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CASE REPORT

Multifocal Keratitis in 23-year-old Woman with β-Thalassemia

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Abstract

Introduction: Multifocal keratitis can result from infectious and non-infectious causes, and its etiology is often challenging to pinpoint. Ocular complications are common in β-thalassemia and can have serious consequences. This case highlights an unusual presentation of multifocal keratitis in a patient with β-thalassemia. **Case Presentation:** A 23-year-old woman with β-thalassemia, diagnosed 12 years ago, was referred by a hematologist for pain in her right eye persisting for the past two weeks. She reported redness, tearing, and light sensitivity. Six months prior, she experienced similar symptoms, which had left a white spot in her right eye. Recently, this spot had multiplied and spread across the ocular surface. Visual acuity (VA) was 6/40 in the right eye on examination. Findings included palpebral spasm, conjunctival and pericorneal injection, and multiple infiltrates on the anterior corneal surface. Fluorescein staining was positive for numerous infiltrates. Schirmer and break-up time (BUT) tests indicated an unstable tear film. Treatment included antibiotic eye ointment, preservative-free artificial tears, mucous membrane pemphigoid (MMPs) inhibitors, and oral ascorbic acid. Two weeks later, VA improved to 6/9, with a reduction in infiltrates and fluorescein staining. **Conclusion:** Prompt management is essential for preserving vision and preventing complications in ocular surface diseases while diagnostic procedures are underway.

Keywords: multifocal keratitis; punctate epithelial keratitis; β-thalassemia

Introduction

Both infectious agents and non-infectious processes can cause multifocal keratitis, and its cause can be hard to determine, especially in immunocompromised patients.[1] Thalassemia is a severe genetic blood disorder caused by mutations in the globin gene, leading to the excessive destruction of red blood cells. Globally, over 42,000 newborns are diagnosed with β-thalassemia each year.[2] Without transfusions, β-thalassemia major can be fatal by age three.[3] Key developments include guidelines for safe blood product processing, non-invasive methods to assess iron overload, oral iron chelators, and strategies for managing specific complications. Improved medical care and consistent iron chelation therapy (ICT) have enhanced quality of life and extended life expectancy, but certain adverse events may still arise.[4],[5],[6]

Ocular complications are frequently encountered and can result in significant consequences. Patients with β-thalassemia often exhibit various ophthalmologic issues, including changes in visual acuity (VA), cataracts and lens opacities, loss of iris pattern, reduced axial length, lens thickening, increased corneal curvature, astigmatism, tear function abnormalities, and retinal issues. Retinal complications may include retinal pigment epithelium (RPE) degeneration, optic neuropathy, tortuous retinal vessels, and vitreoretinal hemorrhage.[7],[8],[9] In this study, we aimed to evaluate an unusual presentation of multifocal keratitis in a patient with β-thalassemia.

Case presentation

This case report presents a 23-year-old woman whom the Haemato-Oncologist consulted at an oncology outpatient clinic. She had a chief complaint

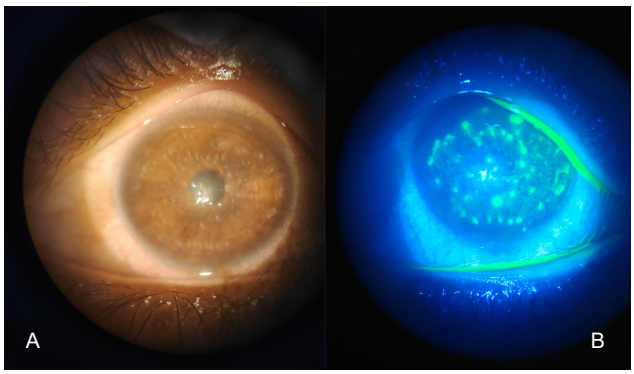

Figure 1. The initial clinical presentation of multifocal and multiform keratitis in thalassemia mayor patient, (A) in diffuse illumination and; (B) Stain with fluorescein.

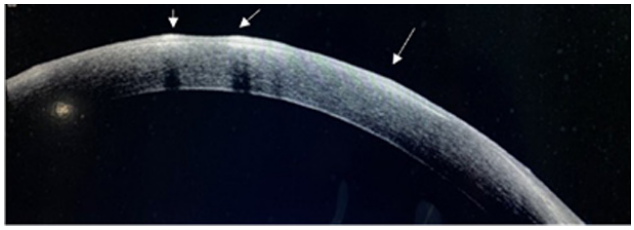

Figure 2. Anterior OCT showing epithelial keratitis (arrows) after three weeks of therapy.

of pain in her right eye in the last two weeks. The pain occurred with the red eye, watery, and light sensitivity. The vision has also worsened since the patient had the complaints. There was no history of any foreign body in her eye, and she had never had any scratches from plants or other solid things. Six months ago, the patient had the same symptoms, with white spots in the center of the right eye. However, these spots have been multiplying and spreading on the ocular surface in the last two weeks.

The patient was diagnosed with thalassemia β mayor 16 years ago, in the first decade of life, and treated with deferasirox and blood transfusion every month. The history of other disease was herpes infection three years ago. History of wearing spectacles, trauma, and any surgical procedure were denied. Two days before the consultation, the patient came to a clinic because of the complaint and was treated with chloramphenicol eye ointment. Six months ago, when the first symptom appeared, a local clinic prescribed the patient topical eyedrops: an eyedrop in the pink bottle (suggested an antibiotics) and an eyedrop in the white bottle (suggested artificial tears).

From the ocular examination for the right eye, VA was 6/40 with no pinhole improvement, while the left eye was within the normal limit of 6/6. Intraocular Pressure of both eyes was within normal limits. The blepharospasm, conjunctival injection, paracorneal injection, and multiple infiltrates in the entire surface of the cornea (Figure 1). The staining was positive, as many of the infiltrates with fluorescein. The anterior segment inspection of the left eye was within normal limits. A dry eye examination was performed; the Schirmer test on the right eye showed 10 mm in length and 20 mm in the left eye. The break-up time showed the unstable tear film of both eyes, as proven by the 3-second break after the fluorescein was applied. The anterior optical coherence tomography (OCT) shows hyperreflectivity in the epithelial layer, in this case, a punctate epithelial keratitis form (Figure 2).

The initial medication was antibiotic eye ointment, eye drops, non-preservative artificial tears combined with MMPs inhibitor and oral ascorbic acid. Moxifloxacin eyedrop every four hours in combination with chloramphenicol eye ointment every 24 hours before bed, artificial tears non-preservative every two hours for both eyes, doxycycline capsules 100 mg every 12 hours orally, vitamin C tablet 500 mg every 12 hours orally were prescribed. The first diagnostic procedure was corneal scrapping with no bacterial or fungal appearance.

Follow-up was performed at the external eye disease division, ophthalmology outpatient clinics, Dr Soetomo General Hospital, Surabaya, East Java. In the first follow-up, the VA was improved to 6/30, and additional therapy was added: fluometholone eyedrops every four hours for right eye. The second follow-up was five days after that, and the patient said the pain was much reduced. The VA improved to 6/20, the peripheral corneal lesion also decreased, and the corneal sensibility was normal during the examination (Figure 3). Polyvinylpyrrolidone non-preservative eyedrops (protagenta, Cendo Pharmaceutical, Indonesia) every six hours for right eye was prescribed to give more humidity in both eyes. Two weeks after treatment, the VA improved to 6/9.

Discussion and conclusions

Punctate epithelial keratitis (PEK) encompasses a spectrum of microscopic alterations in the corneal epithelium, ranging from granular changes to erosive and inflammatory lesions. Punctate epithelial erosions (PEE) are defined as localized areas of epithelial cell damage or abnormalities in the cornea that demonstrate fluorescein staining (Figure 4). Representative ocular conditions associated with PEK and PEE are depicted in Table 1. Inflammatory cells may infiltrate the stromal layer via epithelial defects, primarily from the tear film or, less commonly, through direct leukocyte infiltration at the limbus, such as following laser in situ keratomileusis (LASIK). In cases of endothelial compromise, inflammatory cells may migrate into the stroma from the aqueous humor. Furthermore, stromal inflammation can induce neovascularization, allowing inflammatory cells to penetrate the stroma directly through the newly formed blood and lymphatic vessels within a vascularized cornea.[1],[10]

Adenoviral keratoconjunctivitis is transmitted through direct contact with ocular or respiratory secretions,

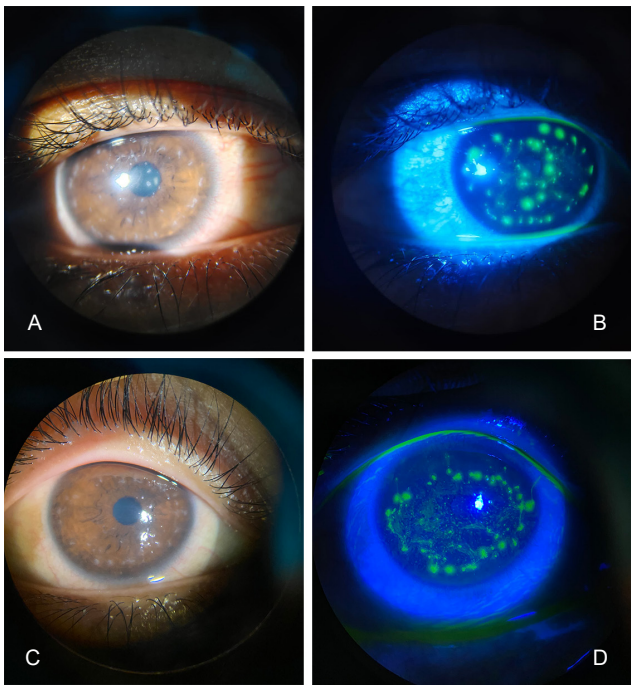

Figure 3. (A) Follow up after one-day treatment with; (B) Fluorescein stain; (C) Six days after treatment, the results showed better diffuse illumination, and (D) the peripheral lesion decreased compared to the previous examination.

exposure to contaminated fomites, or utilization of infected swimming pools. The risk of transmission is elevated in densely populated environments such as schools, long-term care facilities, military barracks, and summer camps. Corneal symptoms typically include epiphora, photophobia, and a foreign-body sensation.[1],[2] Unlike in this case, in about 70% of cases, the symptoms of adenovirus keratoconjunctivitis may progress to the other eye, though the symptoms may be milder for the other eye.[11] A pronounced follicular conjunctivitis emerges within seven to ten days following inoculation, often accompanied by punctate epithelial keratitis. Subsequently, multifocal subepithelial (stromal) corneal infiltrates typically develop within seven to fourteen days after the initial onset of ocular symptoms. The presence of subepithelial infiltrates is associated with persistent photophobia and visual impairment, which may endure for months to years.[1],[2]

Herpes simplex keratitis is a prevalent and potentially vision-threatening condition resulting from recurrent corneal infections with the herpes simplex virus (HSV). This condition can arise from a primary ocular HSV infection or subsequent recurrences. Following an initial ocular infection, the virus migrates to the trigeminal ganglion via the ophthalmic division of the trigeminal nerve (V1), where it establishes latency. Upon reactivation, HSV returns to the cornea, triggering an inflammatory response. The infection may involve multiple ocular structures, including the conjunctiva, cornea, anterior chamber, iris, lens, vitreous, and retina. Recurrence of HSV within the cornea leads to the development of herpes simplex keratitis.[12],[13],[14] Manifestations of herpes simplex keratitis encompass herpetic dendrites, geographic ulcers, stromal keratitis, disciform keratitis, and neurotrophic keratopathy, with herpetic stromal keratitis being the most prevalent. The hallmark of stromal keratitis is a central ulcer bed with ulcerated margins, characterized by terminal buds visible with special stains (e.g., fluorescein and rose bengal), which are absent in the current case. A reduction in corneal sensation is also observed in HSV keratitis, although this finding appears normal in our patient. In the absence of an adequate immune response, such as in cases of immunodeficiency or improper corticosteroid use, the virus may penetrate deeper into the cornea, compromising the stromal layer and potentially leading to more severe involvement of the corneal stroma.[15],[16]

Varicella-zoster virus (VZV) infection typically occurs during childhood and is transmitted through airborne droplets, direct contact, and person-to-person transmission. Herpes zoster, or shingles, results from the reactivation of latent VZV in a sensory nerve ganglion, often years after the initial infection. It generally presents as a unilateral maculopapular or vesicular rash confined to a single dermatome. When VZV affects the ophthalmic branch (V1) of the trigeminal nerve (V), it leads to herpes zoster ophthalmicus (HZO). Although HZO does not always involve the eye, approximately 50% of cases are associated with ocular complications, including conjunctivitis, uveitis, episcleritis, keratitis, and retinitis.[17],[18] Epithelial keratitis can manifest as punctate or pseudodendritic keratitis. Punctate keratitis is marked by scattered, fluorescein-stained, swollen lesions on the corneal surface, believed to harbor a live replicating virus. Pseudodendrites resemble the branching lesions seen in HSV keratitis, however, unlike HSV dendrites, which are brightly stained ulcers with terminal bulbs, HZO pseudodendrites are non-erosive mucous plaques that stain minimally and lack terminal bulbs.[19],[20] In our patient, pseudodendrites were not visible with fluorescein staining. However, the OCT revealed swollen lesions on the superficial surface of the cornea, resembling those seen in HZO keratitis.

Thygeson superficial punctate keratitis (TSPK) is characterized by recurrent episodes of gray-white opacities

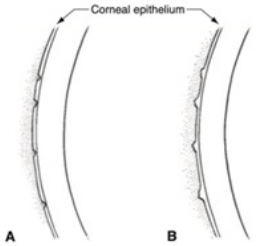

Figure 4. Punctate lesions of the corneal epithelium: (A) Punctate epithelial erosions; and (B) Punctate epithelial keratitis.

Table 1. Probable diagnosis in the manifestation of punctate epithelial keratitis and erosions[1]

Findings	Example of ocular condition
Punctate epithelial erosions	Dry eye Toxic reaction Atopic keratoconjunctivitis
Punctate epithelial keratitis	Adenovirus keratoconjunctivitis Herpes simplex virus epithelial keratitis Herpes zoster virus epithelial keratitis Thygeson superficial punctate keratitis

in the corneal epithelium, often affecting both eyes but sometimes asymmetrically. Common symptoms include photophobia, tearing, blurred vision, and eye irritation. While the progression and prognosis of the disease are well-documented, its exact cause remains unknown. Some theories suggest virus-mediated immunity, especially following viral keratitis.[21] Immune-based etiology has also been proposed, and multiple autoimmune disorders have been positively implicated in patients with TSPK.[22] The typical presentation of TSPK involves an elevated or flat, round to oval-shaped, grayish-white lesion located in the central intraepithelial corneal area, with minimal stromal edema or inflammation beneath it. The acute lesion may exhibit minimal fluorescein staining. Occasionally, the lesion is described as having a star-like appearance, and in the later stages, subepithelial fibrosis or an anterior stromal scar may develop. Around 20 lesions are typically observed in each eye, although up to 50 lesions have been reported. These lesions typically resolve without residual trace within four to six weeks. Corneal sensitivity is generally intact, and the conjunctiva remains unaffected, except in some cases where mild redness or filament formation may occur.[23] β-thalassemia is an autoimmune disease, but the positive fluorescein staining that persists after the acute phase does not indicate a TSPK in our case.

Ocular manifestations in β-thalassemia may be associated with the underlying disease, iron overload, or the use of chelating agents. Ocular surface disease, as evidenced by alterations in tear function parameters, has been reported in two studies. Lens opacities are observed in 9.3–44% of cases, according to five studies. Both lenticular opacities and RPE degeneration show a positive correlation with the administration of desferrioxamine and deferriprone, as noted in two studies. Ocular fundus abnormalities characteristic of pseudoxanthoma elasticum (PXE), such as *peau d'orange*, angioid streaks, pattern dystrophy-like changes, and optic disc drusen, have been documented in seven studies. In a cohort study by Jafari et al.[24] involving 54 asymptomatic thalassemia major patients, ocular findings were identified in 68.5% of the participants. These included dry eye (33.3%), cataracts (10.2%), RPE degeneration (16.7%), color vision deficiency (3.7%), and visual field defects (33.7%). Moreover, the frequency of blood transfusions exhibited a positive correlation with the presence of ocular abnormalities ($p = 0.005$).[25]

Haghpanah et al.[26] conducted a study to assess the prevalence of abnormal ocular findings in a cohort of 79 patients with transfusion-dependent β-thalassemia (TDT) aged over 18 and undergoing ICT. Three patients (3.8%) exhibited a VA greater than 0.1 logMAR among the participants. The mean intraocular pressure (IOP) was 14.88 ± 3.34 mmHg, ranging from 6 to 25 mmHg. Fundus abnormalities were detected in eight patients (10.1%). Additionally, four patients (5.1%) were diagnosed with dry eye, with one patient using deferasirox and three patients using a combination of deferoxamine and deferiprone for the past two years.[26]

Ocular surface disease, as evidenced by changes in tear function parameters (decreased BUT, increased Rose Bengal staining, and reduced Schirmer test values), has been linked to goblet cell depletion and squamous metaplasia of the conjunctiva. Potential contributing factors include deficiencies in trace elements and vitamins and peroxidative damage induced by either vitamin E deficiency or environmental UV radiation. UV radiation leads to the accumulation of intracellular peroxides in cultured epithelial cells. Patients with thalassemia appear to be particularly vulnerable to UV-induced peroxidative tissue damage due to secondary iron overload resulting from chronic blood transfusions. Vitamin E, a potent antioxidant, protects against oxidative stress. The reduced plasma levels of vitamin E observed in β-thalassemia patients may disrupt the oxidant or antioxidant balance, increasing the susceptibility of the ocular surface to oxidative damage in vitro. A study involving rats with iron overload identified hemosiderin deposits in macrophages predominantly within the connective tissue of lacrimal glands, which may account for the impaired Schirmer test results indicative of reduced tear production.[25],[26]

β-thalassemia may present with various signs, both structural and functional. Ocular findings in β-thalassemia may correlate to the disease, iron overload, or the chelating agents used. Tear function parameters can decrease and lead to dry eye manifestation; if not treated, keratitis will occur. Studies have not yet discussed the clinical appearance of keratitis in thalamus patients. The primary etiology of multiforme keratitis in this case is still unknown because of the limitation of the diagnostic procedure. Initial management with lubrication, topical antibiotics, MMPs inhibitors, and ascorbic acid is crucial to preserve VA.

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