• Letter to the Editor •

Primary conjunctival tuberculosis in two middle-aged women

Zhi-Qiao Liang[1], Qin Zhang[1], Ming-Wei Zhao[1], Xiao-Xin Li[2], Ming-Wu Li[3]

[1]Department of Ophthalmology, Peking University People's Hospital, Beijing 100044, China
[2]Department of Ophthalmology, Xiamen Eye Center of Xiamen University, Xiamen 361003, Fujian Province, China
[3]Department of Ophthalmology, Peking University International Hospital, Beijing 102206, China
Correspondence to: Ming-Wu Li. Department of Ophthalmology, Peking University International Hospital, Shengmingyuan Street 1st, Changping District, Beijing 102206, China. drlmwlmw@163.com
Received: 2019-01-14 Accepted: 2019-07-08

DOI:10.18240/ijo.2020.01.25

Citation: Liang ZQ, Zhang Q, Zhao MW, Li XX, Li MW. Primary conjunctival tuberculosis in two middle-aged women. *Int J Ophthalmol* 2020;13(1):180-183

Dear Editor,

We are writing to present two case reports on primary conjunctival tuberculosis (TB) in two middle-aged women. TB is an airborne communicable disease and is identified as the second leading cause of death from infectious disease worldwide[1]. TB primarily affects the lung, but may also affects extrapulmonary organs, including the eye[2]. Ocular TB consists of a group of manifestations caused by the acid-fast bacillus M. Tuberculosis. The first conjunctival TB case was recorded by Koaster in 1873[3]. At present, this entity is a rare condition and the standards of diagnosis and treatment have yet to be well-established. The aim of this study was to report two cases of primary conjunctival TB in two middle-aged women who were presented with swollen eyelids and foreign body sensation.

CASE REPORT

Case 1 A 58-year-old retired woman complained about swelling in her right lower eyelid and pain in the right periocular area that had been persistent for about 1mo. On examination, the visual acuity was 20/20 in right eye and intraocular pressure (IOP) was within normal limits. The right lower eyelid was observed to have thickened and there was a salmon-pink, "fleshy" patch mass spotted in the fornix conjunctiva. The mass showed a smooth surface with whitish mucous discharge (Figure 1A). The cornea was clear and the anterior chamber (AC) was free of cells or flare. The posterior segment was identified as normal. The fellow eye examination was within normal limits. Without palpable preauricular or other regional lymphadenopathy, the patient didn't exhibit any other signs of systemic abnormality. Bacille Calmette-Guerin scar was clearly observed on her left upper arm. She had visited Thailand for sightseeing 1mo prior to the onset of the mass. Besides, she had no record of keeping pets at home, such as dogs, cats and parrots. Her lab investigations were all shown to be within normal limits. There were no evidence of immune-suppression status, including acquired immune deficiency syndrome (AIDS). No significant abnormalities could be detected from her chest X-ray (CXR) and electrocardiograph. According to the history, symptoms and signs, a preliminary diagnosis of right lower eyelid conjunctival mucosal-associated lymphoid tissue (MALT) was made.

She received mass excision operation. Under topical anesthesia with benoxinate hydro chloride (20 mL:80 mg) and local anesthesia with lidocaine (2%), the mass was excised and sent for histopathological examination. We recommended that she use ofloxacin eye ointment (3.5 g:10.5 mg) twice per day to prevent infection following the surgery. The postoperation period was uneventful. Four days later, we received the biopsy report, stating that necrotizing granulomatous inflammation (Figure 1B) and Ziehl-Neelsen acid-fast stain were positive (Figure 1C), which suggested the diagnosis of TB.

Then she was taken some further investigations. Purified protein derivative (PPD) placement produced a strongly positive test (16×28 mm^2 induration with blisters). Both Rapid Gold Immuno-Assay Test for TB-IgG and T-Spot TB were positive. Due to a lack of pulmonary specific lesions, we diagnosed this condition as primary conjunctival TB. Then she followed the 4-drug regiment (RIPE therapy)[4] for 12mo and no recurrence ensued within a 12-month follow-up period (Figure 1D).

Case 2 A 62-year-old woman complained about foreign body sensation in both eyes that had been persistent for 2wk. On examination, the visual acuity was 20/20 in both eye and IOP was within normal limits. Both lower eyelids were observed to have thickened. In right lower fornix conjunctiva, some small pink masses were spotted to mix together in a bigger

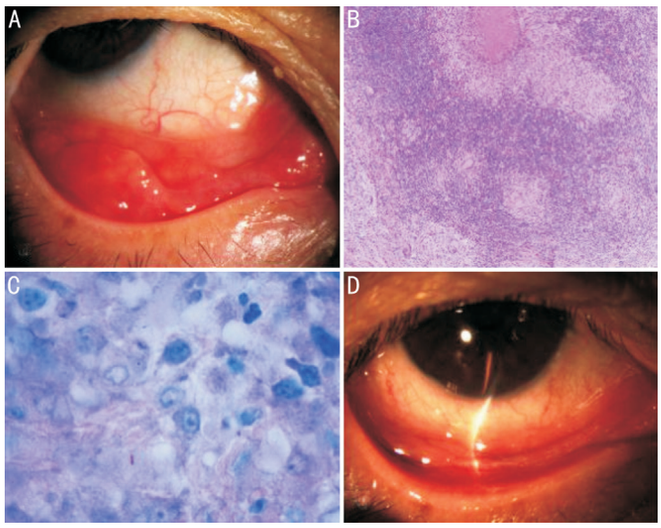

Figure 1 Case 1 A: Right lower eyelid was thickened and there was a salmon-pink, "fleshy" patch mass in the fornix conjunctiva, which had a smooth surface with whitish mucous discharge; B: The biopsy report suggested necrotizing granulomatous inflammation. Granulomas in a lymph node: upper part shows a necrotizing granuloma with central caseous necrosis, which is surrounded with epithelioid histiocytes (light color) and one giant multinucleated giant cell. The outer layer is lymphocyte (darker small blue cells). In the lower part, also shows several granulomas without central necrosis. Center is epithelioid histiocytes admixed with multinucleated giant cells, the outer layer is lymphocyte. C: Ziehl-Neelsen acid-fast stain was positive; D: After taking the 4-drug regiment (RIPE therapy) for 12mo, the conjunctival lesion had completed healed and no recurrence.

one without obvious discharge. On the left side, there were some follicle-like masses discovered (Figure 2A, 2B). No abnormality was detected in both corneas, ACs, lens, or posterior segments. There was no palpable preauricular pain. It was 3y earlier that she felt chest pain on her left side without any other accompanying symptoms. Her lab investigations were shown to be within normal limits. There were no evidence of immune-suppression status, including AIDS. No significant abnormality could be observed from her CXR, renal ultrasonography and superficial lymph node ultrasonography. PPD placement produced a strongly positive test (15×15 mm^2 induration with blisters). T-Spot TB was positive as well.

In addition to these, she underwent anterior segmental optical coherence tomography (AS-OCT) and *in vivo* confocal microscopy (IVCM). AS-OCT revealed plenty of solid masses in both fornix conjunctiva (Figure 2C, 2D), which was contradictory to our slit lamp examination. IVCM showed a mass of subepithelial round cell infiltrate, cells with multilobate nucleus compatible with neutrophils and many encapsulated epithelial microcysts with round cell infiltrate (Figure 2E). Besides, there were many dendritic cells discovered in the basal epithelial layer of tarsal conjunctiva (Figure 2F) and perfused blood vessels surrounded by round cells and

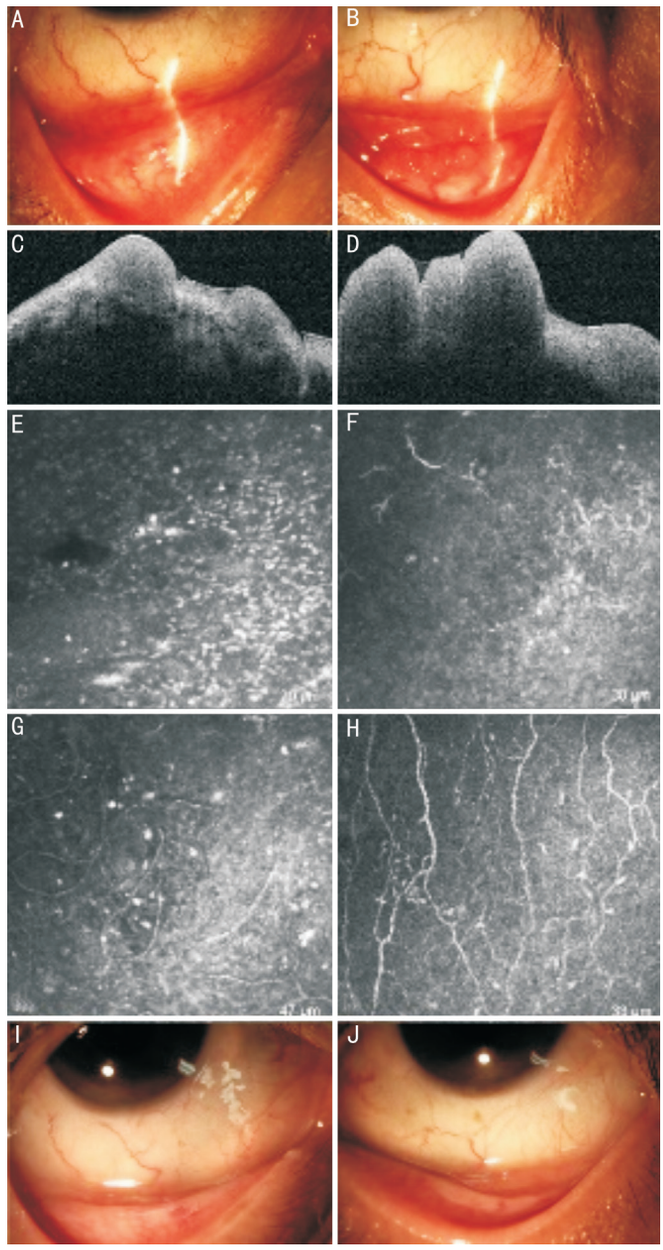

Figure 2 Case 2 A: In right lower fornix conjunctiva, there were some small pink masses mixing together in a bigger one without obvious discharge; B: In left lower fornix conjunctiva, there were some follicle-like masses; C, D: Anterior segmental optical coherence tomography revealed many solid masses were found in both lower fornix conjunctiva; E: A large amount of subepithelial round cell infiltrate, cells with multilobate nucleus compatible with neutrophils and many encapsulated epithelial microcysts with round cell infiltrate (20 μm); F: Dendritic cells detected in the basal epithelial layer of tarsal conjunctiva (30 μm); G: The left thickened conjunctiva showed many perfused blood vessels surrounded by round cells and hyperreflective structures (47 μm); H: Many Langerhans cells were found in the subepithelial layer of the left cornea (33 μm); I, J: After taking the 4-drug regiment (RIPE therapy) for 6mo, the fornix conjunctival masses were gradually faded.

hyperreflective structures (Figure 2G). Many Langerhans cells were found to be present in the subepithelial layer of both

corneas, the number of which was much higher as compared to normal conjunctiva (Figure 2H). Based on these findings, the clinical diagnosis of primary conjunctival TB in both eyes was made. We recommended that she undergo surgery for biopsy but she refused. Then she followed the 4-drug regiment (RIPE therapy)[4] for 12mo and the fornix conjunctival masses faded away gradually (Figure 2I, 2J).

DISCUSSION

TB is identified as a severe global health problem, which causes millions of people in poor health condition each year and ranks among the leading cause of fatality worldwide[1]. In 2014, the World Health Assembly ambitiously published their target to eradicate TB as a public health threat by 2035[5].

TB primarily affects the lung. Despite this, it has also been found to damage other organs, including the eye. TB affects the eye through direct infection of the tubercle bacillus or *via* a hypersensitivity reaction to the bacillus located elsewhere in the body. Ocular lesions resulting from M. Tuberculosis are diverse and are capable of impairing any structure of the eye and adnexa[6].

Conjunctival TB sites frequently involved subconjunctival tissue[7], bulber conjunctiva[8-11] and tarsal conjunctiva[12-13]. Infrequently, they may arise in fornix conjunctiva[14-15], as in our cases. Nevertheless, we suggest that the actual incidence is significantly higher than expected as it will be easily overlooked both by patients and by doctors.

The immunoallergic state of the patient could lead to the different kinds of clinical manifestations[14]. Based on the observation made of 160 cases of conjunctival TB, Eyre (1912) divided the morphological characteristics of conjunctival lesion into 4 categories[3]: ulcerative, nodular, hypertrophic granulomatous and pedunculated. Our patient showed the signs of hypertrophic granulomatous type. Other contributory factors in causing granulomatous inflammations of conjunctiva must be kept in mind, such as foreign-body granulomas, sarcoidosis, parinaud ocular glandular syndrome and syphilis[16]. In our cases, there was no history or microscopic evidence of any foreign body. In the first case, the granulomas were necrotized, surrounded with epithelioid histiocytes and rimmed with lymphocytes, which was found to be inconsistent with the characteristics associated with sarcoidosis. In the second case, angiotensin-converting enzyme level was within normal limits and no significant abnormality were detected from CXR, thus ruling out the possibility of sarcoidosis. The lab investigations of both patients were all within normal limits including treponema pallidum haemagglutination.

In case 1, the initial clinical presentation was suggestive of conjunctival MALT. However, the conjunctival histologic features of necrotizing granulomatous inflammation and positive Ziehl-Neelsen acid-fast stain result pointed to the diagnosis of TB. Due to the lack of pulmonary specific lesions, a diagnosis of primary conjunctival TB was made. Not only can the conjunctival reaction arise from contact with a contaminated finger or tissue[14], it can also be caused by inappropriate response of activated T cells left exposed to tubercular antigen in the lymph nodes and subsequently migrated to the conjunctival surface[9].

In case 2, we applied AS-OCT and IVCM to explore the characteristics of the fornix conjunctival masses. AS-OCT is viewed as a reliable tool to measure the cross-sectional area of corneal and anterior segment diseases, especially conjunctival diseases, like conjunctivochalasis[17], pterygium, pinguecula[18], melanoma, nevi[19-20] and conjunctival lymphoma[19]. In our case, the AS-OCT findings revealed nothing abnormal in respect to epithelial appearance and thickness. A sub-epithelial mass was identified as being hyporeflective and there was shadowing of the underlying tissue. Instead of follicle-like masses, it was confirmed as solid masses that was quite contrary to the results of our slit lamp examination.

IVCM is a novel, non-invasive technique that is capable of providing high-resolution images of living tissues and can be accurate to the cellular level[21-22]. The illumination and observation systems need to focus on the same focal point, which is the optical principle of this novel technique[23]. It has been applied to performing study on a wide range of infectious, especially in diagnosing of microbial keratitis, where it may assist with the identification of filamentary fungi and acanthamoeba cysts[22-23].

To the best of our knowledge, this was the first time IVCM has been reported from individuals with conjunctival TB. There are evidences suggesting both conjunctiva and cornea are in the inflammatory state. Not only could we find much more subepithelial round cell infiltrate and cells with multilobate nucleus than normal conjunctiva, we could also discover many Langerhans cells in the subepithelial layer of cornea. Despite this, we have yet to observe any special structure from IVCM in comparison with classic histopathology of biopsy specimens.

To conclude, making the diagnosis of conjunctival TB can be challenging as there are a variety of manifestations and the diagnostic criteria is not uniform at a global scale.The diagnosis of conjunctival TB should be kept in mind when the patients exhibiting symptoms of chronic conjunctivitis, swollen eyelids or foreign body sensation without significant improvement by taking conservative treatments. Palpable preauricular or other regional lymphadenopathy may provide a clue to the diagnosis of conjunctival TB. Once conjunctival TB is being considered, further diagnostic testing needs to be performed, including tuberculin skin testing and interferon-gamma release assay, though they are not absolute reliable

because of the false positive and false negative possibilities. The gold standard of diagnosis of conjunctival TB is biopsy. Non-invasive methods, including AS-OCT and IVCM, are recognized as the reliable tools to examine the cross-sectional area of conjunctival masses. Maybe in the future, with more studies on AS-OCT and IVCM of conjunctival diseases, we will have more alternative choices to diagnose and monitor this entity.

ACKNOWLEDGEMENTS

Authors' contributions: Liang ZQ and Zhang Q recruited the patients. Liang ZQ wrote the manuscript. Li MW, Li XX, and Zhao MW reviewed the manuscript. All authors have approved the manuscript.

Conflicts of Interest: Liang ZQ, None; **Zhang Q,** None; **Zhao MW,** None; **Li XX,** None; **Li MW,** None.

REFERENCES

1 Global tuberculosis report 2015. World Health Orgnization 2015. http://www.who.int/entity/tb/publications/global_report/en/index.html.

2 Gupta V, Shoughy SS, Mahajan S, Khairallah M, Rosenbaum JT, Curi A, Tabbara KF. Clinics of ocular tuberculosis. *Ocul Immunol Inflamm* 2015;23(1):14-24.

3 Hadj MKK, Hadrich M, Bouslah H, Ben Abdelaziz A, Charrada A, Aissa W. The hunterian lecture on tuberculosis of the conjunctiva: its etiology, pathology, and diagnosis. *Lancet* 1912;179(4629):1319-1328.

4 Helm CJ, Holland GN. Ocular tuberculosis. *Surv Ophthalmol* 1993;38(3):229-256.

5 Zumla A, George A, Sharma V, Herbert RHN, Oxley A, Oliver M. The WHO 2014 Global tuberculosis report—further to go. *Lancet Glob Heal* 2015;3(1):e10-e12.

6 Alvarez GG, Roth VR, Hodge W. Ocular tuberculosis: diagnostic and treatment challenges. *Int J Infect Dis* 2009;13(4):432-435.

7 Biswas J, Kumar SK, Rupauliha P, Misra S, Bharadwaj I, Therese L. Detection of Mycobacterium tuberculosis by nested polymerase chain reaction in a case of subconjunctival tuberculosis. *Cornea* 2002;21(1):123-125.

8 Feinstein E, Farooq AV, Lin AY, Traish AS. Bilateral conjunctival tuberculosis presenting as mass lesions. *Can J Ophthalmol* 2015;50(1):e11-e13.

9 Sharma K, Kalakoti P, Juneja R, Sahu, Singh V, Subramanian PS. Re-emphasizing Thygeson's warning: conjunctival phlyctenulosis as presenting sign of impending clinical tuberculosis. *Can J Ophthalmol* 2014;49(6):e135-e137.

10 Libby GF. Tuberculosis of the bulbar conjunctiva. *Trans Am Ophthalmol Soc* 1914;13(Pt 3):784-786.1.

11 Browning SH. Tuberculosis of conjunctiva. *Proc R Soc Med* 1943;36(8):407-408.

12 Rose JS, Arthur A, Raju R, Thomas M. Primary conjunctival tuberculosis in a 14 year old girl. *Indian J Tuberc* 2011;58(1):32-34.

13 Brar RK, Singh A, Deshpande AH, Gargade CB, Das S. Primary conjunctival tuberculosis presenting as dry eye: a rare case report and review of the literature. *Ocul Oncol Pathol* 2017;3(4):276-278.

14 Sollom AW. Primary conjunctival tuberculosis. *Br J Ophthalmol* 1967;51(10):685-687.

15 Solmaz N, Önder F, Demir N, Altuntaş Aydın Ö. Primary conjunctival tuberculosis. *Turk J Ophthalmol* 2018;48(1):39-41.

16 Fernandes M, Vemuganti GK, Pasricha G, Bansal AK, Sangwan VS. Unilateral tuberculous conjunctivitis with tarsal necrosis. *Arch Ophthalmol* 2003;121(10):1475-1478.

17 Gumus K, Crockett CH, Pflugfelder SC. Anterior segment optical coherence tomography: a diagnostic instrument for conjunctivochalasis. *Am J Ophthalmol* 2010;150(6):798-806.

18 Soliman W, Mohamed TA. Spectral domain anterior segment optical coherence tomography assessment of pterygium and pinguecula. *Acta Ophthalmol* 2012;90(5):461-465.

19 Nanji AA, Sayyad FE, Galor A, Dubovy S, Karp CL. High-resolution optical coherence tomography as an adjunctive tool in the diagnosis of corneal and conjunctival pathology. *Ocul Surf* 2015;13(3):226-235.

20 Thomas BJ, Galor A, Nanji AA, El Sayyad F, Wang JH, Dubovy SR, Joag MG, Karp CL. Ultra high-resolution anterior segment optical coherence tomography in the diagnosis and management of ocular surface squamous neoplasia. *Ocul Surf* 2014;12(1):46-58.

21 Long Q, Zuo YG, Yang X, Gao TT, Liu J, Li Y. Clinical features and *in vivo* confocal microscopy assessment in 12 patients with ocular cicatricial pemphigoid. *Int J Ophthalmol* 2016;9(5):730-737.

22 Hu VH, Weiss HA, Massae P, Courtright P, Makupa W, Mabey DC, Bailey RL, Burton MJ. *In vivo* confocal microscopy in scarring trachoma. *Ophthalmology* 2011;118(11):2138-2146.

23 Hu VH, Holland MJ, Cree IA, Pullin J, Weiss HA, Massae P, Makupa W, Mabey DC, Bailey RL, Burton MJ, Luthert P. In vivo confocal microscopy and histopathology of the conjunctiva in trachomatous scarring and normal tissue: a systematic comparison. *Br J Ophthalmol* 2013;97(10):1333-1337.