Case Report

Is it fungal? No, it is not. A case of *Pythium* keratitis from Sri Lanka

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Abstract:

Infectious agents are the commonest cause of corneal ulcers. *Pythium insidiosum* is a fungus-like aquatic oomycete capable of rarely causing human infections. Keratitis caused by *Pythium insidiosum* is associated with high ocular morbidity.

A 13-year-old boy from rural Sri Lanka presented with pain and tearing in the left eye for several days. While there was no history of trauma, he had bathed in a lake. A central corneal ulcer with satellite lesions was found on examination. The ulcer was non-responsive to topical and systemic antimicrobial therapy, and he underwent penetrating keratoplasty. However, the infection recurred and a second penetrating keratoplasty was performed a week later. Fungal studies indicated that both his corneal buttons were positive for *Pythium* species. Continued aggressive antimicrobial therapy resulted in a quiet, vascularised eye with retained perception of light vision.

Pythium keratitis requires prompt and adequate surgical and medical treatment. Clinicians' awareness is important to diagnose this entity early.

Keywords: Pythium, pythiosis, keratitis, corneal ulcer, penetrating keratoplasty

Introduction

The most common cause of keratitis (inflammation of cornea) is microbial infection which can lead to corneal ulceration and blindness.[1] *Pythium* is a parasitic oomycete that was previously classified as a fungus due to its comparable morphology to fungi.[2] However, it does not contain ergosterol in the cell membrane, which is the target site of most antifungal agents.[3]

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Pythium insidiosum is a rare, but important human and animal pathogen, recognized as causing sight-threatening keratitis in humans.[4] Many such patients have been reported from India and Thailand[5,6] while one patient has been reported from Sri Lanka.[7]

There is a significant overlap in the clinical presentation of keratitis caused by *Pythium* and fungi. For instance, epithelial defect, stromal infiltrate with feathery margins, satellite lesions, endothelial exudates, hypopyon and perforation are common to both *Pythium* and fungi.[3] Clinicians therefore tend to treat *Pythium* keratitis with topical and/or systemic antifungals that may not result in clinical improvement.[3]

Unless microbiologists are familiar with this organism, *Pythium* could be misidentified in the laboratory owing to its morphological resemblance to filamentous fungi. Cases of *Pythium* may therefore be under-reported. We report this uncommon case of keratitis in an adolescent to raise awareness among medical professionals.

Case Report:

A 13-year-old boy presented to the National Eye Hospital, Sri Lanka, with left sided eye pain, irritation, profuse tearing and loss of vision for a month. He had been treated initially at a local hospital for three weeks in north central Sri Lanka. On presentation, he had only a light perception in his diseased eye while the other eye had normal vision. He could not recall any ocular trauma preceding these symptoms. However, he had a recent history of bathing in a lake. He denied any previous ocular conditions and he was otherwise healthy.

When he presented initially at the local hospital, visual acuity was 6/18 in the left eye and 6/6 in the right eye. Despite aggressive medical treatment for two weeks with topical 0.5% moxifloxacin 1 drop 2 hourly, 5% natamycin 1 drop 4 hourly, oral ciprofloxacin 500mg 12 hourly and itraconazole 200mg 12 hourly, his vision had deteriorated.

On examination at the National Eye Hospital, he had a central corneal ulcer measuring 3 x 4 mm with irregular margins and multiple surrounding satellite lesions (Figure 1). There was severe conjunctival congestion and mild chemosis. Anterior chamber reaction was present with a 1 mm hypopyon. His globe tension was normal, and the lens was clear. The posterior segment view was not obtainable. Posterior segment B-scan showed clear vitreous with attached retina. Blood investigations revealed he had a normal complete blood count and inflammatory markers. He was normo-glycaemic.

The day after his admission to the National Eye Hospital, a penetrating keratoplasty was performed with corneal trephination of 7 x 7.5mm. An intraoperative washout of the anterior chamber was performed with 1% amphotericin B and natamycin (5%). On postoperative day one, the graft was clear with a persistent 1 mm hypopyon and a small organized hyphaema. His vision improved to hand movement detection. Intraocular pressure was normal. Concurrent topical therapy with 0.5% gatifloxacin (1 drop 2 hourly), 0.3% fortified gentamicin (1 drop 4 hourly), 5% natamycin (1 drop 4 hourly), 0.15% amphotericin B (1 drop 4 hourly) and oral itraconazole 200mg 12 hourly was continued.

By postoperative day 5, the patient's graft became re-infected with multiple suture infiltrates and persistent hypopyon. A larger repeat penetrating keratoplasty was conducted with continuation of the same topical and oral antimicrobial agents.

Gram stain and culture of corneal buttons were negative for bacterial pathogens. However, direct microscopy of the first corneal button with 10% KOH revealed aseptate broad filaments with occasional right angled branches mimicking fungi of *Mucorales*. The direct smear of the repeat corneal button also became positive for similar looking filaments.

Two weeks after inoculation, growth of white, flat, expanding submerged colonies were seen in the fungal culture medium (Sabouraud Dextrose Agar) of both specimens (Figure 2). Tease mounts with lactophenol cotton blue showed hyaline, sparsely septate broad filaments with some branches at right angles (Figure 3). There were endplate-like structures at the end of some filaments. These compatible morphological features allowed the organism to be identified as *Pythium* species.

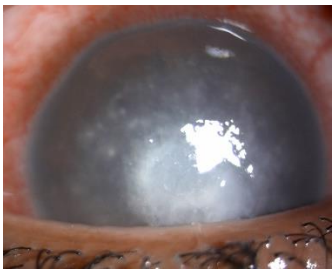

Figure 1: corneal ulcer at presentation to NEH

Figure 2: culture on SDA after 2 weeks of incubation at 26 ^{0}C

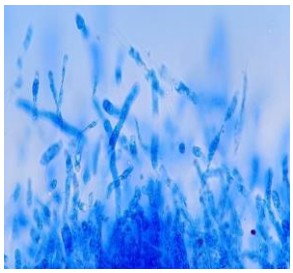

Figure 3: tease mount (Lactophenol cotton blue x 400)

Unfortunately, by the time the aetiology was identified, the patient had already undergone the second penetrating keratoplasty due to failure of the repeat graft, with development of severe anterior chamber inflammatory response. Repeated anterior chamber washouts were performed and resulted in eventual resolution of the inflammatory membrane and hypopyon. Since the infection was eradicated by this time, medical therapy targeting *Pythium* was not indicated in this patient. The patient's vision was maintained at perception of light. His posterior segment ultrasonography was normal throughout.

The time line of the clinical course is shown in figure 4.

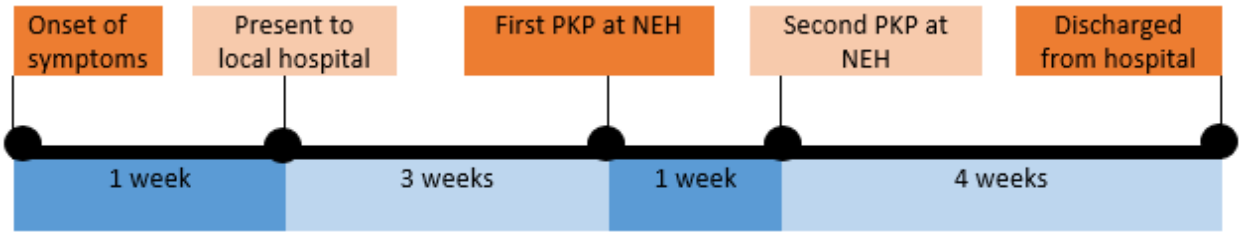

Figure 4: Time line of the clinical course

Discussion:

Among the aetiological agents of fungal keratitis, about 10%–23% of fungal isolates are reported as unidentified due to the lack of sporulation in culture. *P. insidiosum* accounts for 5.5% of unidentified fungal isolates using DNA sequencing.[8]

Possible risk factors for the development of *Pythium* keratitis include exposure to aquatic environments, dirty water, mud, clay, agricultural areas, soil, and dust.[3] This patient is from a rural area of the north central province of Sri Lanka, where residents live in close contact with agriculture and related water bodies.

Clinical signs of *Pythium* keratitis may overlap with that of fungal keratitis. Epithelial defect, feathery margin infiltration and satellite lesions may be seen in both conditions. However, certain features such as patchy reticular dot infiltrates, tentacular projections, guttering, cotton wool like stromal infiltration with indistinct edges and early limbal involvement are considered to be differentiating features from fungal keratitis.[3]

Management of ocular pythiosis is challenging. Due to its rarity, its similarity with fungal infections, and lack of awareness, ophthalmologists may not initially suspect pythium keratitis.[3] *Pythium* keratitis is associated with a poor visual prognosis. High virulence, rapid proliferation rate/ rapid progression and high recurrence rate are some reasons for devastating outcomes. An early penetrating keratoplasty and complete resection leaving unaffected margin is mandatory to achieve a satisfactory outcome.[3]

Since *Pythium* lacks ergosterol in its cell membrane, and ergosterol is the target site of action for most antifungals, antifungals are ineffective against *Pythium* keratitis. In-vitro susceptibility studies have demonstrated the effectiveness of protein synthesis inhibitors like linezolid and azithromycin which are now recommended as first line in the treatment of *Pythium* keratitis.[3]

Knowledge of ophthalmologists and microbiologists on *Pythium* keratitis is important for early diagnosis, which would permit appropriate medical therapy and early surgical intervention.[3] A high degree of suspicion must be maintained in presumed fungal keratitis, which shows poor response to standard antifungal therapy [9].

Declarations

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Conflicts of Interest: No cnflicts of interest.
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Ethics statement: Consent for publication was obtained from the patient and the guardian
Authors' contributions: PGRISW and LSMS carried out laboratory work for the identification of Pythium sp. from the corneal button specimens. SCDS and KRD involved in the clinical management of the patient and provided the patient information for the manuscript. PGRISW wrote the manuscript. PIJ supervised the laboratory procedures and manuscript writing.

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