out of 425 patients (12.7%). Ear drops containing ciprofloxacin and dexamethasone sodium phosphate were administered to patients with otitis externa. After two weeks' follow-up, recovery was achieved in all patients. No treatment was given to patients with a normal ear canal, and no problems were encountered in this group during the two-week follow-up period. We detected tick-borne tympanic membrane perforation in only one patient that had a small perforation on the tympanic membrane while removing the tick attached to that membrane. This patient was not given any treatment but followed-up, and the perforation closed spontaneously during the two-week follow-up period. And no complications were encountered except minimal bleeding secondary to trauma in the external ear canal of patients, as a result of the unsuccessful tick removal attempt made by the relatives of the patients.

Discussion

Tick and tick-borne diseases affect both animals and humans directly or as a vector of different pathogens (10). Although ticks are less commonly seen in the external auditory canal (otoacariasis) compared to the other parts of the body, otoacariasis is commonly found in many parts of the world, including Madagascar, Chile, USA, Nepal, Malaysia, South Africa, India, Sri Lanka, and Turkey (11-19).

O. megnini, the spinose ear tick, displays a one-host life history and feeds on large ungulates such as horse, cattle, sheep, cow, and goats (20). It occasionally parasitizes dogs and humans. The larval and two nymphal stages of O. megnini feed in the ears of their host (Figures 2-5). Living conditions may differ among tick species. Ariyarathne et al. (5) investigated otoacariasis cases in five different districts of Sri Lanka, and they found that the Dermacentor auratus tick was the major tick species associated with human otoacariasis in all five districts, with O. megnini only being found in the Nuwara Eliya district. The Nuwara Eliya district is located at a higher elevation of 1800 m above the sea level with a mean annual temperature of 16 °C and an annual rainfall of 2300 mm. Our study area has an elevation and mean annual temperature similar to the Nuwara Eliya district and

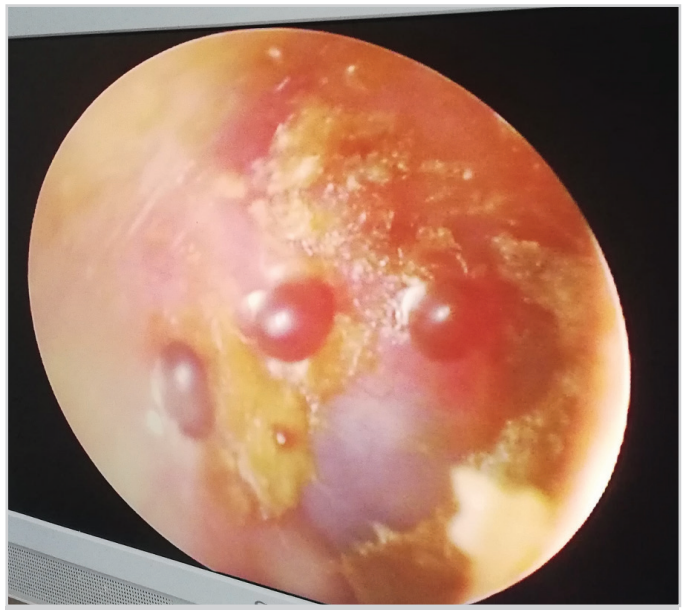

Figure 2. A patient with four larval ticks in the right ear canal

Figure 3. The larval form of the tick after removal

is located at a high elevation of 1530 m with a mean annual temperature of 7.1 °C and an annual rainfall of 467 mm. O. megnini was the only causative agent of otoacariasis in all our patients. O. megnini shows seasonal dynamics, with a high larval activity during the warmer and dryer months (8). In our district that is located in Eastern Anatolia, where our study was carried out, the summer season is hot and dry, and the winter season is cold and snowy. In our study, 81% of the patients with larval ticks were admitted to our hospital in summer, and there were no patients with a larval tick in the external ear canal in winter. Winter conditions of our district are not suitable for O. megnini. Furthermore, only 27 of the 425 patients were admitted to our hospital during winter, and there were only adult/nymph ticks in the ear canal of these 27 patients. It is likely that in these 27 patients, the tick had settled in the ears before winter. Because our district is a rural and socio-culturally underdeveloped area, patients can present to the hospital days or weeks after the onset of their

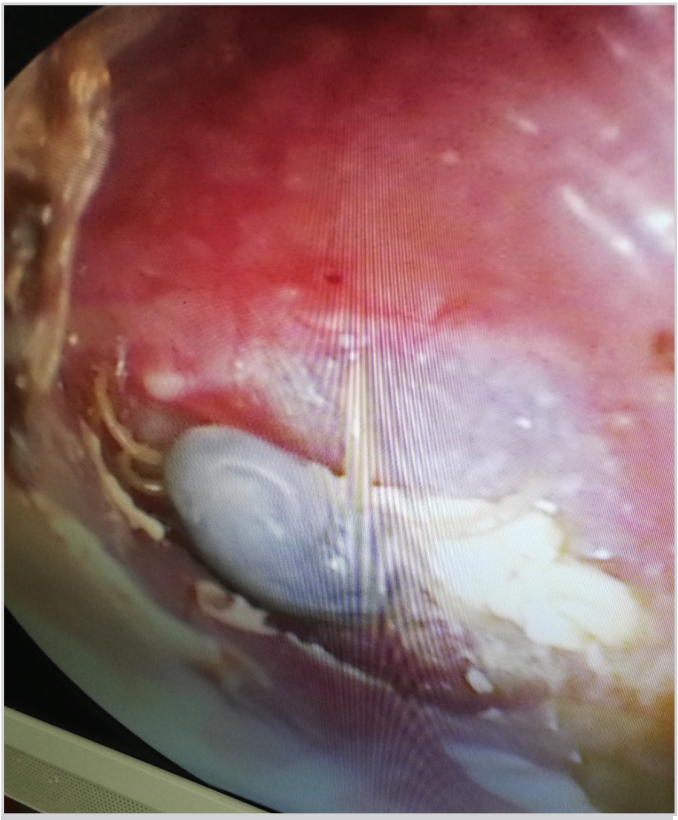

Figure 4. Nymphal form of tick in ear canal

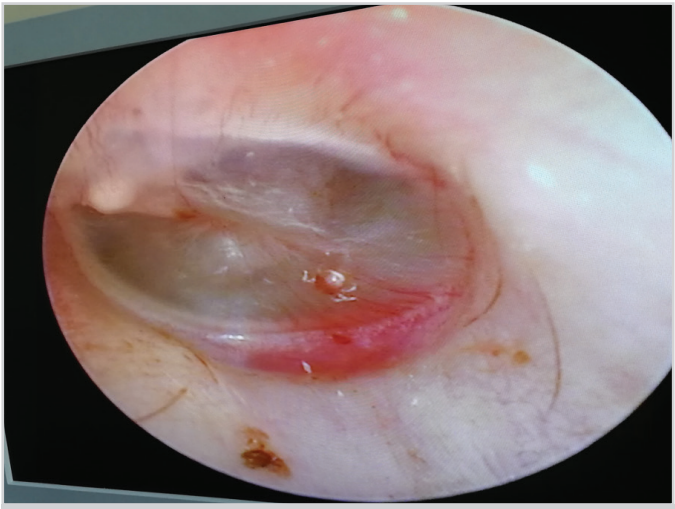

Figure 5. Nymphal form of tick on tympanic membrane

complaints. At the time of their admission to the hospital, 47.5% of our 425 patients with ticks reported that they had complaints for at least two weeks. During the interviews, the villagers stated that they knew when the ticks got into their ear, but they did not have the means or the opportunity to travel to the hospital; hence, they were late. We learned from the patients that some people in the villages attempted to remove the ticks with traditional methods, such as removing visible ticks with tweezers or by pouring milk, onion juice or oil into the ear canal to remove invisible ticks. A tick in the outer canal is such a common and known problem in this region that most of the patients stated that they suspected they had ticks in their ear canal before the examination. Conversations with the patients and their relatives revealed that all of these methods were successful from time to time. None of our patients presented with a complication as a result of the unsuccessful tick removal attempts by their relatives, except minimal bleeding secondary to trauma in the external ear canal. We also did not observe any complication, except for bleeding from time to time due to trauma in the external auditory skin canal, in the interventions performed by the emergency physicians.

In our study, 238 of the 425 patients (56%) were women between the ages of 19–65 years. Agriculture and livestock are the main sources of income in the district. The families of all the patients in whom we detected ticks were either themselves engaged or had a neighbor within 100 meters of their home who was engaged in animal husbandry. In the district, the houses are situated very close to each other, and the barns are built in the same garden as the house. Sheep, goats, cows, and horses are reared in barns in this region, and the patients stated that they occasionally see ticks on the animals or on the ground. In the district, adult women are typically involved in gardening, animal nutrition, and breeding. These facts demonstrate why ticks are more common in adult women in this district. Indudharan et al. (21) showed that 70% of human intra-aural tick infestations in Malaysia were in children aged 0–10 years. Two subsequent studies in Sri Lanka by Dilrukshi et al. (18) and Ariyarathne et al. (5) reported that children below 10 years of age and women had a high risk for intra-aural tick infestations. In the referred studies, the higher numbers of children and women affected were attributed to these two groups being co-exposed during daily activities, such as gardening and gathering forest produce.

The literature generally recommends tick removal by mechanical methods instead of chemical methods (22). Gökdoğan et al. (19) stated that they removed ticks mechanically with the help of alligator forceps from the ear canal of 31 patients aged between 17–72 years without the need for general anesthesia. Ariyarathne et al. (5) reported 426 patients aged between 2 months–84 years, with a tick in the ear canal for a three-year period; however, they did not mention the methodology for tick removal and they stated that they saw only one tick in each patient. In our study, we had 425 patients with 527 ticks in a period of one year. As far as we know from the literature, our study is the largest series in the literature on cases with ear ticks. The ages of 425 patients included in our study ranged from 4 months to 81 years, and ticks were removed mechanically with alligator forceps or an ear curette without requiring sedation or general anesthesia in all patients except two. These two patients, aged 7 and 8 years, had a larval form of the tick, and the ticks were

removed with an ear curette under sedation. In none of the patients, local anesthesia or chemical solution was used.

In our experience, for several reasons, removing ticks from the ear canal is easier than removing any other type of other foreign bodies. Firstly, ticks engorged with blood occlude the ear canal completely or near completely and are easily visible and can be removed using alligator forceps by holding them from their soft abdomen. Secondly, ticks that have not yet occluded the ear canal are easily removed by holding their legs with alligator forceps. However, the main aspect of difficulty in tick removal involves removing the larval form of the tick. This larval form is difficult both to see and to remove. Because of its particularly small size, it is occasionally impossible to see the larval tick with an otoscope; but they can be seen in the hidden areas of the ear canal with an endoscope (Figure 6). This is a significant issue, particularly in patients with a bony protrusion in the ear canal. We remove all the nymph and adult ticks and most of the larval ticks with alligator forceps, but this latter approach may not work in patients with a bony protrusion and larval ticks in the ear canal; in these patients, we remove ticks with an ear curette.

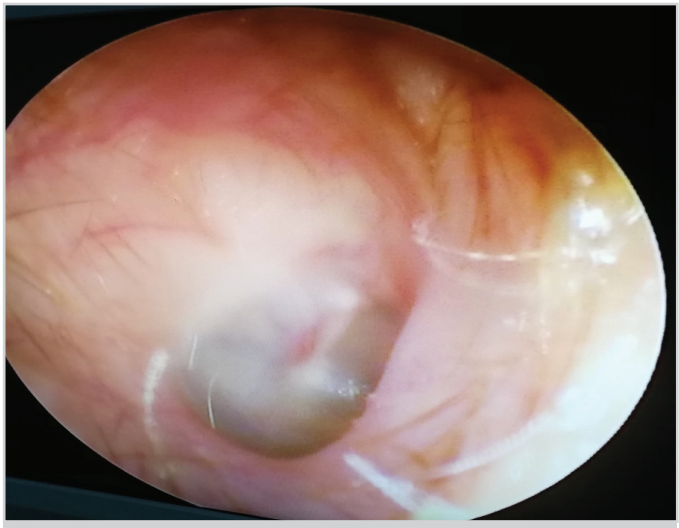

Figure 6a. A patient with hidden larval tick in the right ear canal. The photograph was taken with 30° endoscope. Although there was a larval tick, it was not visible in this position

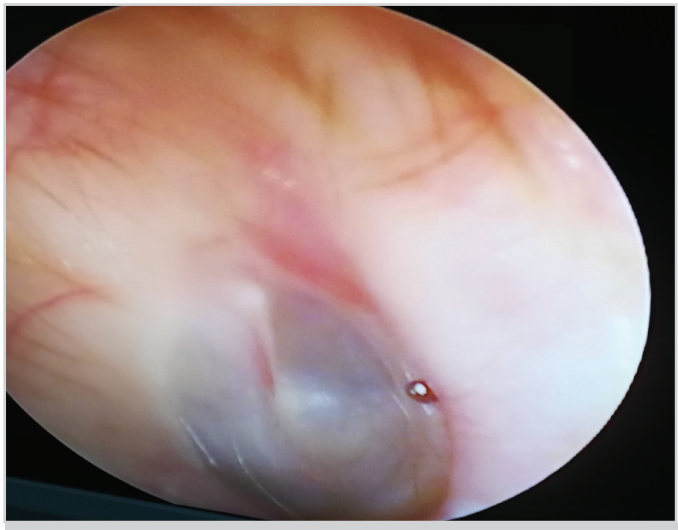

Figure 6b. The ear of the patient in **Figure 6a**. The hidden larval tick was visible by turning the 30° endoscope

The major symptom of a larval tick in the ear canal was pain. We had many patients with ear pain and normal otoscopic findings, and with the assistance of an endoscope, we identified larval forms of the ticks in the ear canal's hidden areas. Therefore, if the otoscopic findings and complaints of the patient do not match, particularly in cases of normal otoscopy and pain complaint, we perform an ear examination with an endoscope in all of these patients.

Pain was the major complaint in 62% of the patients (46 out of 74) with a larval tick, and in 8% of the patients (29 out of 351) with an adult or nymph tick. In patients with an adult or nymph tick, sensation of a moving foreign body was the major complaint in 69% of the patients (241 out of 351). During tick removal, we observed that all of the 74 larval ticks attached to the ear canal and sucked blood. It is likely that ticks in the ear canal cause pain during feeding. Pain was documented as a major complaint in a minority of patients with a nymph or adult tick, and during removal of these ticks, we observed that more than 90% of adult or nymph ticks were freely moving in the ear canal without attaching themselves to the canal wall. Some ticks were so engorged that they completely blocked the ear canal and caused hearing loss, and patients' hearing problems resolved after tick removal. Eight of the ticks that completely blocked the ear canal were dead; most likely they were stuck in the ear canal and could not detach themselves (Figure 7).

Figure 7. An adult dead tick after removal. It was entirely obstructing the ear canal, and was probably stuck in the canal and could not get out

All other ticks were alive when they were removed. Facial paralysis or paresis and tick-related bleeding in the external ear canal were not observed in any of the patients. Tinnitus was described by some patients as a very rare symptom.

We did not encounter any systemic complications in any of our patients. Since none of the patients had a systemic finding, they were not referred to infectious diseases. No systemic symptoms or signs were observed during the follow-ups. Since tick is an endemic public health problem in the region, all patients were aware and informed about ticks and none of them described a systemic disease related to ticks in any other person in the past years. From our clinical observations and interviews with the patients and their relatives, we concluded that neither the current patients nor the previous patients that had ticks in their external ear canals in the past years had systemic disease. Fifty-three of the 425 patients had external otitis and were treated with local ear drops. In one patient, perforation was observed after the nymphal tick attached to the eardrum was removed. This perforation was in the tympanic membrane and resolved during the two-week follow-up.

Conclusion

To conclude, ticks in the ear is endemic in our district and poses a public health problem. Eradication of ticks in a rural area is not doable. Tick infestations could be minimized by taking various precautions. Ticks on livestock can be controlled by acaricides. Spraying the stables and soil areas around the house with acaricides will control the ticks on the ground. In tick-prevalent regions, increasing the presence of tick-eating animals, such as partridges, pheasants, chickens, rabbits, and geese on pasture areas where animals graze during the summer months may have an important role in controlling tick population. In addition, educating the general public on preventive methods is important. Our study is the largest series in the literature on cases with ear ticks.

Ethics Committee Approval: The study was approved by the Muş Provincial Health Directorate and Muş Malazgirt State Hospital Chief Physician on 18.02.2021, and the protocol number is 35465298-799.

Informed Consent: Informed consent was not received because of retrospective design of the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: O.A., S.K., Concept: O.A., S.K., Ş.G.K., A.B.Y., Design: O.A., S.K., Ş.G.K., A.B.Y., Data Collection and/or Processing: O.A., S.K., Analysis and/or Interpretation: O.A., S.K., Ş.G.K., A.B.Y., Literature Search: O.A., S.K., Ş.G.K., A.B.Y., Writing: O.A., S.K., Ş.G.K., A.B.Y.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Main Points

- Ticks in the ear is endemic in our district (Muş, Turkey) and poses a public health problem.
- In our study, which is the largest series in the literature, we had 425 patients with 527 ticks.
- Ticks were removed mechanically with alligator forceps or an ear curette in all patients.
- Larval form of the ticks is occasionally impossible to see with an otoscope, and endoscopic examination is essential.
- Tick infestations could be minimized with various precautions and educating the general public on preventive methods.

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Direct Health Expenditure Analysis Related to Hearing Loss in Individuals Using Hearing Aids and Cochlear Implants

Original Investigation

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Abstract

Objective: This study aimed to investigate the expenditures related to hearing devices and compare the differences in expenditures in child and adult users.

Methods: A preliminary questionnaire was developed and conducted amongst hearing aid and cochlear implant users. A total of 178 patients (57.3% were hearing aid users, 42.7% were cochlear implant users) were included in the study and grouped as adults (first group, 50 patients), and children 1< (second group, 123 patients).

Results: The results of the study showed that individuals used approximately 4.5% of their annual income as health expenditure related to hearing loss. This rate was over 5% for child users, and about 2.7% for adult users. Moreover, the expenditure made by adult users was below the amount of expenditure made for children in all health expenditure indicators.

Conclusion: Supporting the family budget for hearing loss expenditures not covered by the public health insurance will minimize the financial problems caused by the disability.

Keywords: Health economics, health expenditures, hearing loss, hearing aids, cochlear implants

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Introduction

Direct and indirect expenditures due to hearing loss are a financial and moral burden on families. People with sensorineural hearing loss should use their hearing device lifelong. The expenditures are not limited to the hearing devices themselves as there are several potential additional costs (such as batteries, accessories, repairs, replacements). The fact that cochlear implants (CIs) require surgical intervention makes them costly compared to amplification devices (1). The expected lifetime cost of a child with prelingual profound hearing loss can exceed one million US dollars ($), mainly due to their need for special education and low work productivity (2). Therefore,

devices cause high costs for both users (and their families) and governments.

Like in many countries, healthcare financing in Turkey consists of taxes, social insurance premiums, out-of-pocket payments, and private health insurance in a mixed model. The Social Security Institution (SSI) pays part or the entire of the device costs of a hearing aid (HA) and a CI for candidates who meet specific prespecified criteria. Expenditures for the remaining costs are out-of-pocket payments by patients themselves or households. The adverse effects of out-of-pocket expenditures are seen among individuals who need healthcare the most and cannot receive this care because they do not have the capacity to pay, and therefore their disease is not treated (3). Out-of-pocket health expenditure made by households in Turkey for expenses such as treatment or medicine was approximately US$ 5 billion 919 million in 2019. In the same year, the ratio of household out-of-pocket health expenditure to total health expenditure was reported as 16.7% (4). In Turkey, additional auditory rehabilitation, advanced CI models (such as processor upgrade costs with advanced features), and the remaining HA cost must be paid out-of-pocket by the user or the parent.

The conditions of healthcare financing are country-specific and cannot be estimated relative to other countries, as differences in healthcare affect the results of cost analysis (5). There are three types of financial costs for individuals with hearing loss (6). The first is the direct medical costs, which reflect the cost of all resources used during the assessment, treatment, and follow-up. The second is the direct non-medical costs arising from the patient's need for healthcare intervention (such as hospital transportation costs). The last is the indirect or time costs, which measure the time and the labor loss of the patient because of the intervention or their medical condition. All these costs are considered equivalent to missed opportunities to acquire them (7). As this goes on for a long time, families may be exposed to high time and travel costs. This study investigated the direct hearing loss related costs of pediatric and adult HA or CI users in Turkey. The current study should also verify the hypothesis that costs for children are higher than for adults, and costs for a CI are higher than those for a HA.

Methods

The study was approved by the Clinical Research Ethics Committee of İstanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty (Approval no. 11/06/2020-70543). The written consent of all participants (or their parents) was obtained after they were informed about the study. The study is a descriptive and cross-sectional research. We developed and applied a preliminary questionnaire based on existing devices for expenditures related to hearing loss. Experts were consulted in the preparation of the questionnaire used in the data collection phase. These experts include audiologists, health economists, and clinicians. The questionnaire we used has a content that will illuminate the expenditures of the family for the individual with hearing loss and the process that the family goes through due to this loss. Expenditures consist of out-of-pocket expenditures. Out-of-pocket health expenditure is the expenditure that households make directly to service providers for health-related goods or services that are not partially or fully reimbursed by any person or institution.

We gathered the data from more than 15 months of administration in a clinical setting and then matched them to a comprehensive database. We calculated the sample size using power analysis. In the study, we used the 5% first type error (α), 0.5 Cohen medium standardized effect size, distribution ratio of 3 between groups (if child participant is 3x, adult participant x, the reason for this is that pediatric patients require more clinical appointments compared to adults to monitor hearing and language development processes more closely and to avoid possible problems), and 80% power (20% second type error, β). The required minimum sample size was calculated with the help of the G-Power program and found to be minimum 170 patients, namely, 43 for the first group, and 127 for the second group. In the study, the data collection phase was terminated when we reached the specified minimum number of observations, and we created the dataset with 178 patients, 50 in the first group and 128 in the second group.

We queried the demographic characteristics of the patients, such as age, gender, device used, and comorbidities to see the profile of the participants. The first part of the research questionnaire contains demographic and hearing loss information about the individuals. The second part of the research questionnaire contains information about the individual, relating to background and economic burden.

Before the questions about their expenditure and income levels, patients were asked about details as their health plan, state support for the device or battery, annual clinic visit frequency, whether they borrowed money to purchase the device and their subjective perception of the hearing loss expenditures. Four closed-ended questions (yes or no) were asked to investigate subjective perceptions of the participants for hearing loss and hearing device costs. These questions are whether hearing loss expenditures negatively affect the family budget, whether the expenditures are necessary for better communication skills of the patients, whether the expenditures limit the basic living expenses, and whether the renewal period determined for the device support is sufficient.

In the third part of the study, we presented descriptive statistics of data on the expenditures and the incomes of the patients. We divided their hearing loss expenditures into two

subgroups. Expenditures are the amount of direct payments made for the device itself, annual battery payments, annual earmold payments, annual accessory payments. The sum of these items is the total direct hearing loss expenditure. We also inquired about their annual direct non-health expenditures incurred due to hearing loss. These consist of annual food and transportation expenditures. We then calculated the annual total health expenditure, which is the sum of annual total direct health expenditure and the annual direct non-health expenditure. At this stage, we also calculated the share of the total direct health and non-health expenditures (food + transportation) in the annual income.

In this study, we mainly investigated two aspects: first, we compared the costs, and the expenditures incurred from purchasing the HAs or CIs, and then we queried whether or not there were differences between the expenditures incurred by adults and children. We also queried the patients' direct non-health expenditures (such as transportation, food) and tried revealing the financial burdens arising from hearing loss in the budget by proportioning these expenditures according to the share of their income. We also queried the patients' subjective expenditure perception and conditions, such as clinical visits, family history of hearing loss, and comorbidities, along with demographic characteristics of the patients. The answers are based on the information given by the parents (if a child) or by the individuals themselves (if adult).

Statistical Analysis

In the analysis, we used frequency and percentage for categorical variables and mean/standard deviation descriptive statistics for numerical variables in the presentation and intergroup comparisons of demographic and clinical data of patients. Also, in the comparison of the health expenditure and cost data of the patients between the groups and in the statistical significance test, we used the Mann–Whitney U test for the comparisons of the two groups, and the Kruskal–Wallis test for the comparisons of more than two groups. We used the 0.05 level for statistical significance in both mean comparison tests. We also used skewness and kurtosis values for distributing the data. We used Microsoft Office 365 Excel for the calculation of health expenditures and the SPSS (Statistical Package for the Social Sciences) 23.0 package program for the statistical analysis of the data.

Results

Data on the demographics of the participants and the brands of their devices are presented in Table 1 and Figure 1. Other information about the HAs, state supports, and users' subjective perceptions of the expenditures are presented in Figures 2 and 3.

Table 1. Demographic and hearing loss information

Characteristics	Total	Patient	
	(n=178) 100%	Child (n=128) 71.9%	Adult (n=50) 28.1%
Age (months)			
Min-max (median)	18–926 (105.5)	18–290 (74.5)	201–926 (517.0)
Mean ± SD	203.08±222.18	86.23±53.135	502.22±209.826
Gender	178 (100.0%)	128 (100.0%)	50 (100.0%)
Female	92 (51.7%)	60 (46.9%)	32 (64.0%)
Male	86 (48.3%)	68 (53.1%)	18 (36.0%)
Type of hearing device	178 (100.0%)	128 (100.0%)	50 (100.0%)
Hearing aid	102 (57.3%)	65 (50.8%)	37 (74.0%)
Cochlear implant	73 (41.0%)	61 (47.7%)	12 (24.0%)
Bimodal	3 (1.7%)	2 (1.6%)	1 (2.0%)
Side of hearing device	178 (100.0%)	128 (100.0%)	50 (100.0%)
Unilateral	56 (31.5%)	27 (21.1%)	29 (58.0%)
Bilateral	122 (68.5%)	101 (78.9%)	21 (42.0%)
Usage time (months)			
Min-max (median)	2–840 (25)	2–268 (18)	4–840 (296)
Mean ± SD	113.57±191.26	33.66±41.825	318.12±261.21
Comorbidities	178 (100.0%)	128 (100.0%)	50 (100.0%)
None	133 (74.7%)	103 (80.5%)	30 (60.0%)
One	36 (20.2%)	19 (14.8%)	17 (34.0%)
At least two	9 (5.1%)	6 (4.7%)	3 (6.0%)
Hearing loss in family	178 (100.0%)	128 (100.0%)	50 (100.0%)
None	119 (66.9%)	84 (65.6%)	35 (70.0%)
One	40 (22.5%)	31 (24.2%)	9 (18.0%)
At least two	19 (10.7%)	13 (10.2%)	6 (12.0%)
Using IC/CI in family	178 (100.0%)	128 (100.0%)	50 (100.0%)
None	144 (80.9%)	101 (78.9%)	43 (86.0%)
Hearing aid	15 (8.4%)	11 (8.6%)	4 (8.0%)
Cochlear implant	19 (10.7%)	16 (12.5%)	3 (6.0%)
Annual clinical visit frequency	178 (100.0%)	128 (100.0%)	50 (100.0%)
1-2 times	113 (63.5%)	71 (55.5%)	42 (84.0%)
3-4 times	43 (24.2%)	41 (32.0%)	2 (4.0%)
More than 5 times	22 (12.4%)	16 (12.5%)	6 (12.0%)

SD: Standard deviation

On clinical appointment days, 26.4% of the participants spend about 1 hour, 41% spend about 2 hours, 19% about 3 hours, and the rest spend more than 4 hours at the hospital.

84.2% of the participants lived in the same city as the study center and the average transportation cost of the participants was US$26.119±77 per year. The findings are presented in Table 2.

We also compared the differences in the expenditures based on whether the participants used the HA or the CI for themselves or for their children. As shown in Table 2, in all health expenditure indicators, adult users' expenditures are lower than those of child users. Annual battery expenditure, annual total direct health expenditure, annual transportation expenditure, annual food expenditure, annual total health expenditure and the share of annual total health expenditure in income level were higher in children than in adult patients, and the difference was statistically significant ($p<0.05$).

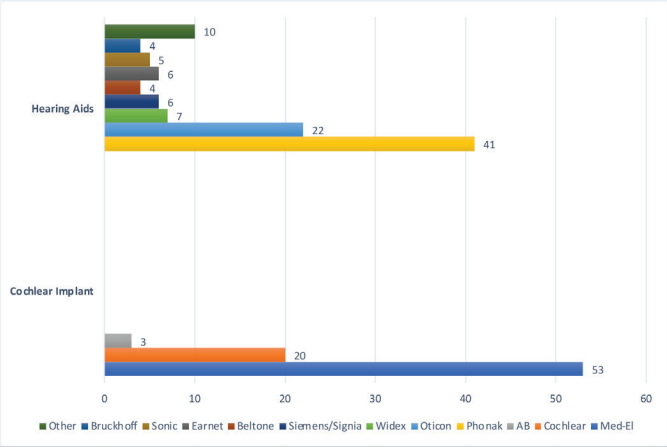

Figure 1. Brands of hearing devices

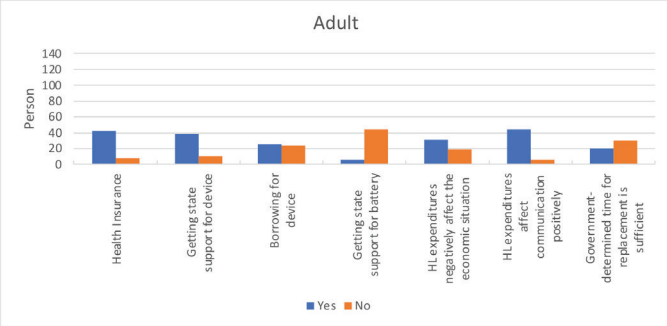

Figure 2. Borrowing, supports, and subjective perception of expenditures for adult users

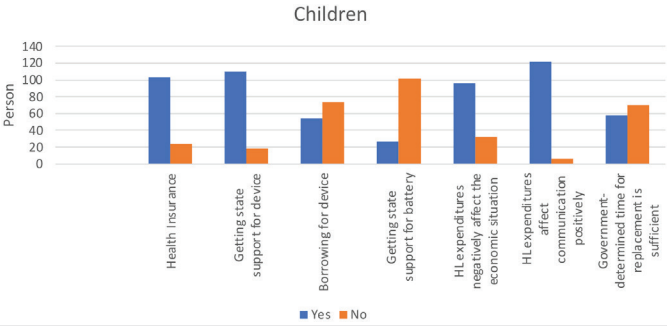

Figure 3. Borrowing, supports, and subjective perception of expenditures for pediatric users

One of the important indicators for us in terms of patients' health expenditure level is the share of their annual total health expenditure in their income. This indicator shows us how much of their annual income is used by patients as health expenditure related to hearing loss. The calculation made on a total of 178 patients showed that these individuals used approximately 4.5% of their annual incomes as health expenditure related to hearing loss. While this rate was as high as 5% in child patients, it was approximately 2.7% in adult patients.

In the last part of the study, we analyzed participants' HA and CI expenditures in further detail. The findings are presented in Table 3. According to this analysis, the amount paid by the family for the device, the average annual battery expenditure, annual accessory expenditure, annual total direct health expenditure, annual total health expenditure, share of annual total health expenditure in income were statistically significantly different among the groups. While the group with the highest health expenditure in all expenditure items used both, when CIs and HAs were compared, the level and the share of the health expenditures related to CIs were found to be higher than those for HAs. The annual health expenditure of those who use bilateral devices was 14% of their income. Additionally, the share of health expenditures related to CIs in annual income was approximately 5.8%, and that related to HAs was approximately 3% of participants' annual incomes.

Discussion

Out-of-pocket health expenditures can create financial hardship by forcing people to choose between health expenses and other needs (8). In 2015, the global population spending more than 10% of their household budget on health services was 12.7%, and the portion of the population spending more than 25% on health services was 3% (8). The World Health Organization stated that the cost of hearing aids should be equal to or not exceed 3% of the gross national product per capita (9). In a survey of more than 40,000 households using the National Family Opinion panel in the US, hearing loss was shown to negatively impact household income on-average up to $12,000 per year, depending on the degree of hearing loss (10). However, there are limited studies investigating out-of-pocket costs for hearing devices from the perspective of families (11). To the best of our knowledge, our study is the first to investigate the expenditures of hearing device users in Turkey. The main result of our study is that families spend about 4.5% of their annual income on out-of-pocket health expenditures due to hearing loss.

Cost is one of the primary reasons for non-adoption of hearing devices (12). According to the MarkeTrak VII Survey, 76% of the respondents mentioned financial constraints as a barrier

to HA adoption, 64% said they could not afford hearing aids, and nearly half (49%) indicated cost as a definite reason why they don't use hearing aids (13). Because of low savings rates in developing countries, patients often borrow from family, friends, or moneylenders, or sell their property (14). In the presented study, 44.9% of the participants borrowed to buy or upgrade their hearing devices. HA and CI users must pay for any failures or device accessories (alternative costs such as assistive listening devices, waterproof case) that fall out of warranty. In our study, many of the participants (71.3%) reported that their basic living expenses (such as clothing and food or their social activities) were limited by expenditures related to hearing loss. Parents of pediatric device users (75%) reported more limitations than adults (62%). This result is associated with the hypothesis that pediatric (5%) device users spend more than adults (2.7%). In a similar study that evaluated the direct medical cost of CIs in France, average costs in the first year of implant use were reported to be €34,686 per child and €31,946 per adult (5). A previous study investigated mothers' willingness to pay (WTP) for healthcare costs for themselves and their children. The average WTP for mothers and for children were $37 and $57, respectively (15). Another study reported that most parents considered no other options that could improve their child's quality of life to the same extent and parents were willing to pay substantial monthly amounts for CIs (16).

HA and CI users should followed-up with regular fine-tuning appointments to achieve maximum efficiency with their device. Considering factors such as age and experience in our clinical practice, we provide our patients with more frequent appointments in the early period of after they start using their hearing devices and reduce this frequency in the later period of their follow up. Our study showed that pediatric device users made more frequent clinic visits per year than adults, as expected, and a substantial portion of all participants (36.6%) visited our clinic more than three times a year (Table 1). A study of the time and out-of-pocket

Table 2. Costs and expenditure of the hearing loss by patients ($)**

Characteristics	Total	Patient		
	(n=178) 100%	Child (n=128) 71.9%	Adult (n=50) 28.1%	p-value
The amount paid by the family for the device Mean ± SD	394.4±62.3	428.12±70.8	305.41±31.1	0.240
Annual battery expenditure Mean ± SD	117.65±126.9	130.6±141.5	84.4±68.7	0.029*
Annual earmold expenditure Mean ± SD	13.45±21.5	14.11±23.1	11.04±13.5	0.907
Annual accessory expenditure Mean ± SD	38.75±114	46.23±129.1	19.88±56.7	0.198
Annual total direct health expenditure Mean ± SD	169.52 ±211.5	191.6±238.8	113.1±102.3	0.026*
Annual transportation expenditure Mean ± SD	26.11±77.4	33.6±90.1	6.76±8.75	0.037*
Annual food expenditure Mean ± SD	8.65±22.5	10.14±26.3	4.88±5.29	0.034*
Annual total health expenditure Mean ± SD	204.3±230.9	235.3±253.3	124.7±103.1	0.004*
Share of annual total health expenditure in income Mean ± SD	0.044±0.051	0.050±0.057	0.027±0.027	0.007*

SD: Standard deviation, *Significant at 0.05 according to the Mann–Whitney U test, **(US$1 is approximately 8.5 Turkish Liras; the monthly minimum wage in Turkey is approximately $332.4, August 2021)

Table 3. Costs and expenditure of the hearing loss by devices ($)**

Characteristics	Total	Patient			
	(n=178) (100%)	Hearing aid (n=102) 57.3%	Cochlear implant (n=73) 41%	Both (n=3) 1.7%	p-value
The amount paid by the family for the device Mean ± SD	393.7±62.3	398.9±282.2	395.9±271.6	156.8±271.7	0.000
Annual battery expenditure Mean ± SD	117.6±129	82.87±68.7	156.6±148.3	352.3±440.7	0.000*
Annual earmold expenditure Mean ± SD	13.46±21.5	18.42±16.9	7.54±25.76	0.00±0.00	0.000
Annual accessory expenditure Mean ± SD	38.7±114	6.53±32.5	72.5±128.3	313.6±543.3	0.000*
Annual total direct health expenditure Mean ± SD	169.5±211.5	107.1±77.3	236.1±233.4	668.9±981.05	0.000*
Annual transportation expenditure Mean ± SD	26.1±77.4	14.36±39	42.19±109.7	33.72±52.2	0.055
Annual food expenditure Mean ± SD	8.65±22.5	6.02±6.23	12.32±34.35	9.80±8.95	0.054
Annual total health expenditure Mean ± SD	204.2±230.9	127.5±89.6	290.5±259.6	712.4±963.1	0.000*
Share of annual total health expenditure in income Mean ± SD	0.044±0.051	0.0303±0.036	0.058±0.057	0.14±0.14	0.000*

SD: Standard deviation, *Significant at 0.05 according to the Kruskal–Wallis test, **(US$1 is approximately 8.5 Turkish Liras; the monthly minimum wage in Turkey is approximately 332.4 dollars, August 2021)

expenditures of families participating in the pediatric CI program has shown that those who were in the first two years of the program or who live far from the implant center spent more time and incurred higher costs. The study also reported that the largest out-of-pocket cost was travel expenses, with 44% and 16% of families receiving financial support for travel expenses (7). Molinier et al. (5) estimated that annual travel costs accounted for 7% of the total direct costs.

Transportation and food expenses and loss of workforce during hospital appointments are a burden on family economy. Nevertheless, 93.3% of the participants and the parents stated that they believed the expenditures for hearing loss or for hospital appointments were necessary for effective communication in the current study. 76.3% of the participants spent more than 1 hour at the hospital. Failures in the hearing devices, connection problems of equipment, and previous appointments taking longer than expected can increase time spent in the hospital. The use of objective fitting methods in patients without a clear behavioral response may also prolong this time. As a result, patients with hearing loss spend a particular time and costs while traveling for treatment. Time and travel costs can be reduced by expanding comprehensive audiology services across the country, providing financial assistance to families living away from the center, or by expanding remote health services.

Kochkin (17) reported that the income levels declined in both treated and untreated hearing loss groups as their hearing loss worsened, and this income decline is reduced by half in HA owners. As we expected, the annual expenditure of HA users were lower compared to that of CI users, not counting the earmold and the average expense for the device. Because earmolds are usually not required for CI users and the full cost of the CI is covered by the SSI in Turkey (excluding upgrade and change of processor costs). A study investigating the cost of hearing devices in a middle-income country reported that the short-term costs were higher for a CI than for an HA, but higher in the long-term for individuals using HA. This was explained by the fact that while individuals using an HA have to replace the device every 5 years, those using a CI only have to pay for the treatment or the rehabilitation costs for the first 6 years after implantation (18). Additionally, that alternative expenditures were higher in the pediatric group than in the adult group was a result that we expected and supported our hypothesis (Table 2). Currency fluctuations can increase expenditures related to hearing loss and HAs. Long-term studies, such as panel data or time series analysis, can be planned to better understand the effect of the exchange rate, changing over time, on hearing loss-related expenses.

It has been previously shown that children from families with higher estimated incomes had faster rates of receptive language development but slower rates of expressive language development compared to children from families with lower estimated incomes (19). Spending a large portion of the family budget on basic living expenditures can negatively affect the language development of a person who have hearing loss by limiting the time and costs spent on hearing loss. Besides, as this continues for a long time, families may be exposed to high time and travel costs. Therefore, future research should well investigate the impact of direct and indirect costs of HAs on the family budget, in addition to a comprehensive analysis of direct medical and rehabilitation costs.

This study may have had some possible limitations while investigating the expenditures related to hearing loss. Firstly, it is possible that some patients or parents may have reported their expenses higher than the actual. Secondly, while our research emphasized the expenses related to the hearing devices, it may have compromised our findings' accuracy due to the retrospective nature of the study. This was because some patients may not have remembered the costs correctly and instead reported overall estimates. It is also necessary to expand the research to other parts of the country to reach more specific conclusions. Additionally, we planned to compare a cohort and a group with controlled variables in our next study to avoid biased interpretations, as it would be nearly impossible to compare all variables in our study.

Conclusion

Hearing loss is an important problem that negatively affects all developmental areas of individuals. Deaf individuals not only lose their hearing, but also experience secondary problems caused by hearing loss. These problems are speech disorder, voice disorder, social isolation, psychological, academic, occupational, and economic problems. The treatment of sensorineural hearing loss is costly, laborious, and long-term. It also causes many economic, social, and emotional problems for patients and their families. The basic approach in eliminating these problems is the early diagnosis and treatment of hearing loss. In addition, the inclusion of children or adults with CIs in the auditory rehabilitation program is of great importance for post-implant success. The development of auditory skills should be followed closely by the audiologist and should be a part of routine control. The given auditory exercises should be adapted to daily life. However, financial expenditures are required for the methods to be applied in this process. Although partial support is provided by the state in line with social health plans, there are cases where the individuals themselves have to spend out-of-pocket.

Out-of-pocket expenditures may cause individuals/households to not receive the health services they need, face the risk of unforeseen expenditures when they want to receive them and may lead to shortage of money. So, it is necessary to understand the effects of direct and indirect expenditures related to hearing loss on the family economy

to include these costs in payment programs. To overcome financial problems and to create equal opportunities for disadvantaged groups, support from municipalities/non-governmental organizations and state funds to families/users for expenses outside the scope of social security will minimize the restrictions created by disability.

Ethics Committee Approval: The study was approved by the clinical research ethics committee of Cerrahpaşa Medical Faculty (Approval no. 11/06/2020-70543).

Informed Consent: The written consent of all participants (or their parents) was obtained after they were informed about the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.D., C.B., E.K., R.D., M.A., Y.Z.Y., A.A., Design: B.D., C.B., E.K., R.D., Y.O., Y.Z.Y., A.A., Data Collection and/or Processing: B.D., R.D., Y.O., M.A., Analysis and/or Interpretation: B.D., C.B., E.K., R.D., Y.Z.Y., A.A., Literature Search: B.D., R.D., Y.O., M.A., Writing: B.D., C.B., R.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Main Points

- Participants' health expenditures related to hearing loss were approximately 4.5% of their annual income.
- Approximately 5.8% of the annual income of cochlear implant users and approximately 3% of the annual income of hearing aid users were spent on hearing loss-related expenditures.
- While the rate of health expenditures for pediatric patients was over 5%, this rate was about 2.7% for adult patients.

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Effects of the Lunar Cycle, Seasons and the Meteorological Factors on Peripheral Vertigo

Original Investigation

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Abstract

Objective: This study aimed to determine whether peripheral vertigo is related to the lunar cycle, the seasons, or meteorological factors, in patients who presented to the ear, nose, and throat clinic.

Methods: All the patients, diagnosed with vertigo between January 2020 and January 2022, were identified through a retrospective review of our hospital database. The clinical and demographic data of the patients were recorded. Daily humidity (minimum, average, and maximum; %), daily temperature (minimum, average, and maximum; ˚C), daily average and maximum wind speed (m/min), daily air pressure (minimum and average maximum; hPa) and wind direction (degrees) values were noted. Also, the phases of the moon, i.e., first quarter, new moon, last quarter, and full moon periods were determined.

Results: A total of 5,432 patients were included in the study. No statistically significant differences were noted among them with respect to the lunar cycle (p=0.233). However, patient density was found to increase in the winter months.

Conclusion: This study concluded that the frequency of diseases is related to meteorological factors, nonetheless, no statistical relationship was found between the lunar cycle and the frequency of patient entries.

Keywords: Vertigo, meteorological factors, lunar cycle, season, benign paroxysmal positional vertigo

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Introduction

Dizziness is a general term for a feeling of disorientation. Vertigo is a subtype of dizziness arising from an imbalance in the vestibular system, and autonomic symptoms such as pallor, sweating, vomiting, and nausea are generally related to vertigo (1). Vertigo occurs as episodes in decreasing density, and gradually with age becomes a reason for frequently presenting to hospital. The most common reasons for this are acute vestibular neuronitis, benign paroxysmal positional vertigo (BPPV), labyrinthitis, migraine, anxiety disorders and Ménière's disease (2). Vertebrobasilar

ischemia and retrocochlear tumors are the less common reasons (3). BPPV causes more than 40% of vertigo diagnoses seen in the first phase and is the most frequent cause of lifetime vertigo. In BPPV, patients usually complain about short vertigo episodes triggered by position changes. Incidents usually take only seconds and last less than a minute (4).

The thought of the effects of the lunar cycle on human health goes way back. In a study conducted in 1987, 64% of the doctors and 80% of the nurses working in the emergency room expressed that they believed the moon had an effect on humans health (5).

The effort of trying to identify a connection between human health and the lunar cycle by both the society and the healthcare professionals led to academical studies on this topic. Many of these studies revealed the absence of any relationship between many diseases and the lunar cycle; however, it is known that the lunar cycle may have an effect on sleep and other physiological processes (6, 7). This relationship is basically explained by the decrease in melatonin secretion and the change in body fluid balance due to the brightness in the full moon period (8). There are limited numbers of studies examining otorhinolaryngological diseases and lunar cycle (9). Since the lunar cycle changes liquid balance, we think that it might have effects on endolymph in semicircular canals.

The effects of meteorological factors on otorhinolaryngological diseases have been supported with the results of scientific studies. These revealed that temperature, humidity, atmospheric air pressure changes, and wind and precipitation could affect the occurrence of many otorhinolaryngological diseases and that the frequency of presenting with otorhinolaryngological diseases varied seasonally. The patient populations examined in these studies show differences as they were conducted in different geographical regions and under different climate conditions. This has brought about of different results as well as results that supported each other (9, 10).

In our study, we aimed to reveal any possible relationship between the lunar cycle, the seasons and meteorological factors in patients who presented to our otorhinolaryngology outpatient clinic with peripheral vertigo.

Methods

Study Population and Ethics

The study protocol was approved by the Ethical Committee of Adıyaman University (decision date: 16.02.2022, decision no: 2022/2-14). The database of our hospital was retrospectively reviewed, and all the patients diagnosed with vertigo between January 2020 and January 2022 were identified. Clinical and demographical data of the patients were recorded.

Method of Measurement

Seasons were defined as: summer, June 1–August 31; autumn September 1–November 30; winter December 1–February 28, and spring, March 1–May 31.

Astronomic data were taken from www.timeanddate.com (11). The lunar phases were defined as the new moon, the first quarter, the full moon, and the last quarter. The relationship of the lunar cycle and seasonality with the incidence of vertigo, its severity, epidemiological data and accompanying diseases were reviewed. In addition, meteorological data such as temperature (°C), daily humidity (%), daily maximum and average wind speed (m/min), wind direction (degrees) and daily air pressure (hPa) were obtained from the Adıyaman provincial directorate of meteorology and examined.

Statistical Analysis

Data were analyzed with the Statistical Software for Social Sciences IBM SPSS v25 (Armonk, NY: IBM Corp., USA). The compliance of the variables to normal distribution was examined using histogram graphics and the Kolmogorov-Smirnov test. Mean, standard deviation and median values were used to present descriptive analyses. Categorical variables were compared with the Pearson's chi-square test and these variables were presented as frequency (n) and percentage (%). Numerical variables were compared between the groups using the independent samples t-test. A p-value of less than 0.05 was evaluated as statistically significant.

Results

Patients who presented to the Otorhinolaryngology outpatient clinic with a complaint of peripheral vertigo between January 2020 and January 2022 were statistically compared with respect to the lunar cycle and the seasons. A total of 5,432 cases, 3,382 (62.3%) female and 2,050 (37.7%) male, were included in the study. The average age of females was 45.05±16.78 years and average age of males was 47.10±17.10 years. Statistically significant differences were found when female and male patients were compared by age (p=0.000) (Table 1). By lunar cycle, 25.0% of the female patients had presented during the first quarter, 26.3% during full moon, 25.4% during the third quarter, and 23.2% during

Table 1. Descriptives and demographics of the patients

		Male n=2,050 (37.7%)	Female n=3,382 (62.3%)	p-value*
Age	Mean ± SD	47.10±17.10	45.05±16.78	0.000
	Median (min-max)	47.0 (18–67)	44.0 (18–61)	

*Independent samples t-test was used, SD: Standard deviation, min-max: Minimum-maximum

new moon. For the male patients 24.3% had presented during the first quarter, 24.5% during full moon, 27.5% during the third quarter, and 23.7% during new moon. No statistically significant differences were found with respect to gender (p=0.233) (Table 2).

When compared by seasons, 16.8% of female patients were found to have presented in spring, 25.8% in summer, 25.5% in autumn, and 31.9% in winter. For the male patients, 20.3% were found to have presented in spring, 25.3% in summer, 25.1% in autumn, and 29.3% in winter. Statistically significant differences were found between the genders in terms of the seasons they presented to the clinic (p=0.009) (Table 3). Patient admissions were seen to have increased in winter. In terms of the distribution of the patients, the highest number of patient admissions was in February with 637 (11.72%) patients, followed by January with 601 (11.06%) patients. The month with the least patient admissions was May with 226 (4.16) patients (Table 4). When the number of patients were reviewed with respect to temperature, humidity, pressure and wind, no significant correlations were found, however, an increase was seen in the number of patients as a negative correlation with the decrease in temperature (Figure 1). The patients had mostly presented in winter.

Discussion

Human physiology is affected by yearly rhythms, e.g., by the lunar cycle and the seasons. The frequency of emergency presentations for reasons such as birth, sleep, rupture of abdominal aorta and intracranial aneurysm, acute coronary events, gastrointestinal bleeding, psychiatric episodes in children and adults, post-surgical bleeding and complications, stroke, epileptic and psychogenic seizures, kidney transplant results, trauma are the common cases associated with the lunar cycle (6, 7, 12-15). The belief that some parts of the body are related to some positions of the moon is expressed with "zodiacal constellations". According to this belief system, the success of surgical procedures on the body part that is thought to be related to the special phases of the moon is lower during full moon. It was reported that this phase had an effect on patients' decision for their day of surgery (16). The effects of the lunar cycle on human health are said to be mainly based on the changes in the full moon. In the full moon phase, the Earth stands between the sun and

Table 2. Relationship between sex and lunar cycle

		Lunar cycle					
Sex		**First quarter**	**Full moon**	**Third quarter**	**New moon**	**Total**	**p-value***
Female	count	846	891	859	786	3,382	0.233
	% within sex	25.0%	26.3%	25.4%	23.2%	100.0%	
	% within lunar	62.9%	64.0%	60.4%	61.8%	62.3%	
Male	count	498	502	564	486	2,050	
	% within sex	24.3%	24.5%	27.5%	23.7%	100.0%	
	% within lunar	37.1%	36.0%	39.6%	38.2%	37.7%	
Total	count	1,344	1,393	1,423	1,272	5,432	
	% within sex	24.7%	25.6%	26.2%	23.4%	100.0%	
	% within lunar	100.0%	100.0%	100.0%	100.0%	100.0%	

*Pearson chi-square test was used

Table 3. Relationship between sex and season

		Season					
Sex		**Autumn**	**Winter**	**Spring**	**Summer**	**Total**	**p-value***
Female	count	862	1,079	568	873	3,382	0.009
	% within sex	25.5%	31.9%	16.8%	25.8%	100.0%	
	% within lunar	62.6%	64.2%	57.7%	62.7%	62.3%	
Male	count	514	601	416	519	2,050	
	% within sex	25.1%	29.3%	20.3%	25.3%	100.0%	
	% within lunar	37.4%	35.8%	42.3%	37.3%	37.7%	
Total	count	1,376	1,680	984	1,392	5,432	
	% within sex	25.3%	30.9%	18.1%	25.6%	100.0%	
	% within lunar	100.0%	100.0%	100.0%	100.0%	100.0%	

*Pearson chi-square test was used

Table 4. Distribution of patients by year and month

	2020 (n)	2021 (n)	Total (n) (%)
January	394	207	601 (11.06%)
February	425	212	637 (11.72%)
March	266	200	466 (8.57%)
April	85	201	286 (5.26%)
May	73	153	226 (4.16%)
June	210	219	429 (7.39%)
July	247	186	433 (7.97%)
August	227	297	524 (9.64%)
September	217	276	493 (9.07%)
October	173	235	408 (7.51%)
November	170	279	449 (8.26%)
December	183	257	440 (8.10%)

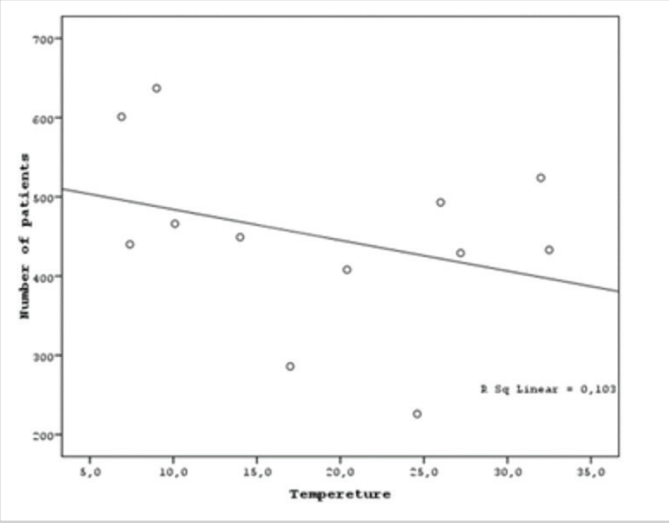

Figure 1. Overall correlation between the average temperature and the number of vertigo patients

the moon. It was asserted that neurohormonal activity may be affected due to electromagnetic changes and gravitational changes in this period (17). It was shown that melatonin levels decreased due to increased light during the full moon phase. Cajochen et al. (7), reported that while a 30% decrease was detected in electroencephalogram delta waves during non-rapid-eye-movement sleep, which is an indicator of deep sleep, during full moon, there was a 5-minute increase in the time to fall asleep and total sleep time decreased by 20 minutes. The authors stated that there were a decrease in the melatonin levels measured during the full moon. In studies reporting that the lunar cycle affected the time of birth, this relationship is explained by the changes in melatonin levels related to the lunar cycle. It was shown that melatonin levels decreased due to increased light during the full moon phase (7). Melatonin levels increased during pregnancy and sharp decreases were observed after delivery (8). Therefore, it was asserted that the decrease in melatonin levels could induce labor.

Altunisik et al. (18), examining the relationship between strokes and the lunar cycle, saw that ischemic stroke frequency increased during the new moon but could not find any statistically significant relationship. In the literature, there are studies examining the relationship between otorhinolaryngology diseases and meteorological factors and the lunar cycle. In their respective studies, Duvdevani et al. (9) and Walker et al. (19) examined the relationship between emergency room presentations with nose-bleeding and the lunar cycle. Full moon phase and other moon phases were compared in both studies and no significant differences were found in terms of presentation frequency. In a study, Akdoğan et al. (20) examined the distribution of patients with vertigo by the lunar cycle but did not find any statistically significant differences.

In our study, we too, did not find statistically significant differences between the phases of the moon and vertigo patient admissions. In the study conducted by Saeed and Omari (21), negative correlation was found between BPPV presentation frequency and temperature while positive correlation was found with atmospheric pressure. In this study, the positive correlation between relative humidity and BPPV was not considered as statistically significant.

In a similar study, Korpon et al. (22) reported that each unit increment in barometric pressure caused an increase of 6.1 diagnoses in BPPV. Negative correlation was found between temperature and BPPV frequency in this study. In the study conducted by Akdoğan et al. (20) with patients who presented to the emergency room with otorhinolaryngological complaints, the frequency of patients diagnosed with vertigo showed a negative correlation with all temperature values (maximum, minimum and average), daily maximum wind speed and daily average wind speed, but positive correlation with daily minimum pressure, daily maximum humidity and daily average humidity. In our study, although there were no statistically significant differences between heat and wind speed and number of vertigo patients, a negative correlation was found. Similar to this study (20), we found a positive correlation with atmospheric pressure and humidity. Also, when the number of patients were examined by months and seasons, it was seen that the numbers of patients had increased in winter. The studies conducted suggest that changes in atmospheric pressure and humidity rate are associated with exacerbated symptoms and frequency of episodes in Ménière's disease. In the study conducted by Gürkov et al. (23) with 126 patients with Ménière's disease, the authors found a significant relationship between atmospheric pressure increase and the probability of a Ménière's episode on the next day. In our study, even though no statistically significant differences were found in vertigo

patients, positive correlation was found between atmospheric pressure and humidity, and the number of patients.

Conclusion

Our study revealed that meteorological factors, unlike the lunar cycle, were associated with the frequency of the disease in the patients with vertigo. These findings greatly support the previous studies reported on this subject in the literature. However, prospective multi-center studies, including regions with different geographical and climatic characteristics, will more clearly reveal the relationship between otorhinolaryngological diseases and meteorological factors.

Ethics Committee Approval: This study was approved by the Adıyaman University Ethics Committee for Non-interventional Studies (decision date: 16.02.2022, decision no: 2022/2-14).

Informed Consent: The present study was a retrospective analysis study. Therefore, there was no need for any informed consent form.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: M.K., E.E.A., C.Y., Design: M.K., E.E.A., C.Y., M.Ka., Data Collection and/or Processing: M.K., C.Y., E.A., Analysis and/or Interpretation: M.K., M.Ka., Literature Search: M.K., E.A., M.Ka., Writing: M.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Main Points

- The lunar cycle is known to affect fluid balances, such as tides, on Earth. It is known that peripheral vertigo is associated with the fluid balance in the vestibular system. The lunar cycle can affect the vestibular system, as it does the tides.
- When vertigo was considered with respect to the seasons, it was seen that the number of patients increased significantly in winter months.
- It was observed that the lunar cycle did not have a significant effect on vertigo.

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Paramedian Forehead Flap in Large Nasal Skin Defects: Twenty-years' Experience

Original Investigation

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Abstract

Objective: Skin cancers occur most commonly in the head and neck region where the nose is the most commonly affected unit. The nose is the part of the face that is most exposed to trauma, sunlight, and other environmental factors. From the aesthetic and functional point of view, reconstruction of the defects occurring after skin cancer removal creates a great challenge for the surgeon. In this retrospective study, we present the success rates achieved in the past 20 years with paramedian forehead flaps used for repairing large defects of the nose.

Methods: The study included 62 patients who underwent paramedian forehead flap due to nasal skin tumor [basal cell carcinoma (BCC) and squamous cell carcinoma (SCC)] in Ege University Faculty of Medicine Otolaryngology Department between 2000 and 2020. Data on follow-up time, patients' age and gender, defect sizes, and tumor types were obtained retrospectively from patient files, histopathologic examination results and patient photographs. Additional diseases such as diabetes, hypertension, and coronary artery disease that could affect flap success, were noted.

Results: Out of 62 patients 29 (46.8%) were female and 33 (53.2%) were male. Their mean age was 61.4 (range: 46–88) years. Mean follow-up period was 125.6 (8–244) months. Of the 62 patients 33 (53.2%) were operated on for BCC and 29 (46.8%) for SCC. Four patients (6.5%) had recurrences during their follow-up. There was no loss of the paramedian forehead flap.

Conclusion: Paramedian forehead flap is a reliable option in the reconstruction of larger defects of the nose even in smokers and elderly patients who have comorbid diseases.

Keywords: Head and neck, basal cell carcinoma, skin cancer, squamous cell carcinoma, surgical excision, reconstructive surgical procedures, pedicled flap, facial plastic surgery

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Introduction

The nose is the part of the face that is most exposed to trauma, sunlight, and other environmental factors. Skin cancers, with increased incidence in the recent years, occur most commonly in the head and neck region, especially in the nasal skin (1, 2). Aesthetic and functional aspects increase the importance of reconstruction in this region after surgical removal of skin tumors, congenital defects, or defects due to trauma.

Although small nasal skin defects can be repaired by primary suturing, skin grafts, rotation or advancement flaps, these methods are not sufficient in larger defects. If the defect contains more than one cosmetic subunit or involves more than 50% of one of the cosmetic subunits, the remaining part of the subunit can be excised and repaired with a paramedian forehead flap (3). Further to its aesthetic importance, the functional significance of the nose also makes repair more difficult in cases of wide defects (full-thickness or cartilage defects). Paramedian forehead flap can be successfully used to repair large defects with the wide tissue support they provide.

The advantages of the forehead area are that the skin is free of terminal hair and quite thick, its color is suitable for the nasal skin, the flap has a strong and wide pedicle, there is strong vascular support, it allows for rotation, and provides wide tissue support. It is usually designed as a supratrochlear artery centered axial flap (4-6).

In this study, we retrospectively investigated the success of paramedian forehead flap in the repair of wide nasal defects and present our twenty-year results.

Methods

All procedures that we performed in the study adhered to the ethical standards of the institutional and/or national research committee and of the Declaration of Helsinki and its subsequent amendments or comparable ethical standards. The study was approved by the Ege University Research Ethical Committee (decision no: 21-8T/17, Aug 26, 2021).

Out of 69 patients who were operated on for nasal skin basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) and underwent paramedian forehead flap repair between 2000 and 2020, 62 whose follow-ups were done in our clinic were included in the study. Data on the follow-up periods, patients' age and gender, tumor types and diameters, and surgical procedures were obtained retrospectively from patient files and histopathologic examination results. Additional diseases such as diabetes, hypertension, and coronary artery disease that could affect the success of the flap were noted.

Most of the patients were treated in two sessions. The first session involved flap design and flap application, the second session involved repairing contour irregularities and cutting the pedicle. Patients with aggressive tumors and large defects were operated on in three stages. The first stage involved tumor excision and advancement flap, if necessary, the second stage involved flap design and flap application, and the third stage involved repairing contour irregularities and cutting the pedicle. All tumor excisions of all patients were done under general anesthesia, and the second and third stages were done under local anesthesia.

The paramedian forehead flap is a pedicled axial flap supplied primarily by the supratrochlear artery. The flap was designed by marking the midline of both eyebrow lines, the glabella, and then advancing 2 cm (1.7–2.2) laterally to mark the supratrochlear artery (Figures 1, 2). Then, depending on the shape of the defect, either a mold was created using a suture foil or the flap was shaped based on measurement (Figure 3). The incisions were made up to the periosteum and dissection was performed on the supraperiosteal plane. In patients with a full-thickness dorsal defect, auricular composite grafts, skin grafts or septal turn-in flaps were used for mucosal repair and conchal and septal cartilage or costa was used for cartilage repair (Figure 4). In addition, the repair was made with conchal cartilage in all patients with alar cartilage defects. In patients with large defects, a malar advancement was performed first, and the paramedian flap was turned six months later. In cases which tumor infiltration to the nasal bone was identified, the bone was thinned with a burr. The pedicle was cut after five weeks in all patients (Figure 5). Pedicle edges were formed and thinned according to the

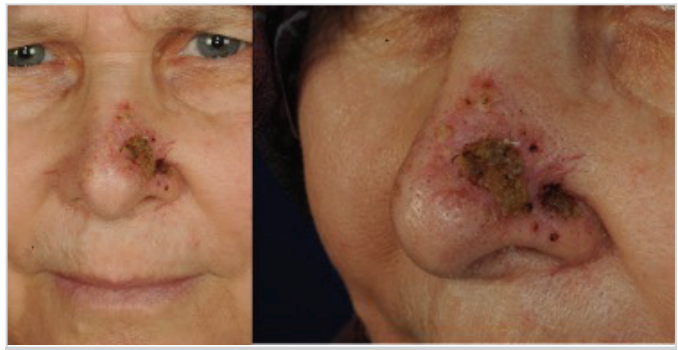

Figure 1. Infiltrative basal cell carcinoma in the supra-alar region of the nose. As seen, the lesion is widespread and crusted

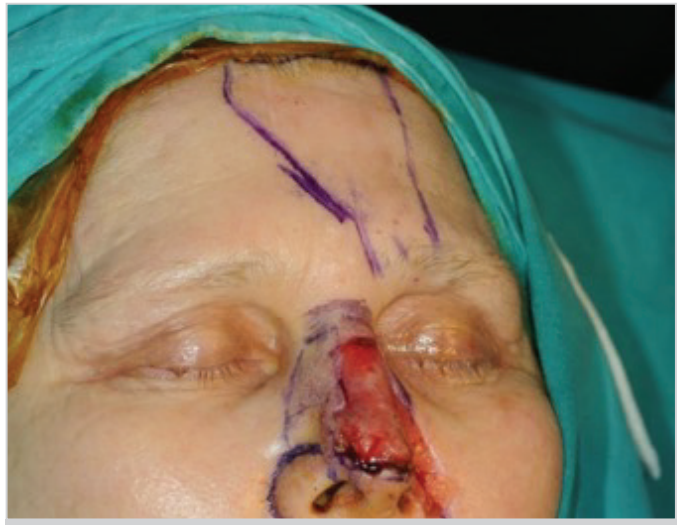

Figure 2. Preparing the flap: The midline of both eyebrows was marked and an approximately a 2-cm area was identified as the estimated pedicle region starting from 2 (1.7–2.2) cm laterally

recipient and the donor sites. The wound was sutured with 5/0 polypropylene sutures.

Defect areas were calculated from photographs with a ruler related to the defect shape. In rectangular shaped defects the area was calculated by computing the rectangular area and in circular shaped defects by computing the circle area.

Statistical Analysis

Statistical Analysis was performed using the IBM SPSS (IBM SPSS Statistics for Windows, version 25.0. Armonk, New York, USA). The Shapiro–Wilk test was used for determining the distribution pattern of the data. The distribution of the groups was parametric. Descriptive statistics was used for statistical analysis. Data were expressed as mean ± standard deviation.

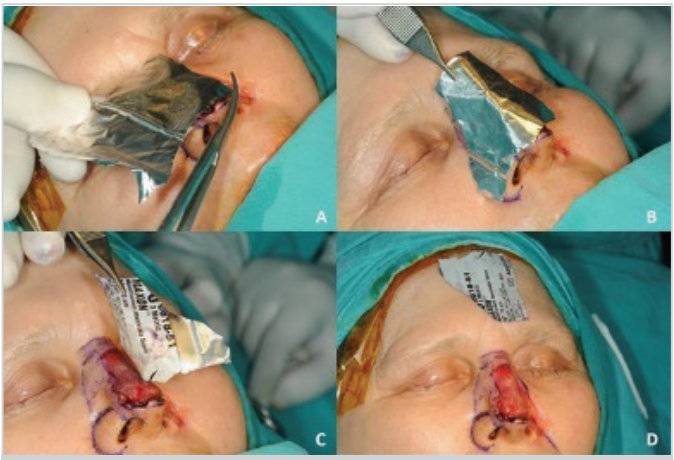

Figure 3. (a-b) Creating template from the intact side using suture foil, (c) modifying template according to the defect area, (d) using template for designing the flap

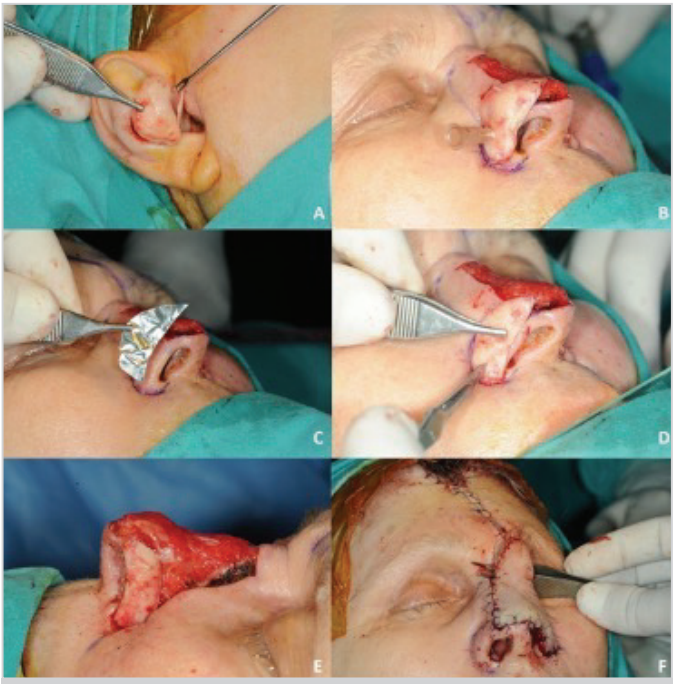

Figure 4. (a) Using the conchal cartilage to reconstruct the alar cartilage, (b-d) shaping the conchal cartilage as an alar cartilage (e) applying the shaped cartilage to the defect area, (f) final status of the flap

Results

Of the 62 patients, 29 (46.8%) were female and 33 (53.2%) were male. Their mean age was calculated as 61.4 (46–88) years. Mean follow-up period was 125.6 (8–244) months. It was shorter than 12 months in 2 patients, 12–60 months in seven patients, 60–120 months in 19 patients, and longer than 120 months in 34 patients. Out of 62 patients 33 (53.2%) were operated on for BCC and 29 (46.8%) for SCC. Among the BCC types, seven (21.2%) superficial, 14 (42.4%) infiltrative, nine (27.3%) nodular, three (9.1%) micronodular subtypes were identified. Four patients (6.4%) had recurrence in their follow-up periods. Of the patients with recurrence, two had BCC (one infiltrative, one micronodular) and two had SCC. One of the BCC recurrences was seen after 22 months, one after 32 months and one of the SCC recurred after 13 months, one after 16 months. Re-excision was performed on patients with recurrence.

When classified according to defect types, eight (12.9%) patients had only skin defects, 36 (58.1%) had skin and cartilage defects, 18 (29%) had full thickness defects. Of the 36 patients with skin + cartilage defect, 23 (63.9%) had both alar cartilage and vestibular skin defect, seven (19.4%) had upper lateral cartilage defect including the overlying skin, and six (11.1%) had both lateral and alar cartilage defect. In the full thickness group, five (8.1%) patients had septal defect, and four (6.5%) had nasal bone defect.

Inner lining was performed with skin grafts in three (4.8%) patients, with septal turn-in flaps in 13 (21%) patients and with composite grafts in two (3.2%) patients. The

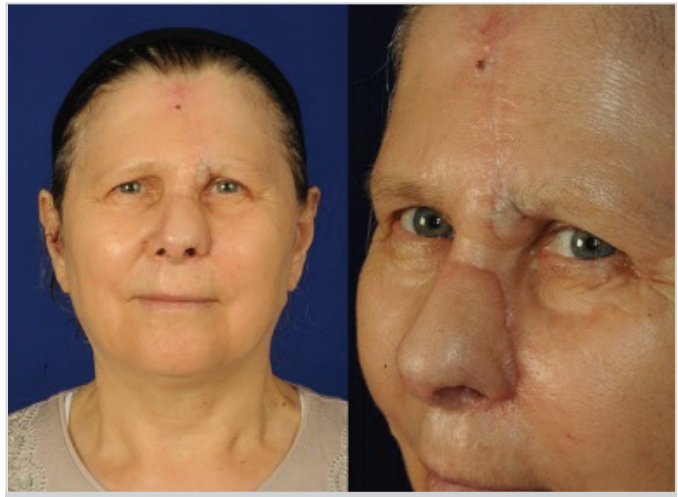

Figure 5. View of the patient eight weeks after pedicle cutting and 13 weeks after the first operation

cartilaginous framework reconstruction was performed with conchal cartilage in 34 (54.8%) patients, with septal cartilage in 13 (21%) patients, both septal + conchal cartilage in six (9.7%) patients and costal cartilage was used in one of these patients.

The operations were performed in two sessions in 50 (80.6%) patients and in three sessions in 12 (19.4%) patients. Because the defect was very wide in three (4.8%) patients, a malar advancement flap was used and waited for six months before the defect was repaired with a paramedian forehead flap.

Dehiscence was seen in three patients in the frontal donor site. All of these patients were smokers. All patients showed improvement in the recipient site without complications. No complications were seen in the cartilage donor ear in any of the patients from which conchal cartilage was taken. No flap necrosis was seen in any of our patients.

Thirty-four patients (54.8%) had hypertension, 17 patients (27.4%) had type 2 diabetes, and six patients (9.7%) had coronary artery disease. Forty-two patients (67.7%) had hypertension and diabetes comorbidity, and 45 patients (72.6%) had hypertension, diabetes, and coronary artery disease comorbidity. Twenty-four patients (38.7%) were smokers.

Discussion

The nose is an important aesthetic unit of the face, and its defects can lead to aesthetic and functional impairments. Nasal skin defects usually occur as a result of tumor surgeries. Secondary healing or primary suturing may be preferred for narrow nasal skin defects. However, there are basically two methods for repairing larger defects, namely, grafts or local flaps. Although both techniques have their own advantages in small defects, the paramedian forehead flap can be successfully applied on wide nasal defects. The success rates of other flaps remain lower than those of the paramedian forehead flap, especially in large defects (7). It is also more successful than other flaps in repairing full-thickness or containing more than one subunit nasal defects (8).

Paramedian forehead flaps can be performed in two or three stages according to the surgeon experience and patient's condition (9-10). In our study, the operations were done in two or three sessions. In patients who have aggressive tumors with large defects, a malar advancement can be performed and then paramedian forehead flap can be performed six months later. This method can provide two benefits. The first is that the defect area may become smaller as time passes, and the second is that it is easy to follow up for early recurrence of aggressive tumors. In our study we used this approach in three (4.8%) patients.

The risk of developing non-melanoma skin tumor recurrence after surgical treatment is less than 5% (11, 12). This rate may increase depending on the size, subtype, and depth of invasion of the tumor. In our study, which included large nasal skin defects and a heterogeneous patient group, recurrence was seen in a total of four patients (6.4%) and this rate were found similar to those reported in the literature.

In general, failure rates in interpolated flaps are reported as 1–6% (13, 14). The facts that the rate of accompanying diseases is high, the average age is high, but that despite this, none of our patients have had flap necrosis suggests that paramedian forehead flaps can be used very reliably in this age group. Still, although there are many studies on the repair of nasal defects, factors affecting flap success, causes of complications and flap success rates are not clear.

There is no clear consensus in the literature on the effect of comorbid diseases on flap success, especially of diabetes mellitus. Some studies found no statistically significant correlation between diabetes and flap success (13). There are studies proving that successful flap division could occur within 1–2 weeks despite any underlying comorbidities (15). In our study, the absence of flap necrosis in any of the patients indicates that with strong and sufficient vascular support, it can be successfully used even in full-thickness defects. The absence of flap necrosis even in patients with additional diseases such as hypertension and diabetes supports this.

Theoretically, the cartilage support applied under the flaps can disrupt flap neovascularization, which can affect flap success (14). The fact that the end borders of the flap especially need this neovascularization makes it even more important. Nutrition by neovascularization is not important until the pedicle is cut. However, in our study, the fact that no flap necrosis was observed in any patient before or after the pedicle was cut, even in patients with additional diseases, suggests that cartilage support can also be safely used with these flaps and that cartilage used for support does not impair flap nutrition. In addition, cartilage necrosis was not detected in patients in whom cartilage was used, as far as could be seen in the second and third sessions.

As the thickness and size of the defect increase, flap success rates can decrease (4). This is caused by insufficient vascular support, especially at the borders of the flap. Also, as flap thickness increases, nutrition by neovascularization may not be sufficient. However, in our study, the absence of necrosis and complications in flaps used in both full thickness and partial defects suggests that these flaps can be reliably used in both partial and full-thickness defects.

The most common complication and important condition affecting flap success is wound site infection (16). Flap necroses secondary to infection are frequently encountered. Particularly in full-thickness defects, the direct encounter of

the flap with the nasal cavity and nasal flora increases this possibility. However, the fact that no wound site infection or flap necrosis due to infection occurred in any of the patients in our study may be due to the strong vascular support of these flaps.

Smoking is another factor affecting flap success. Smoking has been shown to reduce flap success in previous studies (13, 17, 18). However, the complete flap success in smokers in our study may be due to the fact that the supratrochlear artery, which constitutes the main vascular support of these flaps, is strong and resistant to occlusion. But it is also clear that there is a need for studies with higher numbers of patients. Although smoking has not been shown to reduce flap success in our study, dehiscence was seen in the frontal donor site in three patients and all of these patients were smokers. Thereby we can say that smoking actually reduces overall success.

The first limitation of our study is its retrospective design. The second limitation is the lack of a scale indicating the quality-of-life index of the patients. Further studies are necessary to analyze the factors associated with possible complications, such as measures of the subjective evaluation by the patient and re-analysis of arguments with longer case series.

Conclusion

Because aesthetic and functional aspects of the nose increase the importance of defects in this region, appropriate reconstruction of the skin defects of the nose related to tumor surgery, congenital defects or trauma is essential. Paramedian forehead flap is a reliable option if defects contain more than one subunit and in full thickness defects even in smokers and elderly patients who have comorbid diseases.

Ethics Committee Approval: All procedures that we performed in the study adhered to the ethical standards of the institutional and/or national research committee and of the Declaration of Helsinki and its subsequent amendments or comparable ethical standards. The study was approved by the Ege University Research Ethical Committee (decision no: 21-8T/17, Aug 26, 2021).

Informed Consent: Informed consent was obtained from all individual participants included in the study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: F.A., İ.K., Concept: F.A., İ.K., Design: F.A., İ.K., Data Collection and/or Processing: İ.K., M.U., V.B., Analysis and/or Interpretation: M.U., V.B., Literature Search: V.B., Writing: M.U., V.B.

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Main Points

• The paramedian forehead flap is ideal reconstructive choice in many patients and can be safely and reliably performed even in smokers and elderly patients who have comorbid diseases.

• Because of low donor site morbidity and good tissue match outstanding functional and cosmetic results can be achieved.

• The flap can be completed in 2 or 3 stages, depending on the patient's defect, comorbidities, and patient expectations.

• Our forehead flap success and complications rates were found to be similar to the rates in the literature.

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Mucosal Melanoma In Situ of the Oral Cavity: A Case Report and Systematic Review of the Literature

Systematic Review

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Abstract

Objective: Malignant mucosal melanomas of the head and neck comprise a very small portion of all melanomas, particularly in the oral cavity. These lesions are associated with high rates of local recurrence, distant metastasis, and a very poor 5-year survival rate; however, the clinical outcomes of mucosal melanoma in situ of the oral cavity are unclear. Therefore, we present a case report of mucosal melanoma in situ and a systematic review of the literature to shed light on this rare but important disease.

Methods: PubMed, Scopus, and CINAHL were searched per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Studies were only considered for inclusion if they described oral cavity melanoma in situ and documented specific data pertaining to treatment including modality, lesion size, or outcomes.

Results: A total of 28 reported cases from the literature fulfilled the inclusion criteria, as well as one case from our own institution. Men comprised the majority (64.3%) of the cases, and the average age at presentation was 57.4 years. The hard palate was the most common location, and most cases were treated with surgical excision. Eight had no evidence of disease after a minimum of six months of follow-up, one reported spread to the cervical lymph nodes, and only one reported progression with distant metastasis.

Conclusion: Oral mucosal melanoma in situ is a rare entity and most commonly treated with surgical excision. High rates of recurrence necessitate long term follow-up. Further studies may be useful to determine whether adjuvant therapy may play a role in reducing recurrence.

Keywords: Mucosal melanoma in situ, oral cavity, hard palate, management, systematic review

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Introduction

Pigmented lesions of the upper aerodigestive tract often require tissue biopsy to determine if they represent the highly malignant mucosal melanoma. Malignant mucosal melanomas of the head and neck are rare and represent only 1%, of all melanomas; and among these, the most common locations include the

nasal cavity, the paranasal sinuses, and the oral cavity (1). The prognosis for mucosal melanoma of the head and neck is poor, with only a 5-year survival rate of 25–30%, and it is commonly associated with local recurrence as well as distant metastasis (2). A contributing factor to this poor prognosis is the concealed locations in which these tumors arise, which make them less likely to be discovered during routine screenings. Because of this characteristic, these lesions are usually not found until late in the disease course (3). Oral mucosal melanoma in situ (OMMIS) has rarely been reported, and its actual prevalence is therefore unknown.

Mucosal melanoma of the oral cavity has unique characteristics that differentiate it from cutaneous melanoma, but pigmented changes of the oral cavity mucosa is the usual presenting finding. While melanoma in situ is considered a precursor to cutaneous melanoma, mucosal melanomas are not proven to have precursor non-invasive lesions. Oral mucosal melanoma generally is diagnosed at a later age than cutaneous melanoma with most cases occurring between ages 50 and 80, with a median age of 70 years (4). Due to the lack of exposure of the oral cavity and other mucosal regions to light, it is unlikely that UV light plays a role in the development of these lesions. Additionally, these cancers show unique genetic profiles, with BRAF mutations occurring far less frequently in mucosal melanomas relative to cutaneous melanomas. Furthermore, mucosal melanomas show an increased incidence in KIT mutations, occurring in an estimated 39% of these cancers (4). A slightly increased risk in the Japanese population suggests a possible correlation with either hereditary or environmental factors. However, the etiology and pathogenesis of mucosal melanoma still remain largely unknown (4).

Oral mucosal melanomas arise from the malignant transformation of melanocytes. This can occur in the cells found either in the basal layer of the oral epithelium or less commonly in the lamina propria of the oral mucosa. Among mucosal melanomas of the oral cavity, an exceedingly small percentage are identified as mucosal melanoma in situ. These lesions are identified histologically by a radial proliferation of malignant melanocytes along the basal cell layer, which lack invasion through the basement membrane into the lamina propria (5).

Herein, we report a rare case of OMMIS that was evaluated and diagnosed by the patient's dentist and biopsied by her oral and maxillofacial surgeon. The pathology was reviewed and confirmed by an oral pathologist. Furthermore, we conducted a systematic literature review of the documented cases of oral melanoma in situ to further characterize this rare disease and compile diagnosis, treatment, and outcome details to aid in future early diagnosis and management of these lesions.

Case Report

A 45-year-old female was referred for evaluation of a pigmented lesion in the left floor of mouth and the lateral border of the tongue, which was discovered during a routine dental examination (Figure 1). The lesion appeared to grow quickly over the course of two months. The patient reported no history of smoking or other tobacco use and no prior cutaneous or other malignancies or premalignancies. She endorsed current alcohol use of two standard drinks per week. Past medical history and surgical history were noncontributory. Family history was significant for cutaneous melanoma in her maternal aunt. A computed tomography of the oral cavity, neck and chest was performed, showing no signs of other neoplastic signs or disease spread. The patient denied any noticeable symptoms, pain, bleeding, dysgeusia, dysarthria, dysphagia, or lymphadenopathy.

A biopsy was performed, showing an increased number of melanocytes irregularly distributed along the basal epithelial layer (Figure 2). These melanocytes exhibited a nested arrangement. Cells demonstrating nuclear atypia were also observed. Histopathologic examination determined to be consistent with mucosal melanoma in situ.

The patient was evaluated at the multidisciplinary head and neck clinic and the tumor board recommended surgical resection not only to remove the lesion but also to confirm that there were no evidence of invasive malignant melanoma that might require new staging. The initial plan was for complete resection, consisting of a 5-mm margin clearance of visible tumor and to delay reconstruction until definitive pathologic interpretation was completed. Further resection and/or reconstruction would be completed upon confirmation of final pathology clearance. Thus, left partial glossectomy, gingivectomy and floor or mouth resection was performed and the tumor oriented and mapped for the oral and head and neck pathology team. Upon resection, the lesion was found to involve the left floor of the mouth, the

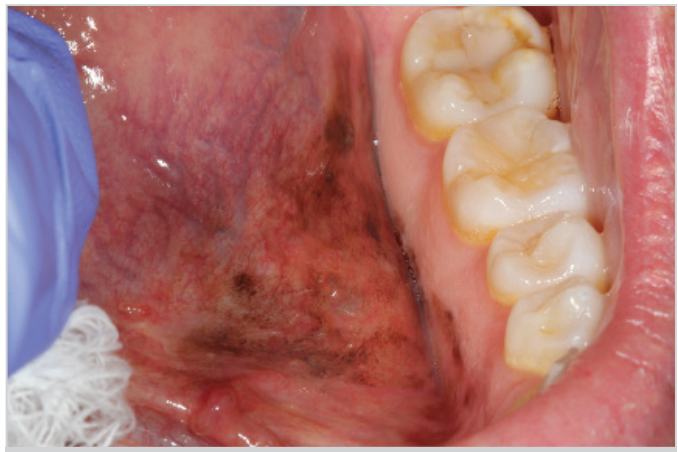

Figure 1. Clinical presentation of lesion on left side of the floor of the mouth prior to surgical resection

Wharton's duct, the ventrolateral tongue, and the lingual mandibular gingiva. A xeroform iodoform petrolatum gauze was placed as a temporary bolster to prevent scarring and tethering and to allow for orientation and reresection if any of the margins were close or involved. The final pathology returned as melanoma in situ measuring 2.2x2x1.4 cm with the closest margin near the gingival edge anteriorly and at the retromolar region.

Thus, reconstruction was planned with a reresection of the retromolar gingiva and the anterior gingival margin, which was determined to be free of pigmented lesion, followed by the reconstruction of the oral cavity, the floor of mouth, and the tongue with local mucosal advancement flaps, allograft, Wharton's duct sialodochoplasty, and bolster placement.

The patient is currently twelve months status post-resection, with no signs of disease (Figure 3). Speech, healing, and swallowing have returned to baseline and examination showed scarring but no return of pigmented lesions. The current plan is to continue follow-up with oral cancer examination and surveillance for five years to rule out signs of disease recurrence.

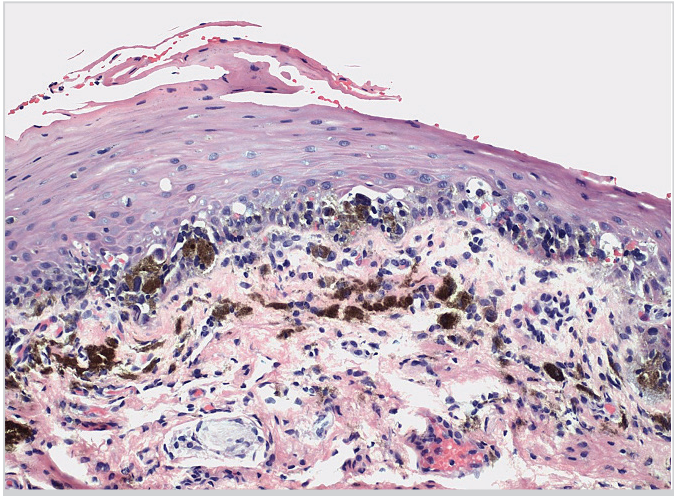

Figure 2. Medium-power photomicrograph showing an irregular proliferation of atypical pigmented melanocytes along the basilar layer of the mucosal epithelium (Note: The melanin observed in the superficial lamina propria represents pigment incontinence, not tumor invasion)

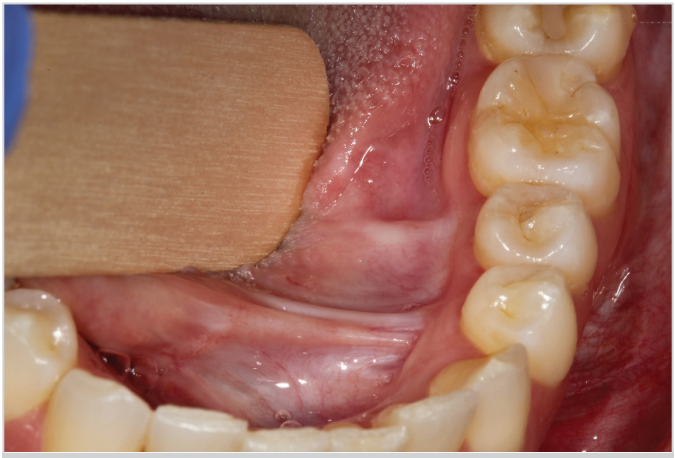

Figure 3. Surgical site 12 months status post resection showing no evidence of disease

Methods

Search Criteria

A systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (6). The following databases were searched: PubMed (National Library of Medicine, National Institutes of Health), Scopus (Elsevier), and CINAHL (EBSCOHost). These databases were searched from inception through January 26, 2022. Search terms were developed by two trained researchers (W.N.J. and N.S.P.) to include themes related to oral mucosal melanoma pertaining to the head and neck region. Furthermore, the databases were manually searched to include any manuscripts which were not captured by the initial search. Full strategy details are included in Appendix 1.

Selection Criteria

All report types were considered for inclusion. Studies were only included if 1) described oral cavity melanoma in situ, and 2) documented specific data pertaining to treatment modality, outcomes, lesion site, etc. Exclusion criteria were studies which did not stratify data on oral mucosal melanoma from other cancers, did not provide any follow-up or outcomes data, or studies reporting oral invasive melanoma with no reporting or cases of melanoma in situ. Exclusion criteria also included non-English studies and studies with no reported DOI.

Data Extraction

All reports from the initial search strategy were imported into the Covidence software (Veritas Health Innovation, Melbourne, Australia). Title and abstract screening and subsequent full text review was conducted independently by two of the authors (W.N.J. and N.S.P.). The data was then extracted and organized into a standardized Excel spreadsheet. Author, patient age and sex, lesion site and size, modality of treatment, and follow-up/outcomes were recorded as available.

Level of Evidence and Quality Assessment

The levels of evidence for the included reports were evaluated according to the Oxford Center for Evidence-Based Medicine (7). The Joanna Briggs Institute (JBI) critical appraisal checklist was used to assess the quality of Case Reports (8 questions) and Case Series (10 questions) (8). Two authors (W.N.J. and N.S.P) reviewed all included studies independently and rated each checklist item as "yes," "no,"

"unclear," or "not applicable." In case of any disagreements, a third reviewer assisted with the appraisal by discussion of the study quality to reach a consensus. The JBI scores assigned to each reviewed report ranged from 0, if none of the criteria were met, to 8 for Case Reports and 10 for Case Series, if all criteria were met. Then the sum of individual questions represented the overall quality of a study. The risk for bias was then assigned based on number of items scored "yes." Studies were then rated as low risk or of good quality when they scored 4 or above and were therefore included in the analysis (8).

Statistical Analysis

Summary statistics were calculated with frequency and percentage for categorical variable (gender) and mean for continuous variable (age).

Results

In total, 19 manuscripts met full inclusion criteria, presenting data on 28 patients diagnosed with melanoma in situ of the oral cavity. Figure 4 details the entire search process. The details, including patient information, description of the lesion, treatment, and outcome regarding these cases can be found in Table 1. These lesions were most common in males representing 18 (64.29%) of the cases. While the entire group age ranged from 16 to 78 years, the average age at presentation was found as 57.35 years. The majority of these cases presented as asymptomatic pigmented lesions, and many were discovered during routine dental examination. Per the Oxford Level of Evidence stratification, all studies were deemed to be Level 4. All 19 reports in Tables 2 and 3 were found to have a low risk of publication bias.

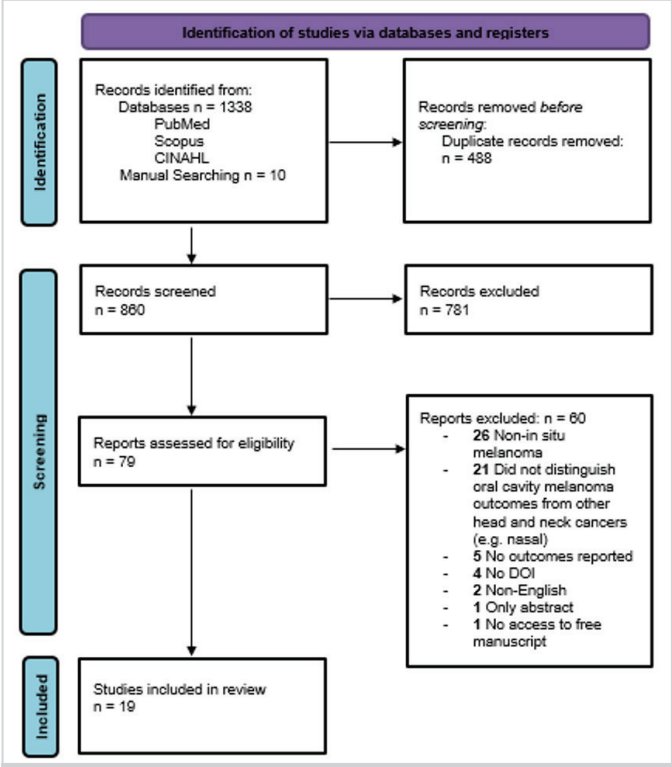

Figure 4. PRISMA diagram detailing database search procedure

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

The most common location for the lesions was the palate, which was found in 13 of the reported cases (46.42%). The gingiva was also found to be commonly affected, with involvement in five of the reported cases (17.86%). Our patient presented with a lesion centered in the floor of the mouth, a case which has not been reported to date. Of the cases reviewed, eight were found to have no evidence of disease after a minimum of six months of follow-up. However, local recurrence was found in eight cases in the series, with one of these reporting spread to the cervical lymph nodes and one reporting distant metastasis. The location of metastasis was not noted. In contrast to the poor prognosis of mucosal melanoma of the oral cavity overall, these data suggest a more promising prognosis for lesions discovered in situ but if the histopathologic examination was reported accurately in all of these cases, a low but important rate of metastasis is possible.

The majority of these lesions were treated with surgical excision, with only three of them receiving adjuvant therapy. Radiotherapy was used in one case for a 2x1.5 cm lesion that had recurred twice following surgical resection with 0.5 mm margins. Following this treatment, no further recurrence was noted after two years of surveillance. Chemotherapy was noted to have been used in two cases. The first case was administered cisplatin and thiosulfate prior to the original surgical resection, and interferon alpha 2b following surgery. The lesion recurred locally twice and following failure to achieve negative margins in the final resection, topical imiquimod was administered for six months and no further recurrence was noted. In the second case, a chemotherapy regimen of cisplatin, vinblastine, and dacarbazine was used following the discovery of spread to the cervical lymph nodes after the original surgical resection. Follow-up for this case was not reported. In the cases in which recurrence was found, the time between initial treatment and recurrence varied widely from 1 month to 84 months.

Discussion

Oral pigmented lesions that are unrelated to hereditary or amalgam related etiologies should undergo biopsy. A biopsy showing OMMIS should prompt a multidisciplinary evaluation and oral pathology review to confirm the absence of invasion. Surgical resection is indicated for treatment and to confirm adjacent sites are not invasive mucosal melanoma. Oral mucosal melanoma and OMMIS most

Table 1. Clinical features, patient characteristics, treatments, outcomes, and follow-up information for previously reported cases of oral mucosal melanoma in situ, as well as the presented case

Authors	OLE	Age, years	Sex	Site	Lesion size	Surgical treatment	Margins	Adjuvant therapy?	Outcome	Time to first recurrence, months	Follow-up, months
Becker et al. (15)	4	46	M	Hard palate	2 cm x 1.5 cm	Surgical excision (extraction of teeth 12, 11, 21)	0.5 mm	Radiotherapy (following 2nd recurrence)	Multiple recurrences	3	24
Breik et al. (16)	4	57	M	Right buccal mucosa	16 mm	Right BM-WLE, SND, and flap reconstruction	>10 mm		No evidence of disease		6
		70	M	Right side of hard palate	14 mm	Right subtotal maxillectomy, ITF clearance, right SND, ALT free flap reconstruction	>10 mm		No evidence of disease		12
Carbone et al. (17)	4	77	M	Gingiva	NA	Hemimaxillectomy	5 mm		No evidence of disease		71
Cardoso et al. (18)	4	67	M	Maxillary alveolar mucosa	3 cm x 1.5 cm	Partial maxillectomy	NA		No evidence of disease		10
Hajar-Serviansky et al. (19)	4	40	M	Lower right half of lip	1.5 cm x 4 cm	Surgical excision and reconstruction	NA		NA		NA
Horiuchi et al. (20)	4	66	F	Internal cheek, vermillion border, perioral skin	NA	NA	NA		NA		NA
Kemp et al. (21)	4	74	M	Maxillary ridge, palate, and buccal mucosa	NA	Surgical excision; recurrence treated w/ additional surgical excision	NA		Local recurrence	25	38
Kuk et al. (22) (6 cases)	4	<58 (4), >58 (2)	M (3), F (3)	Maxilla (5), Lip (1)	NA	Surgical excision	>5 mm (4), <5 mm (2)		NA		NA
Lourenço et al. (23)	4	75	M	Hard palate	NA	None	NA		NA		NA
Luna-Ortiz et al. (24)	4	47	F	Gingiva, palate	NA	Resection of the lesion; extraction from 11 to 16	2 mm		No evidence of disease		24
		58	M	Hard/ soft palate, gingiva	NA	Wide excision of the palate and gingival lesion	1.5 mm		No evidence of disease		8
Magliocca et al. (25)	4	48	M	Mid-anterior hard palate	3 cm x 2 cm	Wide local excision; additional surgery to pre-maxilla (extractions of teeth #6-13)	0.5 cm		No evidence of disease		42
Park et al. (14)	4	72	M	Upper lip, inner labial mucosa	5.3 cm x 4.7 cm	Surgical excision	5 mm	chemotherapy (cisplatin, vinblastine, dacarbazine) for recurrence	Recurrence; locoregional recurrence (cervical lymph nodes)	1	2
Prasad et al. (12)	4	NA	NA	NA	NA	Definitive surgery	NA		Recurrence; distant metastases		NA

Tremblay et al. (26)	4	16	M	Left posterolateral hard palate	4 mm	Full excisional biopsy	NA		NA		NA
Sedassari et al. (27)	4	51	F	Mandibular gingiva	NA	Surgical excision	NA		No evidence of disease		12
Shastri et al. (28)	4	49	M	Hard palate	3 cm x 2.5 cm	Local mucosal surgical excision; recurrences treated w/ additional 10 incision and excisional biopsies over following 10 years	NA		Multiple recurrences		48
		78	M	Hard palate	7 mm	Local mucosal surgical excision; recurrence treated w/ additional wide local excision down to the bone	NA		Local recurrence	1	54
		57	F	Hard palate	3 cm x 2 cm	Local mucosal surgical excision	NA		Local recurrence	84	288
Smith et al. (10)	4	32	F	Palate/ gingiva	NA	NA	NA		NA		NA
Spieth et al. (13)	4	67	M	Left side of hard palate	NA	Partial maxillectomy; two recurrences treated with second partial maxillectomy, multiple gingivectomies & mucosectomies	NA	chemotherapy (cisplatin, thiosulfate, interferon alpha 2b; recurrence treated w/ topical 5% imiquimod cream	Local recurrence post original surgery/ chemo; no evidence of disease post-surgery/ imiquimod	5	13
Wu et al. (29) (5 cases)	4	NA	NA	NA	NA	NA	NA		NA		60
Presented case		45	F	Left floor of mouth	2.2x2x1.4 cm	Partial glossectomy/FOM resection			No evidence of disease		12 (ongoing)
Total cases:		29									

OLE: Oxford Level of Evidence, cm: Centimeter/s, mm: Millimeter/s, F: Female, M: Male, NA: Not available

commonly presents asymptomatically as an irregularly shaped, pigmented, single or multifocal lesion (9). This lesion can appear plaque-like, nodular, or macular. Other possible symptoms include pain, bleeding, ulceration, and difficulty wearing dentures due to the tumor (9). Because early lesions are not normally noticed by patients, they tend to present later in the disease course. Because the appearance of mucosal melanoma can mimic that of benign pigmented or inflammatory lesions, as well as other malignant lesions, it is imperative that a biopsy be performed to rule out melanoma for any suspicious lesion of the oral cavity (10).

The Breslow criteria that are used to assess cutaneous melanoma are less useful in assessing mucosal melanoma due to the lack of a granular layer in many mucosal sites (9). Staging of primary mucosal melanomas of the head and neck primarily utilizes a simplified staging system for primary mucosal melanomas of the head and neck that was developed by Ballantyne in 1970. This system designates three stages: stage I for localized lesions, stage II for spread to regional lymph nodes, and stage III for distant metastasis (11). A more specific microstaging system is also available for further describing stage I disease, developed by Prasad et al. (12) in 2004. This system designates three levels: level I for noninvasive, in situ lesions, level II for superficially invasive disease, and level III for deep invasion into muscle, bone, or cartilage (12). The 7th edition of the American Joint Committee on Cancer Staging Manual included an additional chapter regarding the staging of mucosal melanomas, identifying all mucosal melanomas limited to the mucosa as T3 due to their aggressive nature but does not report on OMMIS. Advanced mucosal melanomas are identified as either T4a or T4b. However, due to the limited number of cases of mucosal melanoma in situ, staging of these lesions was not addressed (11).

In general, because of the potential for rapid progression of these lesions, mucosal melanoma in situ is treated similar to invasive melanoma, with surgical excision (9). For most of the reported cases, treatment consisted of surgical excision, which usually resulted in full remission with no recurrence. In one case, however, surgical excision was supplemented with chemotherapy including cisplatin, thiosulfate, and interferon alpha-2b, but a local gingival recurrence was identified five months post-surgery. Surgical excision was performed again, this time supplemented with topical imiquimod, and resulted in full remission with no recurrence (13). Similarly, in another case, after recurrence and cervical lymph node enlargement was noted, surgical excision was supplemented with a multi-chemotherapy agent, consisting of cisplatin, vinblastine, and dacarbazine, and, at 2-month follow-up, no signs of disease were noted (14). More data are needed to determine if adjuvant radiation therapy or chemotherapy offers any additional protection from recurrence. Finally, the emerging role of immunotherapy in many cancers and cutaneous melanoma may warrant evaluation in mucosal melanoma and melanoma in situ.

Table 2. JBI critical appraisal checklist for case reports

Study	1	2	3	4	5	6	7	8	Total scores
Becker et al. (15)	Y	Y	Y	Y	Y	Y	Y	Y	8
Breik et al. (16)	U	Y	N	Y	Y	Y	Y	Y	6
Carbone et al. (17)	Y	Y	Y	Y	Y	Y	U	Y	7
Cardoso et al. (18)	Y	Y	Y	Y	Y	Y	Y	Y	8
Hajar-Serviansky et al. (19)	Y	Y	Y	Y	Y	U	U	Y	6
Horiuchi et al. (20)	Y	Y	Y	Y	N	N	N	N	4
Kemp et al. (21)	Y	Y	Y	Y	Y	Y	Y	Y	8
Lourenco et al. (23)	Y	N	Y	Y	Y	N	N	N	4
Luna-Ortiz et al. (24)	Y	Y	Y	Y	Y	Y	Y	Y	8
Magliocca et al. (25)	Y	Y	Y	Y	Y	Y	Y	Y	8
Park et al. (14)	Y	Y	Y	Y	Y	Y	N	Y	7
Prasad et al. (12)	Y	Y	Y	Y	U	U	N	N	4
Tremblay et al. (26)	Y	Y	Y	Y	Y	N	N	Y	6
Sedassari et al. (27)	Y	Y	U	Y	Y	U	Y	Y	6
Shastri et al. (28)	Y	Y	Y	Y	Y	Y	Y	N	7
Smith et al. (10)	Y	Y	Y	Y	N	N	N	N	4
Spieth et al. (13)	Y	Y	Y	Y	Y	Y	Y	Y	8

Y: Yes, N: No, U: Unclear, JBI: Joanna Briggs Institute, 1. Were patient's demographic characteristics clearly described? 2. Was the patient's history clearly described and presented as a timeline? 3. Was the current clinical condition of the patient on presentation clearly described? 4. Were diagnostic tests or assessment methods and the results clearly described? 5. Was the intervention(s) or treatment procedure(s) clearly described? 6. Was the post-intervention clinical condition clearly described? 7. Were adverse events (harms) or unanticipated events identified and described? 8. Does the case report provide takeaway lessons?

Table 3. JBI critical appraisal checklist for case series

Study	1	2	3	4	5	6	7	8	9	10	Total scores
Kuk et al. (22)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Wu et al. (29)	Y	Y	Y	Y	Y	N	Y	Y	N	Y	8

Y: Yes, N: No, 1. Were there clear criteria for inclusion in the case series? 2. Was the condition measured in a standard, reliable way for all participants included in the case series? 3. Were valid methods used for identification of the condition for all participants included in the case series? 4. Did the case series have consecutive inclusion of participants? 5. Did the case series have complete inclusion of participants? 6. Was there clear reporting of demographics of the participants in the study? 7. Was there clear reporting of clinical information of the participants? 8. Were the outcomes or follow-up results of cases clearly reported? 9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information? 10. Was statistical analysis appropriate?

Limitations of this study included the retrospective nature of the analysis and lack of independent oral pathologic review to confirm the in situ nature of these pigmented diagnoses. Additionally, true surgical margin analysis and adjuvant decision making were not reported. For the presented case, surgical excision alone has been effective thus far, with no signs of recurrence at twelve months of follow-up. Given the high rate of recurrence for mucosal melanoma and limited data on OMMIS, long-term follow-up is important.

Conclusion

In this study, we reviewed 28 previously reported cases of OMMIS, as well as one case from our own institution which is the first known case of mucosal melanoma in situ of the floor of mouth. The majority of the reported malignancies were diagnosed during a routine dental visit based on visible pigmented changes and treated effectively with complete surgical resection alone. However, long term follow-up is essential given the potential risk of recurrence demonstrated in the cases presented in this review. The role of adjuvant therapy cannot be determined based on this limited data, but further studies may be useful to investigate the indications for and the role in lowering the risk of recurrence.

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Authorship Contributions

Surgical and Medical Practices: P.J., W.N.J., N.S.P., S.A.N., J.H., B.W.N., T.A.D., Concept: P.J., W.N.J., N.S.P., S.A.N., J.H., B.W.N., T.A.D., Design: P.J., W.N.J., N.S.P., S.A.N., T.A.D., Data Collection and/or Processing: P.J., W.N.J., N.S.P., Analysis and/or Interpretation: P.J., W.N.J., N.S.P., S.A.N., J.H., B.W.N., T.A.D., Literature Search: P.J., W.N.J., N.S.P., Writing: P.J., W.N.J., N.S.P., S.A.N., J.H., B.W.N., T.A.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Main Points

• Men comprised the majority (64.3%) of the cases, and the average age at presentation was 57.4 years.

• Hard palate was the most common location.

• Out of 28 cases reported in the literature, eight reported no evidence of disease after a minimum of six-month follow-up, one reported spread to the cervical lymph nodes, and only one reported progression with distant metastasis.

• The role of adjuvant therapy needs to be further researched to define its role in reducing recurrence.

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Appendix 1. Search Strategy

PUBMED: "Mucosal melanoma" AND ("in situ" OR Oral OR "Oral Cavity" OR "Tongue" OR "oropharynx" OR "pharynx" OR Tonsil OR Pillar OR "Buccal Mucosa" OR "Head and neck" OR "Head & neck")
Search date: 1.26.2022
Results: 551
SCOPUS: TITLE-ABS-KEY ("Mucosal melanoma" AND ("in situ" OR oral OR "Oral Cavity" OR "Tongue" OR "oropharynx" OR "pharynx" OR tonsil OR pillar OR "Buccal Mucosa" OR "Head and neck" OR "Head & neck")) AND (LIMIT-TO (LANGUAGE, "English")) AND (LIMIT-TO (SRCTYPE, "j"))
Search date: 1.26.2022
Results: 600
CINAHL: "Mucosal melanoma" AND ("in situ" OR Oral OR "Oral Cavity" OR "Tongue" OR "oropharynx" OR "pharynx" OR Tonsil OR Pillar OR "Buccal Mucosa" OR "Head and neck" OR "Head & neck")
Search date: 1.26.2022
Results: 106

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Surgical Implications of Superior Thyroid Cornu Agenesis in Laryngeal Malignancy

Case Report

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Abstract

The most commonly reported superior thyroid cornu (STC) anatomical variation is in STC syndrome, where the cornu is enlarged or medially displaced. STC agenesis is a rare laryngeal variation that can be unilateral or bilateral. Previous studies have reported STC agenesis in cadaveric or forensic studies in patients with an otherwise normal larynx. We report a case of unilateral STC agenesis in the context of a stage III glottic laryngeal squamous cell carcinoma. The variation was discovered intra-operatively during a total laryngectomy and was clinically unknown beforehand. There were no clinical or histological signs of bony erosion by the tumor. To our knowledge, this is the first report of unilateral STC agenesis in a patient with laryngeal malignancy. This article draws attention to a rare anatomical variant of the larynx and highlights the surgical implications including potential diagnostic challenges and operative considerations.

Keywords: Thyroid cartilage, anatomical variation, agenesis, larynx, laryngectomy, laryngeal malignancy

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Introduction

The larynx is an important structure in the neck that has functions in airway protection, swallowing and phonation. It is suspended from the hyoid bone and comprises an intricate relationship of various cartilages, ligaments, and membranes. The largest cartilage is the thyroid cartilage which is made up of two quadrilateral laminae of hyaline cartilage. Posteriorly, the thyroid laminae project superiorly and inferiorly to form the superior and inferior thyroid cornua, respectively. The superior thyroid cornu (STC) are joined to the hyoid via the lateral thyrohyoid ligament.

The most commonly reported STC anatomical variation is in STC syndrome, where the cornu is enlarged or medially displaced. This can be asymptomatic or present with dysphagia, odynophagia, and throat pain (1). Posterior deviation is less

commonly reported and has the potential to cause unilateral neck pain radiating to the ear, and even compression of the common carotid artery (2). Other reported variations include shortening, asymmetry, and agenesis (unilateral or bilateral) of the STC, although clinical implications of these in terms of patient symptoms are less well established (3, 4). We present a case and the discussion of superior cornu agenesis in the context of laryngeal malignancy.

Case Presentation

A 74-year-old independent and self-caring male had been known to the otolaryngology (ENT) department for dysphonia. This had previously been investigated and considered to be non-specific, but he remained under follow-up due to a strong smoking and alcohol history. His past medical history included T1bN0M0 squamous cell carcinoma (SCC) of the right lung, bladder carcinoma, type 2 diabetes mellitus, hypercholesterolaemia, ischemic heart disease, and transient ischemic attack. He had no history of neck or laryngeal trauma.

In December 2021, endoscopic examination of his larynx revealed a bulky glottic mass involving the anterior commissure. Magnetic resonance imaging of the neck with gadolinium enhancement and computed tomography of the neck and the thorax showed swollen vocal cords with no signs of lymphadenopathy. There were no signs of metastases. The vocal cord lesion was debulked and biopsied under general anesthesia. Histological analysis confirmed the diagnosis of moderately differentiated SCC. The tumor was staged as T3N0M0. The case was discussed at the head and neck multi-disciplinary team (MDT) meeting, and a decision was made to investigate further with a positron emission tomography (PET) scan given his previous lung carcinoma. PET imaging confirmed the absence of nodal involvement, metastases, or changes in the lungs.

He underwent a total laryngectomy en bloc with a right hemithyroidectomy (due to tumor extension to the subglottis with a subsequent high probability of micrometastases to the hemithyroid), and bilateral selective neck dissections (levels II-IV) in February 2022 as per MDT recommendations and discussion with the patient. The procedure was uncomplicated. Intra-operatively, the right STC was not palpable and appeared to be missing. Following completion of the total laryngectomy, the specimen was examined and demonstrated agenesis of the right STC (Figure 1). This was not identified by the reporting radiologists or at the MDT on any previous imaging. The imaging was re-reviewed following surgery and did show absence of the right STC (Figure 2). Intraoperatively, there was no evidence of tumor-related erosion of the cartilage adjacent to the absent STC, or structural variation of any other part of the laryngeal framework apart from the identified endolaryngeal tumor. Histology confirmed an exo-endophytic, transglottic, invasive, moderate/poorly differentiated SCC, fungating through the anterior half of the right vocal cord and into right vocalis musculature (pT3 pN0 pR0). Local excision was confirmed to be complete with clear margins. There was no histological evidence of tumor invasion to other areas of the laryngeal framework including the areas near the site of STC agenesis, or the contralateral STC. There were no immediate postoperative complications. A water-soluble fluoroscopic swallow assessment on the tenth postoperative day confirmed no leak. The patient had an unremarkable postoperative recovery and continued to have laryngectomy training until he was discharged from hospital three weeks later with no planned adjuvant therapy. He remained well at six months follow-up with no signs of recurrence.

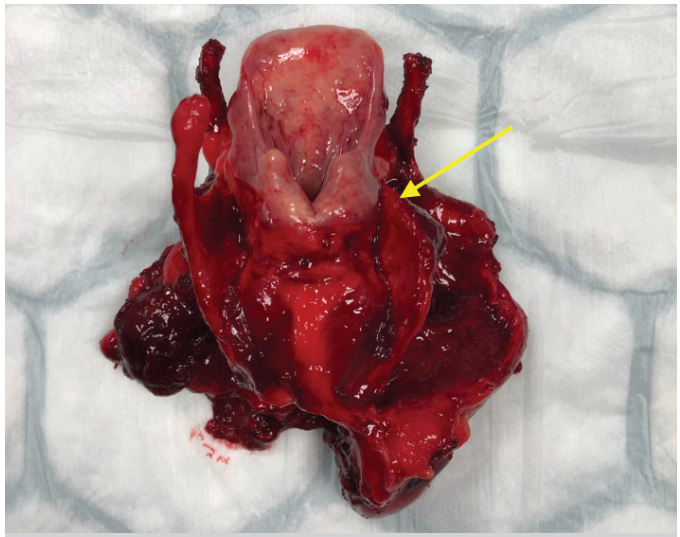

Figure 1. Post-laryngectomy specimen of the excised larynx showing an absent right superior thyroid cornu (yellow arrow)

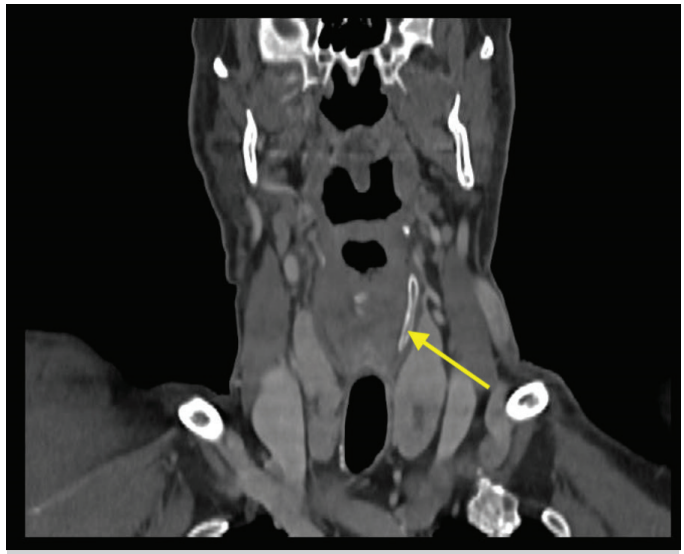

Figure 2. Computed tomography image in the coronal plane showing absence of the right superior thyroid cornu. The yellow arrow shows the left superior thyroid cornu for comparison

Discussion

STC agenesis is a rare laryngeal variation that can be unilateral or bilateral. In cases of unilateral agenesis, absence of the right STC has been reported to be rarer than of the left (3). To our knowledge, this is the first report of unilateral STC agenesis in a patient with laryngeal malignancy. Previous studies have reported STC agenesis in cadaveric or forensic studies in patients with an otherwise normal larynx, with most anatomical variations occurring in males as seen in our case (3, 4). It is unlikely that this varied anatomy causes any functional consequence of the larynx. There is otherwise usually no symptomatology that warrants further investigation in such findings. In addition, a morphometric study analyzing 49 larynxes found no structural imbalance or any difference in fracture risk between normal larynxes and those with STC unilateral agenesis (4). The relevance of abnormalities in the laryngeal framework or hyoid generally bodes significance in the forensic or medicolegal context of laryngeal trauma (accidents, violence, suicide, or iatrogenic). It is important for pathologists to be aware of STC agenesis so that it is not mistaken for laryngeal trauma during post-mortem.

In our case, there is clinical significance for several reasons. Firstly, the laterality of agenesis (right) was congruent with the tumor site. It is therefore possible that the staging of our tumor could have been falsely upgraded from T3 to T4 had this agenesis been noted on imaging prior to the laryngectomy, as it may have been interpreted that there was tumor invasion and erosion of the external surface of the thyroid cartilage. While it is unlikely that this could occur without radiological involvement of the thyroid cartilage and perichondrium, it is possible that such imaging may have caused confusion amongst MDT members in terms of imaging interpretation. This could have altered the patient's clinical course with potential adverse effects on patient care. There may also have been an increased psychological patient burden with a falsely high tumor stage. Therefore, awareness of such anatomical variance in the context of laryngeal malignancy is important for members of the head and neck MDT to recognize to help guide management options.

Secondly, variation in laryngeal anatomy is useful for surgeons to be aware of as this can alter the surgical process in already complex neck procedures such as laryngectomy, laryngopharyngectomy, and even neck explorations in trauma contexts. STC agenesis is particularly relevant to the pharyngeal reconstruction following laryngectomy. The altered anatomy of the laryngeal framework may have an impact on the amount of piriform fossae mucosa available for direct pharyngeal closure. Prior knowledge of this anatomical variant may therefore preempt the surgeon to consider and plan for a free flap reconstruction.

Conclusion

Knowledge of this case adds to the repertoire of data surrounding variable laryngeal anatomy which has its benefits in forensic and medicolegal contexts. The findings in this case may provide new insights into laryngeal anomalies in the context of surgical pathology. Our case expands on the preexisting literature on STC variations beyond the focus of trauma. Further research may be required in order to delve deeper into the potential patient impact of STC variations and agenesis.

Informed Consent: Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.K.G., Z.M., I.A., Concept: K.K.G., Z.M., I.A., Design: K.K.G., Analysis and/or Interpretation: K.K.G., Writing: K.K.G., Z.M., I.A.

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Main Points

- STC agenesis is a rare anatomical variant that usually has a focus in trauma, medicolegal and forensic cases.
- The findings in this case provide new insights into laryngeal variants in the context of surgical pathology.
- It is important to be aware of laryngeal variations in the context of malignancy to avoid falsely upgrading staging and for intra-operative considerations.
- Further research may be required in order to delve deeper into the potential patient impact of STC variations and agenesis.

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Multiple Dermoid Cysts in the Epiglottis Presenting with Dysphonia and Dysphagia: A Rare Case

Case Report

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Abstract

Dermoid cysts are developmental anomalies that occur during midline fusion in embryological life. It is known that they can also be acquired as a result of traumatic and iatrogenic implantation. Laryngeal involvement of dermoid cysts has been reported very rarely in the literature. This report presents a case with multiple dermoid cysts originating from the epiglottis. A 59-year-old male patient was admitted to our clinic with complaints of foreign body sensation in the throat and dysphagia. Multiple cystic lesions originating from the epiglottis were observed in the laryngeal examination of the patient. After radiological examinations, the cysts were completely excised by endolaryngeal surgery. After excision of the lesions, which were reported as dermoid cysts, all complaints of the patient regressed, and no recurrence was observed in the 6th month after the operation and his follow-up continued. Dermoid cysts originating from the epiglottis are very rare, but they should be kept in mind in the differential diagnosis of epiglottis lesions.

Keywords: Dermoid cyst, dysphagia, dysphonia, epiglottis, larengeal cyst

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Introduction

Dermoid cysts are developmental anomalies arising from epithelial cell remnants during midline fusion of the first and second branchial arches in embryological life (1). Although they can be seen at any age, they are more common in young adults (2). Dermoid cysts are painless and slow growing benign lesions. Associated symptoms can vary according to the location of the cyst, its size, and the age of the patient. Only 6.9% of all dermoid cysts are located in the head and neck region, and laryngeal involvement is extremely rare (3). The first dermoid cyst case arising from the epiglottis was reported by McKenzie (4) in 1930, and then few similar cases were presented in the literature (5-7). In all of these cases, single cystic lesions arising from the epiglottis were reported, but no cases with multiple dermoid cysts arising from the epiglottis have been reported in the literature so far.

In this report, we summarize the diagnosis, treatment, and follow-up of multiple

dermoid cysts originating from the epiglottis, which are rare cases.

Case Presentation

A 59-year-old male patient was admitted to our department with complaints of foreign body sensation in the throat and dysphagia that he had for a year. He had voice changes and difficulty in breathing for the last two months. There was no known history of trauma or infection. He had been smoking until two years ago. The consent form was obtained from the patient that his endoscopic laryngeal images and radiological images could be shared in the medical environment.

In the endoscopic laryngeal examination of the patient, two cream-colored, well-contoured masses were observed on the lingual surface of the epiglottis. In addition, there was mucosal thickening between the vallecula and the lingual surface of the epiglottis (Figure 1). The masses were pushing the epiglottis posteromedially. Other laryngeal structures were intact. In the evaluation with magnetic resonance imaging (MRI) and computerized tomography (CT), it was observed that the masses had peripheral contrast enhancement and cystic components (Figures 2a, b).

Complete excision of the laryngeal masses was planned. In the laryngeal suspension, smooth-surfaced, cream-colored cystic lesions were observed on the epiglottis in two different locations. The cysts were not related to each other. The larger of the cysts was approximately 25x20 mm in size and originated from the right lingual surface of the epiglottis, extended to the vallecula, the right pyriform sinus and the right aryepiglottic fold. The other cyst was approximately 15x10 mm in size and limited to the right upper part of the lingual surface of the epiglottis. The cystic lesions were excised completely using the cold dissection method. In addition, multiple cysts smaller than 1 cm and showing as mucosal thickening which were observed in the region during endoscopic examination were excised together with the excess mucosa.

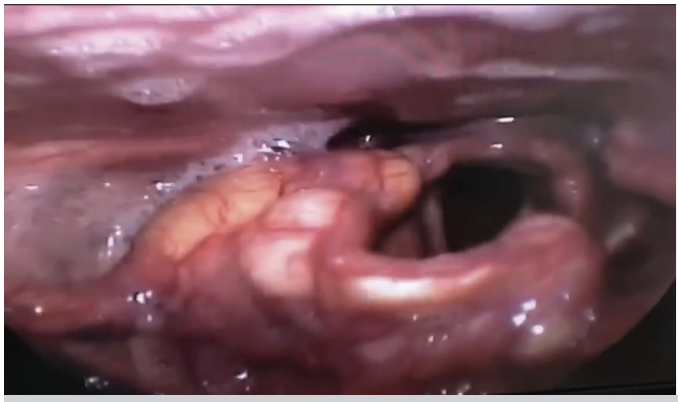

Figure 1. Preoperative imaging of multiple cysts originating from epiglottis

Complications such as bleeding and dyspnea were not observed in the patient after the operation. Histopathological examination findings were consistent with dermoid cyst (Figures 3a, b). All complaints of the patient regressed in the postoperative period. Granulation tissues were seen in the surgical site in the postoperative first week, and no recurrence was observed in the 6th month follow-up examination (Figures 4a, b).

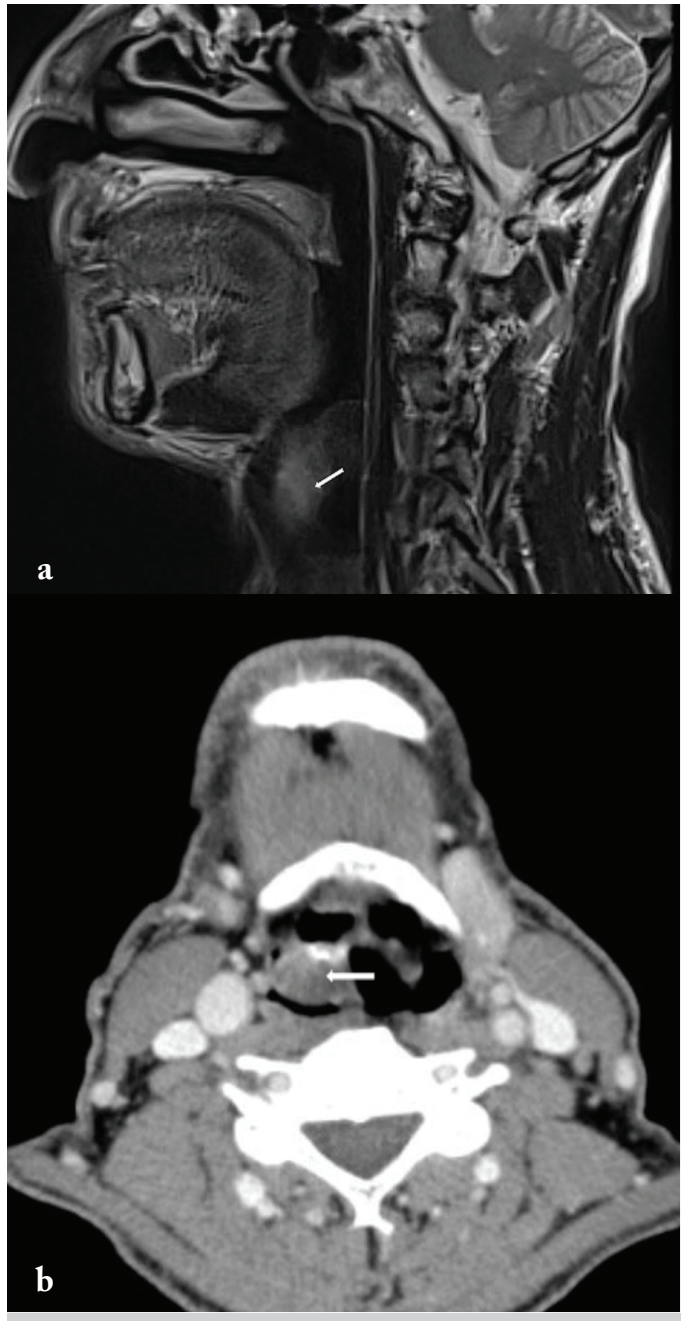

Figure 2. a) View of the cysts originating from the epiglottis in postcontrast sagittal T2-weighted MRI, b) View of the cysts originating from the epiglottis in axial section CT
CT: Computerized tomography, MRI: Magnetic resonance imaging

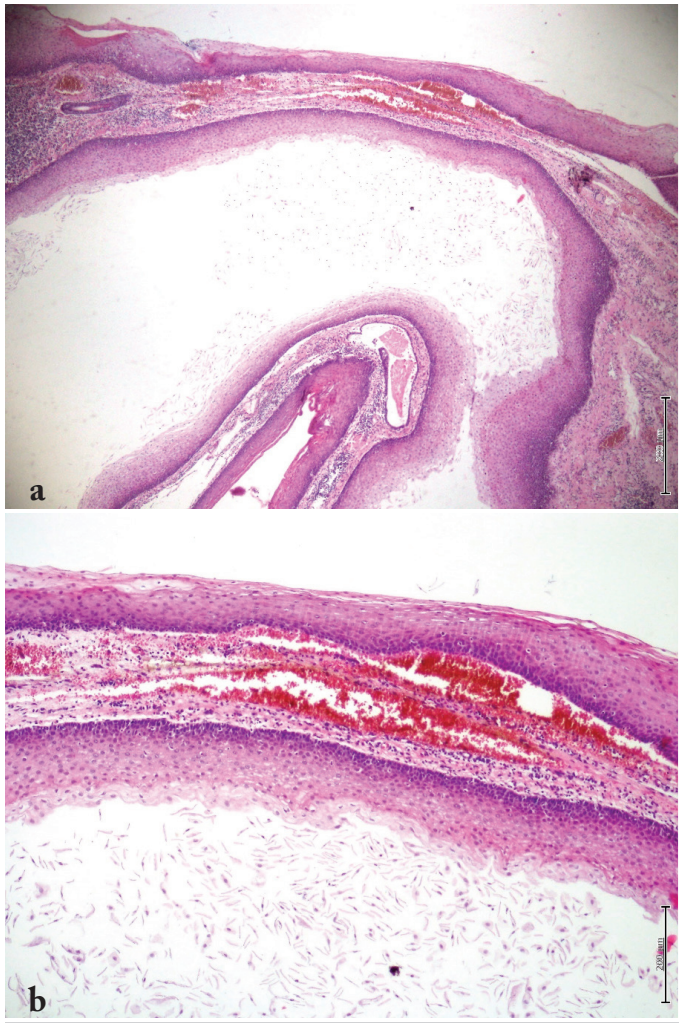

Figure 3. a) Histopathological imaging of the cystic structure in the subepithelial area (H&E, x40), b) Histopathological imaging of the cystic structure lined with stratified squamous epithelium similar to the glottis surface epithelium (H&E, x100)

Discussion

Dermoid cysts are benign lesions that occur during the midline fusion of the branchial arches in embryological life (1). It has also been reported in the literature that they can be acquired as a result of traumatic and iatrogenic implantation (2). Histopathologically, dermoid cysts are sub-grouped as real dermoid, epidermoid and teratoid (7).

Head and neck involvement of dermoid cysts are reported as 6.9% in the literature, and most commonly in the lateral eyebrows, oral cavity, the orbit, and the nasal cavity. Dermoid cysts originating from epiglottis are rarely observed (3).

Dermoid cysts are painless and slow growing benign lesions. Clinically, their symptoms are nonspecific and vary according to the location, the size of the cyst, and the age of the patient. While these cysts arising from the epiglottis may cause feeding and breathing difficulties in infants due to the small airway, they are generally asymptomatic in adults and most of them are diagnosed incidentally. The foreign body sensation in the throat, difficulty in swallowing, and changes in voice are the most commonly observed complaints related to the laryngeal involvement of dermoid cyst in symptomatic adults (8). Our case presented with all of the most common complaints.

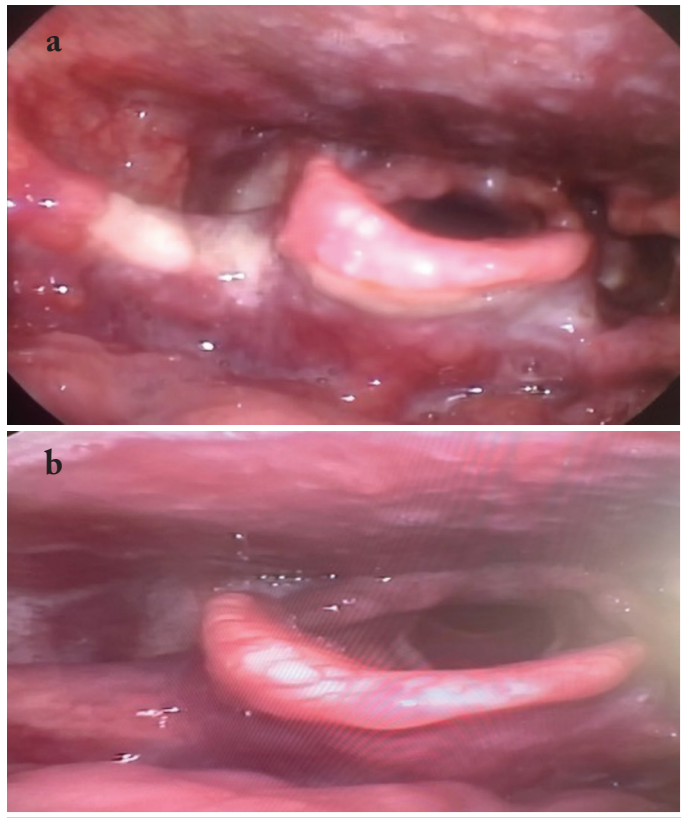

Figure 4. a) View of granulation tissues in the larynx in the 1st week after surgery, b) View of the larynx at 6-month follow-up after surgery

The differential diagnosis of dermoid cysts includes thyroglossal duct cysts, inclusion cysts, branchial cysts, submandibular and sublingual gland masses, lymphoepithelial cysts, lipomas, neurofibromas, hemangiomas and lymphangiomas (6, 7). CT and MRI have an important role in the diagnosis of dermoid cysts. After a detailed endoscopic laryngeal examination, the radiological methods that help the diagnosis provide information about the size and the extent of the cyst, and its relation to the surrounding tissues (9). A fine needle aspiration biopsy is often insufficient for diagnosis and gives non-diagnostic results (10). In our case, the lesions were evaluated using MRI and CT before the treatment was planned, and a biopsy was not performed due to the benign appearance of the lesions and the locations. In the histopathological evaluation performed after the excision of the lesions, a cystic structure lined with stratified keratinized epithelium was detected and the lesions were reported as dermoid cysts.

The only effective treatment for dermoid cysts is surgical excision (10). Although different methods such as conventional, laser or plasma blade are used depending on the location of the lesion and the available technical equipment, the aim is to completely remove the cyst, including the cyst walls (7). It is reported in the literature that the recurrence rates are very low in cases where the cyst is completely excised (9). In this case, complete removal of the cysts was performed with conventional methods and no recurrence was encountered in the follow-up period.

Conclusion

This is the first case in which multiple dermoid cysts arising from the epiglottis are reported in the literature. Although dermoid cysts originating from the epiglottis are very rare, they should be kept in mind in the differential diagnosis of epiglottis lesions. Surgery is the gold standard in treatment, and recurrences are prevented by complete surgical excision of the cysts.

Informed Consent: The consent form was obtained from the patient that his endoscopic laryngeal images and radiological images could be shared in the medical environment.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.S.A., O.Ç., S.C., Concept: E.S.A., O.Ç., S.C., Design: E.S.A., O.Ç., S.C., Data Collection and/or Processing: E.S.A., O.Ç., S.C., Analysis and/or Interpretation: E.S.A., O.Ç., S.C., Literature Search: E.S.A., O.Ç., S.C., Writing: E.S.A., O.Ç., S.C.

Conflict of Interest: There is no conflict of interest to disclose.

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Main Points

- Dermoid cysts are benign lesions that occur during the midline fusion of the branchial arches in embryological life.
- 6.9% of all dermoid cysts are seen in the head and neck region and laryngeal involvement is very rare.
- Computerized tomography and magnetic resonance imaging have an important role in diagnosis. They give information about the structure of the lesion, its relationship with the surrounding tissues and its extension.
- The only effective treatment is surgical excision. Recurrences can be prevented by removing the cyst completely.

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