

OFFICIAL PUBLICATION OF
THE MINISTRY OF HEALTH
AND
UNIVERSITI BRUNEI DARUSSALAM

Brunei International Medical Journal

Volume 19

7 November 2023 (23 Rabiulakhir 1445H)

ACTINOMYCES ODONTOLYTICUS: A RARE CAUSE OF PRIMARY CHRONIC LACRIMAL CANALICULITIS.

Rui Ping CHEW,^{1,2} Akmal Haliza ZAMLI,¹ Julieana MUHAMMAD,² Kamariah ABDUL JALIL.³

¹Department of Ophthalmology, Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia

²Department of Ophthalmology and Visual Science, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia

³Department of Pathology, Faculty of Medicine, Universiti Sultan Zainal Abidin (UniSZA), Jalan Sultan Mahmud, 20400 Kuala Terengganu, Terengganu, Malaysia.

ABSTRACT

Actinomyces odontolyticus is a predominant *Actinomyces* species in the oral cavity, pharynx, and distal esophagus. We report a rare case of primary chronic lacrimal canaliculitis caused by *A. odontolyticus*. A 63-year-old woman presented with left eye epiphora for three years associated with medial upper lid swelling, redness, and chronic yellowish discharge. After clinical examination and investigations, she was successfully treated with topical cefuroxime 5%, topical fluorometholone 0.1%, and intracanalicular syringing with cefuroxime 5%. Spontaneous extrusion of canaliculiths led to complete resolution.

Keywords: *Actinomyces*, *Actinomyces odontolyticus*, Chronic, Lacrimal, primary canaliculitis.

Brunei Int Med J. 2023;19:70-74

Brunei International Medical Journal (BIMJ)

Official Publication of The Ministry of Health and Universiti Brunei Darussalam

EDITORIAL BOARD

Editor-in-Chief	Ketan PANDE
Sub-Editors	Vui Heng CHONG William Chee Fui CHONG
Editorial Board Members	Muhd Syafiq ABDULLAH Alice Moi Ling YONG Ahmad Yazid ABDUL WAHAB Jackson Chee Seng TAN Pemasiri Upali TELISINGHE Pengiran Khairol Asmee PENGIRAN SABTU Dayangku Siti Nur Ashikin PENGIRAN TENGAH

INTERNATIONAL EDITORIAL BOARD MEMBERS

Lawrence HO Khek Yu (Singapore)	Chuen Neng LEE (Singapore)
Wilfred PEH (Singapore)	Emily Felicia Jan Ee SHEN (Singapore)
Surinderpal S BIRRING (United Kingdom)	Leslie GOH (United Kingdom)
John YAP (United Kingdom)	Ian BICKLE (United Kingdom)
Nazar LUQMAN (Australia)	Christopher HAYWARD (Australia)
Jose F LAPENA (Philippines)	

Advisor

Wilfred PEH (Singapore)

Past Editors-in-Chief

Nagamuttu RAVINDRANATHAN
Kenneth Yuh Yen KOK
Chong Vui Heng
William Chong Chee Fui

Proof reader

John WOLSTENHOLME (CfBT Brunei Darussalam)

Aim and Scope of Brunei International Medical Journal

The Brunei International Medical Journal (BIMJ) is a six-monthly peer-reviewed official publication of the Ministry of Health under the auspices of the Clinical Research Unit, Ministry of Health, Brunei Darussalam.

The BIMJ publishes articles ranging from original research papers, review articles, medical practice papers, special reports, audits, case reports, images of interest, education and technical/innovation papers, editorials, commentaries, and letters to the Editor. Topics of interest include all subjects that relate to clinical practice and research in all branches of medicine, basic and clinical including topics related to allied health care fields. The BIMJ welcomes manuscripts from contributors but usually solicits review articles and special reports. Proposals for review papers can be sent to the Managing Editor directly. Please refer to the contact information of the Editorial Office.

INSTRUCTION TO AUTHORS

Manuscript submissions

All manuscripts should be sent to the Managing Editor, BIMJ, Ministry of Health, Brunei Darussalam; e-mail: bimjonline@gmail.com. Subsequent correspondence between the BIMJ and authors will, as far as possible be conducted via email quoting the reference number.

Conditions

Submission of an article for consideration for publication implies the transfer of the copyright from the authors to the BIMJ upon acceptance. The final decision of acceptance rests with the Editor-in-Chief. All accepted papers become the permanent property of the BIMJ and may not be published elsewhere without written permission from the BIMJ.

Ethics

Ethical considerations will be taken into account in the assessment of papers that have experimental investigations of human or animal subjects. Authors should state clearly in the Materials and Methods section of the manuscript that the institutional review board has approved the project. Those investigators without such review boards should ensure that the principles outlined in the Declaration of Helsinki have been followed.

MANUSCRIPT CATEGORIES

Original articles

These include controlled trials, interventional studies, studies of screening and diagnostic tests, outcome studies, cost-effectiveness analyses, and large-scale epidemiological studies. The manuscript should include the following; introduction, materials

and methods, results, and conclusion. The objective should be stated clearly in the introduction. The text should not exceed 2500 words and references not more than 30.

Review articles

These are, in general, invited papers, but unsolicited reviews, if of good quality, may be considered. Reviews are systematic critical assessments of literature and data sources on clinical topics, emphasising factors such as cause, diagnosis, prognosis,

therapy, or prevention. Reviews should be made relevant to our local setting and preferably supported by local data. The text should not exceed 3000 words and references not more than 40.

Special Reports

This section usually consists of invited reports that have a significant impact on healthcare practice and usually cover disease outbreaks, management guidelines, or policy statement papers.

Audits

Audits of relevant topics generally follow the same format as the original article and the text should not exceed 1,500 words and references not more than 20.

Case reports

Case reports should highlight interesting rare cases or provide good learning points. The text should not exceed 1000 words; the number of tables, figures, or both should not be more than two, and references should not be more than 15.

Education section

This section includes papers (i.e. how to interpret ECG or chest radiography) with the particular aim of broadening knowledge or serving as revision materials. Papers will usually be invited but well-written papers on relevant topics may be accepted. The text should not exceed 1500 words and should include not more than 15 figures illustrations and references should not be more than 15.

Images of interest

These are papers presenting unique clinical encounters that are illustrated by photographs, radiographs, or other figures. The image of interest should include a brief description of the case and a discussion of educational aspects. Alternatively, a mini quiz can be presented and answers will be posted in a different section of the publication. A maximum of three relevant references should be included. Only images of high quality (at least 300 dpi) will be acceptable.

Technical innovations

This section includes papers looking at novel or new techniques that have been developed or introduced to the local setting. The text should not exceed 1000 words and should include not more than 10 figures illustrations and references should not be more than 10.

Letters to the Editor

Letters discussing a recent article published in the BIMJ are welcome and should be sent to the Editorial Office by e-mail. The text should not exceed 250 words; have no more than one figure or table, and five references.

Criteria for manuscripts

Manuscripts submitted to the BIMJ should meet the following criteria: the content is original; the writing is clear; the study methods are appropriate; the data are valid; the conclusions are reasonable and supported by the data; the information is important; and the topic has a general medical interest. Manuscripts will be accepted only if both their contents and style meet the standards required by the BIMJ.

Authorship information

Designate one corresponding author and provide a complete address, telephone and fax numbers, and e-mail address. The number of authors of each paper should not be more than twelve; a greater number requires justification. Authors may add a publishable footnote explaining the order of authorship.

Group authorship

If authorship is attributed to a group (either solely or in addition to one or more individual authors), all members of the group must meet the full criteria and requirements for authorship described in the following paragraphs. One or more authors may take responsibility 'for' a group, in which case the other group members are not authors, but may be listed in an acknowledgment.

Authorship requirement

When the BIMJ accepts a paper for publication, authors will be asked to sign statements on (1) financial disclosure, (2) conflict of interest, and (3) copyright transfer. The correspondence author may sign on behalf of co-authors.

Authorship criteria and responsibility

All authors must meet the following criteria: to have participated sufficiently in the work to take public responsibility for the content; to have made substantial contributions to the conception and de-

sign, and the analysis and interpretation of the data (where applicable); to have made substantial contributions to the writing or revision of the manuscript; and to have reviewed the final version of the submitted manuscript and approved it for publication. Authors will be asked to certify that their contribution represents valid work and that neither the manuscript nor one with substantially similar content under their authorship has been published or is being considered for publication elsewhere, except as described in an attachment. If requested, authors shall provide the data on which the manuscript is based for examination by the editors or their assignees.

Financial disclosure or conflict of interest

Any affiliation with or involvement in any organisation or entity with a direct financial interest in the subject matter or materials discussed in the manuscript should be disclosed in an attachment. Any financial or material support should be identified in the manuscript.

Copyright transfer

In consideration of the action of the BIMJ in reviewing and editing a submission, the author/s will transfer, assign, or otherwise convey all copyright ownership to the Clinical Research Unit, RIPAS Hospital, Ministry of Health if such work is published by the BIMJ.

Acknowledgments

Only persons who have made substantial contributions but who do not fulfill the authorship criteria should be acknowledged.

Accepted manuscripts

Authors will be informed of acceptances and accepted manuscripts will be sent for copyediting. During copyediting, there may be some changes made to accommodate the style of the journal format. Attempts will be made to ensure that the overall meaning of the texts is not altered. Authors will be informed by email of the estimated time of publication. Authors may be requested to provide raw data, especially those presented in graphs such as bar charts or figures so that presentations can be constructed following the format and style of the journal. Proofs will be sent to authors to check for any mistakes made during copyediting. Authors are usually given 72 hours to return the proof. No response will be taken as no further corrections are required. Corrections should be kept to a minimum. Otherwise, it may cause a delay in publication.

Offprint

Contributors will not be given any offprint of their published articles. Contributors can obtain an electronic reprint from the journal website.

DISCLAIMER

All articles published, including editorials and letters, represent the opinion of the contributors and do not reflect the official view or policy of the Clinical Research Unit, the Ministry of Health, or the institutions with which the contributors are affiliated to unless this is clearly stated. The appearance of the advertisement does not necessarily constitute an endorsement by the Clinical Research Unit or the Ministry of Health, Brunei Darussalam. Furthermore, the publisher cannot accept responsibility for the correctness or accuracy of the advertisers' text and/or claim or any opinion expressed.

ACTINOMYCES ODONTOLYTICUS: A RARE CAUSE OF PRIMARY CHRONIC LACRIMAL CANALICULITIS.

Rui Ping CHEW,^{1,2} Akmal Haliza ZAMLI,¹ Julieana MUHAMMAD,² Kamariah ABDUL JALIL.³

¹Department of Ophthalmology, Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia

²Department of Ophthalmology and Visual Science, School of Ophthalmology, Kelantan, Malaysia

³Department of Pathology, Faculty of Medicine, Universiti Sultan Zainal Abidin (UniSZA), Jalan Sultan Mahmud, 20400 Kuala Terengganu, Terengganu

ABSTRACT

Actinomyces odontolyticus is a predominant *Actinomyces* species in the oral cavity, pharynx, and distal esophagus. We report a rare case of primary chronic lacrimal canaliculitis caused by *A. odontolyticus*. A 63-year-old woman presented with left eye epiphora for three years associated with medial upper lid swelling, redness, and chronic yellowish discharge. After clinical examination and investigations, she was successfully treated with topical cefuroxime 5%, topical fluorometholone 0.1%, and intracanalicular syringing with cefuroxime 5%. Spontaneous extrusion of canaliculiths led to complete resolution.

Keywords: *Actinomyces*, *Actinomyces odontolyticus*, Chronic, Lacrimal, primary canaliculitis.

INTRODUCTION

Ocular infections caused by *Actinomyces* species is uncommon and associated with blinding condition.¹ It is a gram-positive bacteria that is primarily commensal in normal oral cavities and resides in tonsillar crypts, dental plaques, and carious teeth.² The name is mistakenly interpreted as fungi because of its striking features of filamentous branching and mycelia-like colonies.³

Actinomyces species have been identified in various ocular conditions, including

conjunctivitis, blepharitis, carunculitis, dacryocystitis, lacrimal gland ductulitis, crystalline keratopathy, and endophthalmitis.³ However, *A. odontolyticus*, the causative agent of chronic primary canaliculitis, is relatively rare. While two reported cases of canaliculitis caused by *A. odontolyticus* exhibited different ocular manifestations and were not associated with canaliculith formation,^{4,5} it's important to consider the possibility of this organism's infection in patients with a prolonged history of epiphora and swelling of the medial upper lid.

Corresponding author: Dr Julieana Muhammed, Department of Ophthalmology and Visual Science, School of Medical Sciences, Universiti Sains Malaysia, 6150 Kubang Kerian, Kelantan, Malaysia
Tel: +609 7676372/6362, Fax: +609 7653370
Email: drjulieana@usm.my

CASE REPORT

A 63-year-old woman with underlying hypertension, presented with three years of left eye

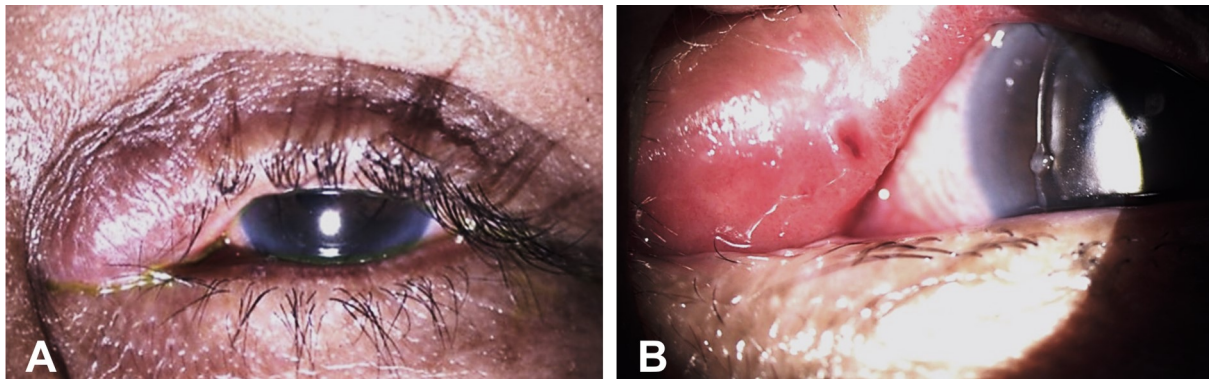


Figure 1: (A) Ill-defined swollen and inflamed mass at the medial end of upper eyelid with pouting and (B) dilated upper punctum of left upper lid (B).

epiphora associated with medial upper lid swelling and redness. She also reported yellowish eye discharge for four months. There was no eye pain or blurring of vision. She denied any prior history of trauma. She had been treated by a private practitioner and was prescribed with combination of topical antibiotics and steroids. However, she had recurrent symptoms.

The ocular examination of the patient showed best corrected visual acuity (BCVA) of 20/20 in the affected eye. There was an ill-defined swollen and inflamed mass at the medial end of the left upper eyelid (Figure 1A) with pouting of the left upper punctum (Figure 1B). There was a presence of yellowish discharge excreted out of the left upper punctum upon pressing on the swelling area. The lid margin was also thickened with medial palpebral conjunctival papillary reaction.

Slit-lamp biomicroscopy examination of the left eye showed that the conjunctiva was diffusely injected. The cornea was clear and absence of anterior chamber activity. The intraocular pressure was normal. Posterior segment examination was unremarkable. Syringing test of both upper and lower puncta showed a hard stop with saline felt in the throat and no regurgitation.

Specimen from left upper punctum discharge and conjunctiva were taken for mi-

crobiological examination. Gram staining showed gram-positive rods, a typical feature of *Actinomyces* species (Figure 2). Further detection was done by Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) and *A. odontolyticus* was isolated.

The patient was initially started on topical ceftazidime 5% every 4 hours and was treated as an outpatient. Upon review at 2 weeks, she claimed the yellowish discharge was reducing, but the swelling and redness persisted. At this stage, a new therapeutic strategy was adopted; topical ceftazidime 5% was changed to topical cefuroxime 5%, instilled 4-hourly. The left upper canaliculi was

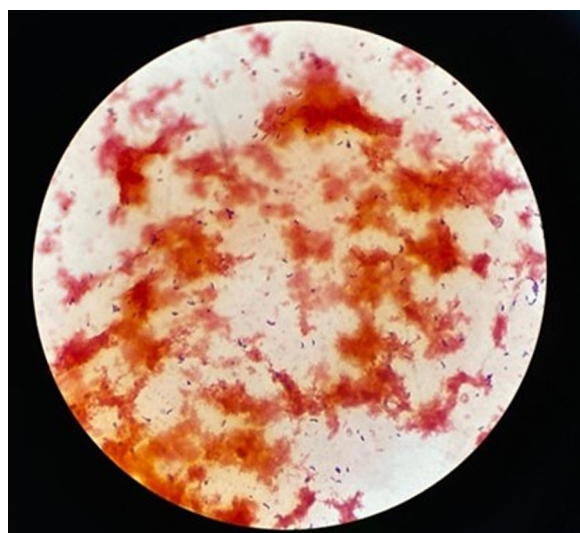


Figure 2: Gram staining of discharge specimen from canaliculi showed positive bacilli of *A. odontolyticus*, viewed under oil-immersion using objective lens of 100X magnification. (Click to enlarge)

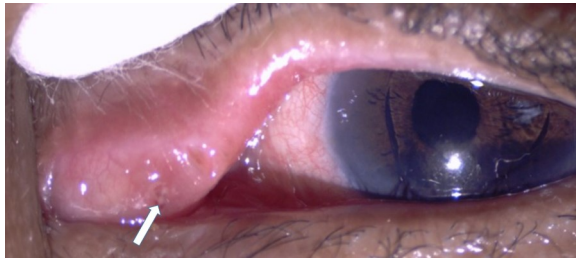


Figure 3: Pericanalicular swelling with canaliculiths seen (white arrow). (Click to enlarge)

also irrigated by syringing twice with a similar topical agent (cefuroxime 5%). Due to the inefficacy of the initial treatment, swabs from the left upper punctum were performed again and yielded negative results. At subsequent follow-up, she had spontaneous extrusion of multiple canaliculiths from the left pericanalicular area (Figure 3). Post extrusion of canaliculiths, she was continued with topical cefuroxime 5%. Topical fluorometholone 0.1% was added to the regime. At 6 weeks of follow-up, the medial upper lid swelling and redness were completely resolved (Figure 4A). The pericanalicular area post spontaneous canaliculith extrusion was well healed with no sinus formation (Figure 4B). The conjunctiva was no longer injected and the patient was symptom-free.

DISCUSSION

The genus *Actinomyces* is a gram-positive non-spore-forming and nonmotile rod naturally resides in the mucous membranes of humans. *A. odontolyticus* was first described

in 1958 as a causative agent in human actinomycosis.³ It is the most prominent species recovered in the oral cavity of children primarily from the plaque on primary teeth, besides the pharynx and distal oesophagus.^{2,6,7} In addition to the mouth, *Actinomyces* organisms are common inhabitants of the gut, genitourinary tract, and skin.²

Previously, *A. odontolyticus* was detected in small numbers from eye secretions/tear fluid.³ It was isolated from conjunctivitis cases and secondary canaliculitis, although, other *Actinomyces* species were identified in patients with post-operative and endogenous endophthalmitis, keratitis, and primary canaliculitis.^{3,4} We described this unusual case of *A. odontolyticus* causing primary chronic canaliculitis that may add to the currently sparse knowledge of rarely described species, its presentation, and management.

Canaliculitis due to *Actinomyces* species exhibit indolent and chronic infection, most commonly associated with yellowish concretions.⁸ *A. israelii* is the commonest gram-positive identified causative organism.^{8,9} *Staphylococcus aureus* and *Streptococcus sp.* are the other gram-positive bacteria identified and cultured in patients with canaliculitis.¹⁰ Other organisms that have been implicated in canaliculitis infections although infrequent are *Haemophilus influenza*, *Corynebacterium sp.*, *Propionibacterium sp.*,

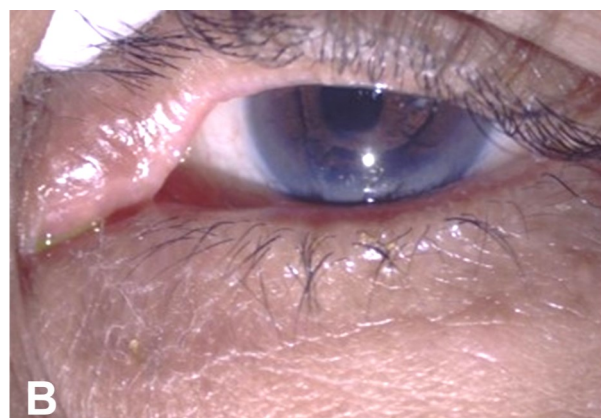
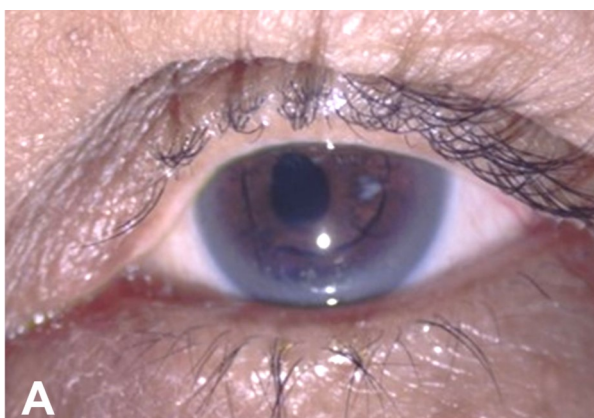


Figure 4: (A) Resolution of medial upper lid swelling and; (B) well healed pericanalicular area post spontaneous canaliculiths extrusion.

and *Moraxella*.¹⁰ It is often misdiagnosed as recurrent infective conjunctivitis, dacryocystitis, or chalazion for its common sign of punctual swelling.¹⁰ Clinically, *A. odontolyticus* exhibits a triad of canaliculitis symptoms and signs similar to other microorganisms causing canaliculitis; (1) pouting punctum, (2) concretions or canaliculith formation, and (3) yellowish discharge. The typical site of involvement is variable. The lower eyelid is more commonly involved in most published data. However, single upper punctum involvement was reported in a case series of canaliculitis due to *Actinomyces* and *Staphylococcus* species.¹⁰

Isolating *A. odontolyticus* presents a challenge due to its anaerobic nature and slow growth on routine culture. Identification of this organism typically relies on histopathology and biopsy material. Recent discoveries have unveiled new *Actinomyces* species that can cause severe infections in isolated cases.¹¹ *A. odontolyticus* has been associated with serious eye conditions such as endophthalmitis and keratitis, leading to the emergence of matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS) as a rapid and reliable method for differentiating *Actinomyces* species.¹² A definitive diagnosis of actinomycotic infections, especially rare ocular infections, holds significant clinical value. In our case, *A. odontolyticus* appeared as gram-positive bacilli on a gram stain slide with a branching pattern, a classical characteristic of *Actinomyces* species. MALDI-TOF-MS successfully identified this pathogenic organism, which had not been previously associated with canaliculitis infection.

Actinomyces species are generally susceptible to beta-lactam antibiotics, and co-administration with beta-lactamase inhibitors can prevent antibiotic resistance and lead to positive outcomes.¹³ Oral cefuroxime, with a minimum inhibitory concentration of 1 mg/L,

is effective against most anaerobes, including *Actinomyces* species.¹⁴ In the treatment of *Actinomyces* species canaliculitis, there have been case series where various topical antibiotics such as cefazolin, ciprofloxacin, chloramphenicol, and penicillin were used with varying responses.¹⁴ However, topical antibiotics alone typically result in partial remission, as observed in our case. Combining topical antibiotics with canaliculi irrigation through syringing has shown promising results.¹⁵ Syringing not only aids in treatment but also helps identify the presence of concretions.¹⁰ Pressing on the lacrimal sac during syringing can facilitate the regurgitation of canaliculiths or concretions. Although no specific clinical guidelines exist for definitive treatment plans in canaliculitis, curettage and punctoplasty of the canaliculi have demonstrated complete resolution of symptoms and signs in the majority of cases.^{10,16-17}

CONCLUSION

Chronic primary canaliculitis caused by *A. odontolyticus* is a rare condition, often leading to misdiagnosis. Successful management of this condition relies on a high index of suspicion, followed by the isolation of the causative organism. Treatment typically involves a combination of topical antibiotics, intracanalicular antibiotic syringing, and the extraction of canaliculiths.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

CONSENT

Written informed consent was obtained from the patient for the publication, which included photographs and the details of the case history.

REFERENCES

- 1: Milman T, Mirani N, Gibler T, Van Gelder RN, Langer PD. Actinomyces israelii endogenous endophthalmitis. *Br J Ophthalmol.* 2008;92(3):427-8. doi: 10.1136/bjo.2007.123596
 - 2: Batty I. Actinomyces odontolyticus, a new species of actinomycete regularly isolated from deep carious dentine. *J Pathol Bacteriol.* 1958;75(2):455-59. doi: 10.1002/path.1700750225.
 - 3: Schaal KP, Lee HJ. Actinomycete infections in humans-a review. *Gene.*1992;115(1-2):201-11. doi: 10.1016/0378-1119(92)90560-c.
 - 4: Takemura M, Yokoi N, Nakamura Y, Komuro A, Sugita J, Kinoshita S. Canaliculitis caused by Actinomyces in a case of dry eye with punctal plug occlusion. *Nihon Ganka Gakkai Zasshi.* 2002;106(7). doi: 10.1016/s0021-5155(02)00654-8
 - 5: Singh CN, Thakker M, Sires BS. Pyogenic granuloma associated with chronic Actinomyces canaliculitis. *Ophthal Plast Reconstr Surg.* 2006;22(3). doi:10.1097/01.iop.0000214529.43021.f4
 - 6: Jensen A, Fagö-Olsen H, Sørensen CH, Kilian M. Molecular mapping to species level of the tonsillar crypt microbiota associated with health and recurrent tonsillitis. *PLoS One.* 2013;8(2):e56418. doi: 10.1371/journal.pone.0056418.
 - 7: Pei Z, Bini EJ, Yang L, Zhou M, Francois F, Blaser MJ. Bacterial biota in the human distal esophagus. *Proc Natl Acad Sci U S A.* 2004;101(12):4250-5. doi: 10.1073/pnas.0306398101.
 - 8: McKellar MJ, Aburn NS. Cast-forming Actinomyces israelii canaliculitis. *Aust N Z J Ophthalmol.*1997;25(4):301-3.
 - 9: Perumal B, Carlson JA, Meyer DR. A Pathological Analysis of Canaliculitis Concretions: More Than Just Actinomyces. *Scientifica (Cairo).* 2016;2016:6313070. doi: 10.1155/2016/6313070.
 - 10: Zhang Q, Xu B, Li XX, Li MW. Clinical characteristics, treatment patterns, and outcomes of primary canaliculitis among patients in Beijing, China. *Biomed Res Int.* 2015;2015:904756. doi: 10.1155/2015/904756.
 - 11: Branquinho DF, Andrade DR, Almeida N, Sofia C. Mediastinitis by Actinomyces meyeri after oesophageal stent placement. *BMJ Case Rep.* 2014;2014:bcr2014204499. doi: 10.1136/bcr-2014-204499.
 - 12: Stingu CS, Borgmann T, Rodloff AC, et al. Rapid identification of oral Actinomyces species cultivated from subgingival biofilm by MALDI-TOF-MS. *J Oral Microbiol.* 2015;7:26110. doi: 10.3402/jom.v7.26110.
 - 13: Smith AJ, Hall V, Thakker B, Gemmell CG. Antimicrobial susceptibility testing of Actinomyces species with 12 antimicrobial agents. *J Antimicrob Chemother.*2005;56(2):407-9. doi: 10.1093/jac/dki206.
 - 14: Cullmann W, Frei R, Krech T. Antibacterial Activity of Oral Antibiotics against Anaerobic Bacteria. *Chemotherapy.*1993;39:169-174. doi: 10.1159/000239122
 - 15: Mohan ER, Kabra S, Udhay P, Madhavan HN. Intracanalicular antibiotics may obviate the need for surgical management of chronic suppurative canaliculitis. *Indian J Ophthalmol.* 2008;56(4):338-40. doi: 10.4103/0301-4738.41423
 - 16: Vécsei VP, Huber-Spitzy V, Arocker-Mettinger E, Steinkogler FJ. Canaliculitis: difficulties in diagnosis, differential diagnosis and comparison between conservative and surgical treatment. *Ophthalmologica.* 1994;208(6):314-7. doi: 10.1159/000310528.
 - 17: Lin SC, Kao SC, Tsai CC, et al. Clinical characteristics and factors associated the outcome of lacrimal canaliculitis. *Acta Ophthalmol.* 2011;89(8):759-63. doi: 10.1111/j.1755-3768.2009.01827.x.
-