Conjunctiva Granuloma, a Rare Presentation of Ocular Leptospirosis Presenting as Conjunctiva Granuloma: Case Series

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ABSTRACT

Diagnosis of ocular leptospirosis is challenging and requires a high index of suspicion of previous leptospiral infection and good laboratory support. This case series focuses on two young females with unilateral conjunctiva granuloma. To the best of our knowledge, these are the first two cases of ocular leptospirosis with conjunctiva granuloma. The definitive diagnosis of ocular leptospirosis was based on laboratory studies in which conjunctival biopsies in these two cases showed positive leptospira DNA. Retrospectively, the history was suggestive as both...
patients had exposure to leptospira organism. In conclusion, a diagnosis of ocular leptospirosis requires a high clinical suspicion index supported by mandatory laboratory investigations.

Keywords: eye manifestations, leptospirosis, ocular infection

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**INTRODUCTION**

Leptospirosis, a zoonotic infection, is distributed worldwide, especially in tropical and subtropical climates. Leptospirosis classically presents as an acute biphasic illness and usually manifests in the eye in the second phase of illness. It can manifest at two months to two years after the acute infection (Nadjm et al. 2005). Leptospirosis remains underdiagnosed although it is commonly found in tropical countries, as laboratory support is needed in its diagnosis. Unsuspecting ophthalmologists are faced with a diagnostic dilemma due to the prolonged asymptomatic period between the systemic illness and ocular manifestation. Uveitis, mainly panuveitis was reported to be the major manifestation (Rathinam et al. 1997). Non granulomatous uveitis, posterior synechiae and hypopyon are the commonest findings reported in anterior segment, while in the posterior segment, vitritis and periphlebitis have been reported (Rathinam et al. 1997). However, no literature has reported on ocular leptospirosis presenting with conjunctiva granuloma yet. We hereby report two atypical cases of ocular leptospirosis which presented with conjunctiva granuloma.

**CASE REPORT**

*Case 1*

A healthy 28-year-old female, who was a veterinarian, presented in July 2016 with the complaint of left upper lid swelling (Figure 1) which gradually increased in size over three weeks duration. It was associated with discomfort and watery eyes. She had no blurring of vision, photophobia, floaters or pain. She recalled of having on and off low-grade fever several months prior to the onset of her ocular symptoms.

On examination, she was a well-built lady, not septic looking. Visual acuity in her right eye was 6/9 (pinhole 6/9) while her left eye was 6/12 (pinhole 6/9). Relative afferent pupillary defect (RAPD) was not

![Figure 1: Left upper eyelid swelling causing mechanical ptosis](image-url)
present. Her extraocular muscle movements were normal and her eyes were orthophoric on Hirschberg test. There was no proptosis. Her left upper eyelids were swollen. Her palpebral conjunctiva was oedematous with mucoid discharge. A large conjunctiva swelling covering almost the entire upper palpebral conjunctiva (Figure 2) was seen. The rest of her ocular examination was unremarkable. There was no retinitis, vitritis, vasculitis or cystoid macula oedema. Examination of her left eye showed normal findings.

She was treated with oral azithromycin 500 mg daily, guttae dexamethasone 0.1% every four hours and ointment dexamethasone on night for two weeks. Despite these treatment, her conjunctiva swellings did not resolve.

Investigations showed leptospira serology IgM was negative and IgG was positive. Other investigations were normal. Incisional biopsy of left conjunctiva was done on 25th August 2016. Leptospira PCR was positive. Histopathology examination of the biopsy revealed tissue lined partly by stratified squamous epithelium. The underlying tissue showed aggregates of non-caseating, granuloma surrounded by lymphocytes, plasma cells and scattered Langhan’s-type multinucleated giant cells (Figure 3). Following her conjunctiva biopsy, guttae dexamethasone 0.1% every six hours, ointment dexamethasone and guttae moxifloxacin 0.5% every six hours was given.

Three weeks later, in September 2016, during one of her follow-ups, her conjunctiva swellings had resolved. She also gave a history of joint pains and swelling over her bilateral ankles, knees and elbows prior to the current follow-up. The swelling and pain resolved after oral prednisolone given by her family Physician. She was referred to medical team for opinion.

Figure 2: Anterior segment photographs showing a large palpebral conjunctiva swelling (yellow arrow)

Figure 3: Histological features of conjunctiva granuloma seen under microscopic examination (X40) with Hematoxylin and Eosin (H&E) stain. Cells on the left shows foreign body multinucleated giant cells (red arrow). Cells on the right shows collection of epithelioid histiocytes (granuloma) (green arrow) in keeping with chronic granulomatous inflammation
Her symptoms were thought to be insignificant by them.

**Case 2**

An 18-year-old female student was admitted in a private hospital and treated as aseptic meningitis secondary to leptospirosis, diagnosed by lumbar puncture. She presented with fever, headache, neck stiffness and photophobia for three days and leptospira serology (IgM) was tested positive and leptospira serology IgG was negative. On the fourth day of admission, while she was on leptospirosis treatment, she developed diffuse conjunctival redness and upper and lower lid swelling of her left eye. She had no reduced vision, photophobia, floaters, pain, purulent eye discharge or history of ocular trauma. She then completed a combination of intravenous (IV) and oral antibiotics (IV Ceftriaxone, Trimethoprim/sulfamethoxazole and Doxycycline).

She was discharged after ten days of admission. However, her left eye redness persisted. Therefore, she sought treatment from a private Ophthalmologist and was given topical antibiotics and steroids but her symptoms were not relieved. Her left eye redness persisted for three months, and it was then that she decided to seek treatment from us on 7th May 2014.

On examination, visual acuity in her right eye was 6/9 while her left eye was 6/12 (pinhole 6/9). There was no RAPD. Her extraocular movements were normal. There was no proptosis and her eyes were symmetrical and orthophoric. Her left upper eyelids were mildly swollen with diffuse conjunctiva suffusion. There was multiple conjunctiva swellings with smooth surface (Figure 4) seen in the temporal and nasal parts of her left bulbar conjunctiva, and upper

![Figure 4: Anterior segment photographs showing multiple conjunctiva swellings at the inferior fornix and temporal bulbar conjunctiva (green arrows).](image)

![Figure 5: Histological features of conjunctiva granuloma seen under microscopic examination (X40) with H&E stain. Here it shows multinucleated giant cells (red arrow) and histiocytes.](image)
and lower lid conjunctiva fornix. Her cornea was clear. The anterior chamber was deep with 1+ cells. There was no keratic precipitate, fibrin, hypopyon, iris atrophy or posterior synechiae. Her lens was clear. Fundus examination was normal. There was no retinal hemorrhage, vasculitis, choroidal folds or macula oedema. Her right eye was normal.

Upon presentation to us, several other investigations were done which was normal and the patient underwent an incisional biopsy of her left conjunctiva was done on 8th September 2014 (Figure 5).

Incision biopsy taken from her left conjunctiva on the 8th of September 2014 was positive for Leptospira PCR and negative for Mycobacterium tuberculosis PCR. Histopathology examination of the biopsy revealed multiple small granulomas and multinucleated giant cells rimmed by dense lymphocytes and plasma cells infiltrates (Figures 5). No central necrosis was present in keeping with non-caseating, granulomatous inflammation. PAS and Grocott stains for fungal bodies as well as Ziehl-Neelson stain for acid fast bacilli were negative. There was also no evidence of malignancy.

She was started on guttae dexamethasone 0.1% every two hours, dexamethasone ointment on night and guttae moxifloxacin 0.5% four hourly. Her conjunctiva swellings and anterior uveitis resolved completely.

**DISCUSSION**

Ocular leptospirosis is postulated to be an autoimmune reaction to the spirochete leptospira interrogans. The commonest feature of ocular leptospirosis is non-granulomatous panuveitis (Rathinam et al. 1997). The exact incidence of systemic leptospirosis presenting with uveitis is unknown, and ranges from 3-92% (Rathinam et al. 2005; Feigin et al. 1975).

To the best of our knowledge, at the time of writing this manuscript, no case was reported with granulomatous conjunctival swelling. This is the first case series to report conjunctival granuloma as an atypical manifestation of ocular leptospirosis. The first case was a case where conjunctival granuloma was the sole feature, while in the second case, the patient had conjunctival granuloma and mild anterior uveitis. The two cases also showed similarities, with both patients being young and healthy females.

Initially, on presentation, both patients were suspected to have cat scratch disease, in view of the conjunctival swelling. The first case was treated with oral azithromycin 500 mg daily for two weeks and topical steroids as she was initially suspected to have cat scratch disease. Azithromycin is also the first line treatment for mild leptospirosis, therefore, this antibiotic would have treated her leptospirosis. The second patient was also treated with a combination of antibiotics. During the acute phase of leptospirosis, there may be afebrile illness, severe fatigue, muscle pain and headache. The leptospiras are rapidly eliminated by the immune system from all host tissues except for immunologically
privileged sites like the brain and eyes after 4 to 7 days of the initial bacteremia. Thus, immunological disease such as uveitis occurs (Rathinam et al. 2005). However, Pappachan et al. 2007 found that patients only developed mild uveitis if they were treated with antibiotics during the acute phase of illness. This explains why in the second case the patient developed mild anterior uveitis as she was treated with systemic antibiotics earlier on.

In 1866, leptospiral uveitis was first reported by Weil and is thought to be a late autoimmune process (Puca et al. 2016; Rathinam et al. 2015). According to Puca et al. 2016, conjunctival swelling usually appears on the third or fourth day. In our second patient, she developed conjunctival swellings on the fourth day of admission, which is a week after the onset of illness.

Conjunctival biopsy for both patients isolated leptospira DNA. Conjunctiva is a highly vascularized tissue, and we hypothesize that leptospira protein would have spread hematogenously and probably became entrapped within the conjunctival tissue. Our patient’s ocular antigen or leptospira protein was perceived as foreign and an immunological reaction was mounted against them. Therefore, we postulate that granulomatous reaction was found at their conjunctiva as some of the leptospira protein were probably entrapped there.

Other diseases such as ocular sarcoidosis, cat scratch disease, lepromatous granuloma and tuberculous granuloma have similar biopsy picture. However, in tuberculous granuloma, the hallmark picture is central caseating necrosis with epitheloid granuloma and Langhans giant cells. In lepromatous leprosy, Lepra cells are found in poorly circumscribed masses. Bartonella henselae causes a granulomatous reaction with intraepithelial neutrophilic abscess. Sarcoid granulomas are non caseating, and consists of stellate inclusions (asteroid bodies) and concentric lamellar calcifications (Schaumann bodies) (Kumar et al. 2013).

In the first case, our patient was infected with the organism earlier but it was only 3 months later during the second phase of illness that she developed her left eyelid swelling. It was only upon further re-evaluation, that leptospira infection was suspected in view of her nature of job which predisposed her to at high risk. Her leptospira serology for IgM was negative as it was taken in the second phase of her illness. However, her leptospira IgG was positive, pointing to a past infection.

The second case had left conjunctiva swellings with multiple granulomatous conjunctival swellings. There was only mild anterior uveitis without any posterior segment involvement. Leptospiral uveitis are usually treated with topical corticosteroids, which are the main therapy in ocular inflammation. Systemic antibiotic therapy during the early phase of infection is unclear to provide any protective role in the prevention of immunologic sequelae such as uveitis. However, a study suggests only a mild disease may develop in those treated
in the septicemic phase (Pappachan et al. 2007).

CONCLUSION

Although rare, one should suspect conjunctiva granuloma to be caused by leptospirosis, especially if there is a suggestive history or physical examination that points to leptospirosis. Tissue biopsy is the ultimate investigation to diagnose conjunctiva swellings with high index of suspicion of leptospirosis. Perhaps, to the practicing ophthalmologists, when faced with an unexplainable conjunctiva swelling, a tissue biopsy should be performed as it is the definitive investigation.

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