Variants of ocular meliodosis in Hospital Selayang.

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Background: *Melioidosis is a multi-system infectious disease which is endemic in Malaysia. Melioidosis causing localized ocular infection has rarely been reported. This study highlights the various ocular manifestations of Melioidosis in patients with positive serology for Burkholderia pseudomallei in Hospital Selayang.*

Case Series: *There were three patients in this series. All were immunocompetent, with no systemic evidence of infection. One case had unilateral disease; the other two were bilateral, with common presenting symptoms of pain, redness and blurring of vision.*

All patients had positive serology for Burkholderia pseudomallei and were treated with intravenous ceftazidime and either oral sulfamethoxazole-trimethoprim (Bactrim) or oral cefuroxime for a minimum of two months.

Conclusions: *Melioidosis can manifest as an ocular infection in both the anterior and posterior segments of the eye. The diagnosis is clinical in nature and early empirical therapy should be commenced whilst awaiting confirmatory serology results.*

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Introduction

Melioidosis is an infectious disease caused by the aerobic bacteria Burkholderia pseudomallei. It is endemic in tropical regions like South East Asia and Northern Australia and can result in multi-system infection. The manifestations of the infection are extremely vast, ranging from ocular infections to soft tissue infections, septicemia, pneumonia, osteomyelitis and central nervous system infection.

Burkholderia pseudomallei is the causative agent in a host of multi system infections.

We report a case series of three patients who were treated for ocular Melioidosis based on clinical features and positive serology tests for Burkholderia pseudomallei.

Methods

This was a retrospective case series of three patients with ocular Melioidosis who presented to Hospital Selayang from 2013-2016.

The demographic details (age and gender), case notes, anterior segment and fundus photographs, blood investigations and ocular investigations were analyzed. All patients had serological testing for Burkholderia pseudomallei (IgM levels) which was sent to Institute of Medical Research, Kuala Lumpur for analysis.

Results

Case 1

A healthy 33-year-old lady presented with a five day history of right eye redness and pain. There were no systemic complaints. She denied any risk factors for Melioidosis such as diabetes mellitus, open wounds and environmental or occupational exposure to soil and water.

On examination, VA OD was 6/24 unaided, OS 6/9. Intraocular pressures in both eyes were normal. The right anterior segment had diffuse injection and superotemporal scleral tenderness. The anterior chamber was deep, with plasmoid, fibrinous aqueous, cellular activity of 4+ and a streak of hypopyon. (Figure 1). Fundus examination revealed a normal optic disc, but details of the fundus in the RE were obscured by the anterior media opacity. On B scan ultrasonography, there were no vitreous opacities or loculations and T-sign was absent. The left eye findings were unremarkable. There was no intraretinal or subretinal fluid on optical coherence tomography. Diagnosis of right eye severe anterior sclerouveitis was made. She was commenced on topical dexamethasone 0.1% hourly, topical homatropine 2% 8-hourly and oral ibuprofen 400mg 12-hourly. Blood investigations revealed mild leukocytosis. As the hypopyon level appeared to be rising, she was commenced on intravenous ceftazidime 1gm 12-hourly, topical moxifloxacin 0.5% hourly and given intracameral moxifloxacin.

Meanwhile the serology for Burkholderia pseudomallei returned positive. Blood and aqueous fluid cultures were negative, as were other infectious screening tests. After four days of IV ceftazidime, the VA OD improved to 6/12. The cellular activity had reduced to 1+ and the hypopyon resolved.

She was discharged with oral bactrim (trimethoprin + sulfamethoxazole) 960 mg 12-hourly for eight weeks. Final VA OD improved to 6/9 unaided, with normal ocular findings.

Case 2

A healthy 21-year-old lady with no past medical history was referred for a four month history of redness and pain

in the left eye, which was initially treated as anterior uveitis. Her blood investigations were positive for toxoplasma IgM, so she had been treated with oral clindamycin and prednisolone. She was working as a traditional healer, which involved intermittent exposure to blood and body fluids.

On examination VA OD was 6/9, OS was HM. The right eye was normal. Intraocular pressures were also normal. Left eye examination revealed keratic precipitates, cellular activity of 1+, posterior synechiae and posterior subcapsular cataract. Fundus examination OS revealed a swollen optic disc, oedematous macula with a partial macular star and vitritis. (Figure 2)

Optical coherence tomography demonstrated intraretinal and subretinal fluid OS.

She was commenced on oral doxycycline 100mg 12-hourly as well as topical dexamethasone 0.1% 4-hourly and topical homatropine 2% 8-hourly. Initially there was improvement; however, a few weeks later her vision deteriorated further and there was increase of cellular activity and vitritis. She was empirically started on IV ceftazidime 1gm 12-hourly which was given for six days and topical moxifloxacin 0.5% 4-hourly. Oral prednisolone was started to hasten the resolution of exudation.

Repeat investigations including infective screening, blood and urine cultures were negative. At this juncture, the serology for Burkholderia pseudomallei returned positive.

As her condition improved, the oral steroids were tapered off. She then completed two months of oral bactrim (trimethoprin + sulfamethoxazole) 960mg 12-hourly. Repeated serology of Burkholderia pseudomallei was negative. She was scheduled for LE synechiolysis with cataract extraction and IOL insertion.

On her pre-operative assessment two months later, both eyes had cells of 3+.VA was 6/12 OD and CF 1 feet OS. The RE fundus examination revealed a hyperemic optic disc and macula striation; however, there was no vitritis or retinitis. The repeated Burkholderia pseudomallei serology was positive with a titre of 1:160. IV ceftazidime 1gm 12-hourly was given for 14 days, followed by oral bactrim for 8 weeks and tapering doses of oral prednisolone.

During follow up, whilst still on bactrim (with history of poor compliance), the VA was 6/12 OD and HM OS. There was anterior chamber reaction of 3+ bilaterally and a hyperemic disc OD. Fundus fluorescein angiogram OD revealed leakage from the disc, perifoveal vasculitis and small vessel vasculitis in all quadrants, but no areas of capillary non-perfusion. Repeated Burkholderia serology was now negative, however, she was noted to have positive Bartonella hensei serology. She was started on oral doxycycline 100mg 12-hourly. She subsequently defaulted follow up.

Case 3

A healthy 10-year-old boy presented with a 2-week history of bilateral eye redness, tearing and generalized blurring of vision, which was preceded by fever that resolved with oral antibiotics and anti-pyretics. He had a history of camping two months ago. On examination, VA OD was 6/18, OS 6/24. Both eyes had conjunctival injection, endothelial dusting, cellular reaction of 3+ and anterior vitreous cells of 1+. Bilateral fundus examination revealed swollen discs with periphlebitis and sheathing in all four quadrants with macula striation. (Figure 3). There was no obvious

retinitis or choroiditis. He was commenced on topical dexamethasone 0.5% 2-hourly and topical homatropine 2% 8-hourly for BE whilst awaiting his blood investigation results. On review two days later, his symptoms remained the same, as did the ocular findings. Baseline blood investigations, infective screening, blood and urine cultures and work up for Tuberculosis was normal. There was no subretinal or intraretinal fluid on Optical Coherence Tomography. He was admitted for BE endogenous endophthalmitis and started on IV ceftazidime 25mg/kg 8-hourly and topical moxifloxacin 0.5% 2-hourly BE. After completion of one week of IV ceftazidime, his symptoms improved and VA BE improved to 6/9, with cellular reaction of 1+, with resolving periphlebitis and optic disc swelling. Leptospira serology was negative, and the Burkholderia pseudomallei serology returned positive. He was discharged with oral cefuroxime 250mg 12-hourly after consulting with the pediatrician. One month later his VA had improved to 6/6 BE with no cellular activity and resolution of vasculitis in both eyes. He completed eight weeks of oral cefuroxime and repeat Burkholderia serology was negative. His final VA was 6/6 BE with normal ocular findings.

Figure 1 (Case 1): Anterior segment photograph showing conjunctival hyperemia with hypopyon OD

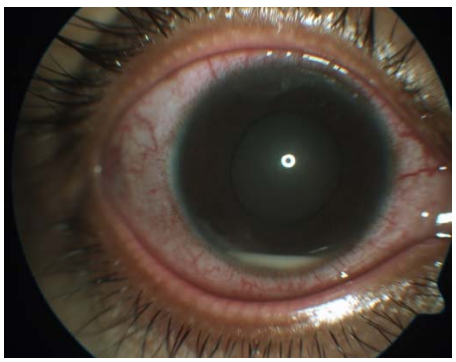

Figure 2 (Case 2): Fundus photo OS showing a swollen optic disc, macular oedema, partial macular star and vitritis

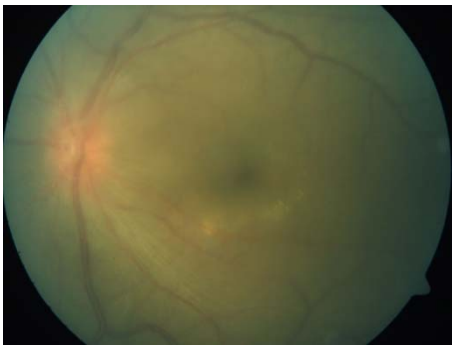

Figure 3 (Case 3): Fundus photo OS showing periphlebitis and optic disc swelling

Discussion

Burkholderia pseudomallei is the causative agent in a host of multi-system infections. The organism is endemic in Southeast Asia and tropical Australia.[1] It is a motile, non-spore forming, aerobic gram negative bacillus which is mostly found in soil and water.[1] Infections secondary to the organism occur following exposure via inhalation, ingestion or skin inoculation to contaminated soil or water.[2] Transmission may rarely occur via contact with infected blood or body fluids in a laboratory setting.[3] There are certain predisposing factors for acquiring melioidosis, the commonest in the Malaysian setting being diabetes mellitus.[4-6] Other risk

factors include environmental and occupational exposure to wet soil and water, chronic renal disease, tuberculosis and immunosuppressed states.

Melioidosis can present as a localized infection, bacteremia or disseminated infection. It can also present as a subclinical infection; however, the incubation period of the disease is not well defined.[1] Melioidosis has even been found to occur without any obvious foci of infection, and the opportunistic nature of the organism results in the infection occurring in healthy immunocompetent individuals without predisposing factors.[7]

The wide spectrum of clinical symptoms, signs and infection sites has earned Melioidosis the title of the "great mimicker".[1, 3, 5] This description has been used to describe the multi-system involvement of Melioidosis. The ocular manifestations of this infection have rarely been reported in the literature. Our case series demonstrates that just like other Melioidosis infections with multi system involvement, isolated ocular Melioidosis can present with various manifestations. The wide spectrum of presentations and lack of clinical evidence of systemic infection renders it a complex clinical problem and poses a diagnostic challenge to the ophthalmologist.

This case series involved three patients with no systemic evidence of Melioidosis who presented with ocular symptoms attributed to Burkholderia pseudomallei, as evidenced by the positive serology results and good response to treatment with intravenous ceftazidime. All the patients were young and healthy with no history of diabetes mellitus or immunosuppression. Two out of the three patients had risk factors that may have contributed to the ocular infection (exposure to blood and history of camping thus having environmental exposure to soil and water), although there was no history of open wounds on the skin.

In case 1, the ocular findings were confined to the anterior segment, however in cases 2 & 3, there were both anterior and posterior segment involvement, with intense inflammation. Ocular fluid (aqueous) was sent for culture in case 1 which did not yield any positive result. This could be due to the scarce volume of fluid available for sampling, resulting in a low yield.

The prevailing gold standard of confirming a clinical diagnosis of Melioidosis is by isolating Burkholderia pseudomallei from clinical specimens.[8, 9] Serological testing is beneficial in endemic areas as it can be used as a preliminary test whilst awaiting positive culture reports which may be time consuming and cause a delay in treatment, however the sensitivity rates are lower than cultures. Examples of serological tests for Melioidosis include indirect hemagglutination assay (IHA), IgM and IgG Enzyme-linked immunosorbent assay (ELISA) and Indirect immunofluorescent test (IFAT).[9] The latter two tests were the serological tests used in our case series, measuring IgM levels. In an evaluation of the assays used in serological testing of Melioidosis, it was found that the IgM-ELISA was 74% sensitive and 99% specific whereas the IgG-ELISA was 96% sensitive and 94% specific.[10]

In all three cases, empirical treatment was commenced whilst awaiting confirmatory serological tests for Burkholderia pseudomallei. Cases 1 & 3 showed good response to treatment with good visual outcomes and no sequelae; Case 2 however defaulted treatment and follow up. The patient in case 2 sought treatment late, hence

further diagnosis and treatment was also delayed.

The recommended treatment for severe septicemic Melioidosis involves a combination of high dose intravenous ceftazidime and trimethoprim-sulphamethoxazole for up to 2 to 4 weeks as the immediate form of therapy, followed by an eradication phase with trimethoprim-sulphamethoxazole or oral doxycycline for 12-20 weeks to prevent recurrences.[11] There are no specific treatment guidelines for localized ocular Melioidosis. The patients in this case series showed a good response with the standard antimicrobial regimes used in combination with topical steroids, as there was a reduction of inflammation and clinical signs after a few days of intravenous ceftazidime in all three cases.

Active ocular Melioidosis is characterized by the patient having symptoms as well as signs of ongoing activity such as inflammation, which correlates with a significant Melioidosis titre. In cases of previous ocular infection, the eye would be quiescent; however, there may be lingering evidence of systemic infection and/or raised titres on serological testing.

The commonest form of presentation of ocular Melioidosis is severe uveitis (which was seen in all 3 cases) and the cases were isolated, without any obvious clues of risks or systemic findings. As ocular Melioidosis can occur in healthy individuals in endemic areas, it is imperative to include Melioidosis serology as a routine blood investigation, as a delay in diagnosis can result in poor visual outcomes, as seen in case 2. Patients with history of exposure to soil, water or blood/body fluids and other risk factors presenting with uveitis which is not responding to the standard treatment of topical steroids should lead the ophthalmologist to consider the diagnosis of ocular Melioidosis and arrange for serological testing. Even in patients without significant history or systemic findings presenting with severe uveitis not responding to treatment (such as in case 1), the ophthalmologist in a region endemic for Melioidosis should consider the possibility of ocular Melioidosis and offer empirical antimicrobial therapy after serological testing has been obtained.

Melioidosis is known in Malaysia for the wide range of systemic infections and it remains a difficult infection to diagnose given its many presentations. As with other forms of Melioidosis, the ocular variant which is localized to the eye may present with various forms of uveitis in a healthy individual. Early treatment can result in complete resolution of infection with no sequelae.

Conclusion

Ocular Melioidosis is commonly underdiagnosed in endemic areas and should be suspected in any severe form of uveitis, especially those which do not respond to the initial treatment. Empirical therapy can be initiated whilst awaiting confirmatory serological testing.

References

1. Puthucheary SD. Melioidosis in Malaysia. Med J Malaysia. 2009;64(4):266-74.
2. Currie BJ. Burkholderia pseudomallei and Burkholderia mallei: melioidosis and Glanders. 2015.
3. Singh M, Mahmood M. Melioidosis: the great mimicker. J Community Hosp Intern Med Perspect. 2017;7(4):245-7.
4. Kingsley PV, Leader M, Nagodawithana NS, Tipre M,

Sathiakumar N. Melioidosis in Malaysia: A Review of Case Reports. PLoS Negl Trop Dis. 2016;10(12):e0005182.
5. Yee KC, Lee MK, Chua CT, Puthucheary SD. Melioidosis, the great mimicker: a report of 10 cases from Malaysia. J Trop Med Hyg. 1988;91(5):249-54.
6. How SH, Ng KH, Jamalludin AR, Shah A, Rathor Y. Melioidosis in Pahang, Malaysia. Med J Malaysia. 2005;60(5):606-13.
7. Zueter A, Yean CY, Abumarzouq M, Rahman ZA, Deris ZZ, Harun A. The epidemiology and clinical spectrum of melioidosis in a teaching hospital in a North-Eastern state of Malaysia: a fifteen-year review. BMC Infect Dis. 2016;16:333.
8. Kritsiriwuthinan K, Wajanarogana S, Choosang K, Homsian J, Rerkthanom S. Production and evaluation of recombinant Burkholderia pseudomallei GroEL and OmpA proteins for serodiagnosis of melioidosis. Acta Trop. 2018;178:333-9.
9. Lau SK, Sridhar S, Ho CC, Chow WN, Lee KC, Lam CW, et al. Laboratory diagnosis of melioidosis: past, present and future. Exp Biol Med (Maywood). 2015;240(6):742-51.
10. Chenthamarakshan V, Vadivelu J, Puthucheary SD. Detection of immunoglobulins M and G using culture filtrate antigen of Burkholderia pseudomallei. Diagn Microbiol Infect Dis. 2001; 39(1):1-7.
11. Inglis TJ, Rolim DB, Rodriguez JL. Clinical guideline for diagnosis and management of melioidosis. Rev Inst Med Trop Sao Paulo. 2006;48(1):1-4.