Endogenous endophthalmitis secondary to melioidosis in paediatric patients: Case series and review article

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ABSTRACT

Endogenous endophthalmitis is a devastating infection of the eye which can lead to permanent blindness. We report two rare cases of paediatric endogenous endophthalmitis secondary to melioidosis with contrasting visual outcomes. Both patients presented with acute painful visual loss with poor vision on presentation after exposure to open water sources (swimming at two separate locations with waterfalls). Both were diagnosed to have melioidosis endogenous endophthalmitis based on the ocular features clinically and via positive melioidosis serology. They otherwise did not exhibit any symptoms and signs suggestive of systemic melioidosis infection. Even though the two children demonstrated severe ocular involvement, ocular culture from vitreous and aqueous sampling taken from one of the patients did not yield any positive results. No ocular sampling was taken from the other patient. After standard antimicrobial treatment, the first patient responded well with good visual recovery without requiring any surgical intervention for the endophthalmitis. In contrast, our second patient ended up with poor visual outcome despite undergoing multiple intravitreal antibiotic injections and early pars plana vitrectomy. This is because he developed extensive retinal detachment due to the aggressive ocular infection. The diagnosis of endogenous endophthalmitis due to ocular melioidosis remains challenging and requires a high index of suspicion in areas endemic for the causative organism. Early empirical antibiotic treatment should be initiated in suspicious cases, even though the treatment outcomes may vary greatly.

1. Introduction

Ocular melioidosis is rarely described in the literature(1). It is a devastating infection of the eye which can lead to permanent blindness. Clinical features range from asymptomatic to typical features of severe uveitis including a red, painful eye with photophobia, floaters, and reduced vision. Up to one-third of patients have bilateral eye involvement. The clinical manifestations...
and outcomes usually correlate with the virulence of the infecting organism[2]. Melioidosis endogenous endophthalmitis is even rarer. Few studies reported that endogenous endophthalmitis is rarely found among the paediatric patients as compared to adults[4,5]. Furthermore, none of the available literature reported any cases of paediatric endogenous endophthalmitis secondary to melioidosis; this has only been reported in adult patients previously[3,4,6,7]. We would like to report on the clinical features and outcomes of two rare cases of paediatric melioidosis endogenous endophthalmitis, as well as to present a review on this condition.

2. Cases report

2.1. Case 1

An 8-year-old girl presented with sudden onset of progressive right eye blurred vision 4 d after swimming at a waterfall. It was associated with pain and redness. She was pre-morbidly well. There was no history of fever, rashes, joint pain, alopecia, loss of weight or appetite and trauma. She was the only one who developed such symptoms amongst her family members who went for the same outing. Visual acuity in the right eye was hand movement (HM). Relative afferent pupillary defect (RAPD) was negative. Eyelids were mildly swollen. Anterior segment examination showed circumcilliary conjunctival injection, corneal oedema and hypopyon. Intraocular pressure was normal. The fundus view was poor. The initial B-scan ultrasonography of the right eye showed flat retina with no vitreous opacity. Left eye vision was 6/6 with normal anterior and posterior segment findings. Systemic examinations were unremarkable. She was diagnosed to have right eye severe anterior uveitis and was started on hourly topical steroid eyedrops. However, the condition worsened within 2 d as B-scan showed vitreous opacities and loculations. (Figure 1). Our infectious diseases colleagues were called in to assist with her diagnosis and management at this time. Serologic testing for melioidosis via enzyme-linked immunoassay was then performed, and the result was positive with high titres (1:320). Otherwise, her full blood count, urine microscopy and cultures, blood cultures and other infective screening for treponemal disease, herpes simplex and toxoplasmosis were unremarkable. She was diagnosed with right eye endogenous endophthalmitis secondary to melioidosis. Intravenous ceftazidime 25 mg/kg TDS and oral amoxicillin/clavulanic acid 20 mg/kg BD were initiated. After completion of systemic antibiotics for a week, visual acuity in the right eye improved to 6/36. Oral amoxicillin/clavulanic acid was continued for 4 months. No vitreous tap or intravitreal antibiotic was given as the child responded well with the antimicrobial agents on board. Two months later, she developed white mature cataract in her right eye (Figure 2) and underwent uneventful right phacoemulsification with intraocular lens implantation and posterior capsulotomy. Her right visual acuity improved further to 6/18 after the cataract surgery.

2.2. Case 2

A 10-year-old boy, also with a recent history of swimming at a waterfall, developed right eye acute redness and pain on the next day. Rapid vision deterioration led him to seek medical attention early. Systemic review was unremarkable. Visual acuity in the right eye was only light perception with positive RAPD. The eyelid was mildly swollen with circumcilliary conjunctival injection, corneal oedema and hypopyon. Intraocular pressure was normal. The fundus view was poor. (Figure 3). The ocular movement was normal in all directions (Figure 4). Anterior and posterior segments of left eye were normal. B-scan ultrasonography of the right eye showed flat retina with no vitreous opacity. Left eye vision was 6/6 with normal anterior and posterior segment findings. Systemic examinations were unremarkable. She was diagnosed to have right eye severe anterior uveitis and was started on hourly topical steroid eyedrops. However, the condition worsened within 2 d as B-scan showed vitreous opacities and loculations. (Figure 1). Our infectious diseases colleagues were called in to assist with her diagnosis and management at this time. Serologic testing for melioidosis via enzyme-linked immunoassay was then performed, and the result was positive with high titres (1:320). Otherwise, her full blood count, urine microscopy and cultures, blood cultures and other infective screening for treponemal disease, herpes simplex and toxoplasmosis were unremarkable. She was diagnosed with right eye endogenous endophthalmitis secondary to melioidosis. Intravenous ceftazidime 25 mg/kg TDS and oral amoxicillin/clavulanic acid 20 mg/kg BD were initiated. After completion of systemic antibiotics for a week, visual acuity in the right eye improved to 6/36. Oral amoxicillin/clavulanic acid was continued for 4 months. No vitreous tap or intravitreal antibiotic was given as the child responded well with the antimicrobial agents on board. Two months later, she developed white mature cataract in her right eye (Figure 2) and underwent uneventful right phacoemulsification with intraocular lens implantation and posterior capsulotomy. Her right visual acuity improved further to 6/18 after the cataract surgery.
injection. There was pus collection in the vitreous cavity. However, the vitreous biopsy showed negative result but melioidosis serology from blood sampling was positive (1:640). He did respond to the treatment initially but 3 weeks later he developed superior and inferior retinal detachment. The right visual acuity remained poor (HM) after vitrectomy with silicone oil tamponade and completion of intravenous ceftazidime 25 mg/kg TDS for 2 weeks and oral amoxicillin/clavulanic acid 20 mg/kg BD for 4 months.

3. Discussion

Melioidosis is an infectious disease caused by the bacterium *Burkholderia pseudomallei* (*B. pseudomallei*). It is a Gram negative, motile rod-shaped bacterium. It is commonly found in contaminated water and soil. It can be acquired by inhalation of dust, ingestion of contaminated water, or contact with contaminated soil, especially through skin abrasions. It is endemic to Southeast Asia including Thailand and Malaysia and also in northern Australia as well as regions between 20° latitude north and south of the equator[8]. Although melioidosis is endemic in Malaysia, the prevalence data is limited. An estimated incidence of melioidosis in Malaysia per 100 000 population was higher in males at 4.8 (2013) and 2.4 (2014) as compared to females at 3.0 (2013) and 1.7 (2014)[9]. Melioidosis is strongly associated with occupational and recreational exposure to surface water and mud, particularly with flooding of rice paddies[10]. Therefore farmers are at higher risk of getting melioidosis due to their exposure to the organism[3]. The route of transmission is through inoculation, inhalation and ingestion. A study regarding seropositive melioidosis conducted in Malaysia showed that children less than 15 years old were the most vulnerable group for melioidosis due to their immature immune system[9]. They found that the region of stay in Malaysia is also one of the independent risk factors for exposure against *B. pseudomallei*. The incidence of seropositive cases per 100 000 population was higher in eastern coast states such as Kelantan, Terengganu and Pahang (8.3 in year 2013 and 4.5 in year 2014). Both our patients were from Kedah, where the stated incidence rate was 2.7 and 1.9 in year 2013 and 2014 respectively[9]. In systemic melioidosis, mostly are asymptomatic or present as a self-limiting, short-term, flu-like illness and can be diagnosed only by serology[11]. In our two patients, both had history of swimming at a waterfall (at different locations) prior to the onset of ocular melioidosis. The organism most likely gained entry from ingestion or contact with contaminated water or soil at the waterfall.

Paediatric endogenous endophthalmitis accounts for only 0.1% to 4% of all cases depending on the country; the highest incidence of cases reported has been in India, with the lowest in the United States[12]. The most common primary source of infection in paediatric endophthalmitis include wound infection, meningitis, endocarditis, urinary tract infection and indwelling intravenous catheters, or haemodialysis fistulas[13]. A high index of suspicion together with thorough history-taking and physical examination are required to determine the source of infection in endogenous endophthalmitis.

The commonest ocular manifestations of melioidosis are orbital cellulitis, followed by endophthalmitis, panophthalmitis, preseptal cellulitis and panuveitis[3]. Among cases reported in a study conducted in India by Murugan et al, the common causative agents for paediatric endogenous endophthalmitis were *Staphylococcus*, *Pseudomonas aeruginosa*, *Neisseria meningitidis* and fungi. None was caused by *B. pseudomallei*. Among the published case reports in adults, a broad disease spectrum was described[2,3]. Most of the patients (63%) with ocular melioidosis presented with eye symptoms instead of systemic complaint. The remaining 37% presented with fever or headache[3]. Ocular symptoms include a painful red eye with sudden severe reduced in vision as seen in both our patients. Vision upon presentation is usually poor (counting fingers or worst). Ocular signs include an afferent pupillary defect, corneal oedema, raised intraocular pressure, hypopyon, retinal infiltrates, subretinal gliosis or subretinal abscess and retinal detachment. The abscess-forming activity of *B. pseudomallei* may explain the reason behind the purulent intraocular findings.

It is postulated that in endogenous endophthalmitis, damage is most probably due to a septic embolus that enters the posterior segment.
| Ref | Symptom | Initial VA | Ocular findings | Investigations | Treatment | Outcome |
|-----|---------|------------|----------------|---------------|-----------|---------|
| [4] | Right eye pain and OD: Light perception headache for 1 d. | Marked chemosis, corneal, vitreous and blood edema, hyphema, and culture showed B. pseudomallei; elevated intraocular pressure; On day 11: Hypopyon and a localized scleral suppuration; The vitreous echoes were heterogeneous with a fluffy retinal surface. | Intravitreal injection of His illness progressed to 1 mg of vancomycin septic shock and multiple hydrochloride, 0.4 mg organ failure, and the of amikacin sulfate, and patient died on day 18. 0.4 mg of dexamethasone sodium phosphate; Topical vancomycin hydrochloride (50 mg/mL) and amikacin sulfate (25 mg/mL); Systemic ceftazidime, cotrimoxazole, and granulocyte colony-stimulating factor were administered. | | |
| [5] | Fever and chills for 1 OD: counting fingers; month with dysuria. | The anterior segment Urine culture showed demonstrated fine keratic precipitates, fibrin over the pupillary margin, posterior synechia at the 2 o’clock position, and a 1-mm hypopyon; Fundus examination revealed grade III opacity with yellowish infiltration (subretinal hypopyon) at the superior midperipheral area of the choroid. | Intravitreal injections of Final visual acuity was vancomycin (1 mg/0.1% 2/6/18 in the right eye. mL) and ceftazidine (2.25 The anterior segment mg/0.1 mL); demonstrated no reaction, Topical vancomycin except residual posterior (25 mg/mL, hourly), synechia. ceftazidime (50 mg/ Fundus examination mL., hourly), and 1% showed choroidal prednisolone acetate (four scarring with subretinal times per day); fibrosis over the area. Four weeks of Four of intravenous of the choroid that was ceftazidine and 3 months previously infiltrated. | | |
| [6] | Fever with dyspnea OS: Hand movement for 12 d, left eye with good light 4+, positive RAPD; inflammation perception was found during admission. | Corneal bedewing, AC cells Hemo culture: no PPV with silicone VA HM, AC deep with o i l, E C C E, IV plasmoid, attached retina. Intraoperative findings: Melioidosis titre 1:5 ceftazidime then oral sulfamethoxazole-trimethoprim. | Hemoculture: no growth; melioidosis growth; Melioidosis titre 1:5 Pavmacyn and ceftazidime. | | |
| | | Conjunctival chemosis, Hemo culture: no IV ceftazidime then VA 3/60, VA with pinhole 4/60; | | | |
| | | Painless visual loss OS: Poor light 1 month then painful perception proptosis for 2 d. | | | |
| | | Right eye contact OD: No light with wood particle perception for 10 d then drop of breast milk into the eye. Four days then acute visual loss for 2 d, IVT vancomycin, ceftazidime at provincial hospital. | Intraop finding: subretinal abscess. | | |
| | | Present study Right eye pain, redness OD: Hand movement and blurred vision for 4 d. | Multiple keratic precipitates Gram stain from Enucleation. IV Good enucleation wound. | | |
| | | Right eye pain, redness OD: Light perception and blurred vision for 1 d. | Intraocular ceftazidime Developed right mature 675 mg TDS for 1 week cataract. Her right visual and oral amoxicillin/acytym improved further chloramycin 552 mg to 8/18 after the cataract B D. She completed surgery. | | |
vascular. This acts as a nidus for dissemination of the organism into the surrounding tissues. It then leads to microbial proliferation with concurrent inflammatory reaction within these tissues after crossing the blood-ocular barrier. Infection then extends from the retina and the choroid to involve the vitreous cavity and thereafter to the anterior chamber of the eye[14]. Therefore, any ocular infection with pus collection in the eyes may warrant further investigation to rule out melioidosis, especially if there was suggestive history and the organism is endemic in that particular locality.

In our patients, both were systemically well. The prompt presentation after their parents noticed the presence of painful eye redness probably contributed to their otherwise good general condition. In the acute bacteremia stage, B. pseudomallei reaches the ocular tissue via blood stream and may not manifest as sepsis where patients might be systemically ill. However, early onset of sepsis does occur, where it was reported in premature very low birth weight neonates[6]. In patients who initially presented with sepsis, parental administration of antibiotic does not lessen the risk of ocular involvement[2]. In ocular melioidosis, a key diagnostic finding associated with an endogenous cause is the presence of a white infiltrate originating in the choroid which might erupt into the vitreous cavity. B-scan ultrasound can help identify vitritis or chorioretinal infiltrates if the posterior segment cannot be visualised. The morbidity in these cases was high whereby these patients may end up with evisceration[5].

Based on the literature search from Pubmed, searching using key words such as paediatric, melioidosis, endogenous, endophthalmitis and ocular melioidosis, we encountered only eight cases of melioidosis endogenous endophthalmitis from year 2006 till 2018[1-3], including our current case series. This is summarised in Table 1. For this review, primarily only those articles relevant to melioidosis endogenous endophthalmitis were included. The subjects’ ages ranged from eight to 70 years old, where the two paediatric subjects were from our case series. Six out of the eight cases of melioidosis endogenous endophthalmitis were from the Southeast Asian countries of Thailand and Malaysia while the remaining two cases were from Taiwan. This reflects the fact that Southeast Asia is an endemic region for melioidosis infection. Recent reports also stated that China, Taiwan and Laos are melioidosis endemic area as well[2].

Five of the subjects presented initially with ocular symptoms such as reduced vision (duration of symptom ranging from as early as one day to progressive visual loss for one-month duration) and painful eye redness; three did not exhibit any symptoms. The three had either delayed onset of ocular findings or had incidental eye findings when they presented with systemic complaints such as fever and constitutional symptoms. One of the studies stated that the right eye is more commonly involved in endogenous endophthalmitis. This is probably due to the more direct route through the right carotid artery[13]. In our review, the affected eye is also predominantly the right eye (in five of the eight patients).

All eight patients had poor visual acuity (counting fingers or worse) at initial presentation. The ocular findings were also wide-ranging and varied, from mild eyelid erythema and conjunctival chemoisis, features of severe anterior uveitis (such as keratic precipitates, anterior chamber cells and hypopyon, and posterior synechiae) to more severe posterior segment inflammation such as vitritis and subretinal abscess. Due to excessive intraocular inflammation, a proper and accurate visualization of the posterior segment might be difficult. This is where the imaging of ocular tissues has its role as a diagnostic modality in detecting the abnormalities and to determine the presence of complications from the disease itself. A B-scan ultrasound can reveal the presence of hyperechoic exudates in the vitreous cavity. Choroidal abscess or retinal detachment can also be identified via B-scan. Thus, the B-scan is an important tool in decision-making regarding further surgical intervention as well as a prognosticator for visual outcome after treatment.

The most reliable way of diagnosing systemic melioidosis infection is through isolation of the organism via cultures of tissue samples. Although B. pseudomallei grows on blood agar and MacConkey agar, it is often dismissed as a culture contaminant or misidentified as Pseudomonas species when non-sterile clinical or environmental specimens are cultured. This is when the serology comes to its role of diagnosis. Melioidosis seropositivity is defined as having a titre of greater than 1:160[9]. Our case series had shown higher rates of seropositivity from blood sampling as compared to vitreous aspirate possibly due to the larger volume sampled. It is also important to obtain cultures other extraocular sites (e.g. urine, cerebrospinal fluid, pus collection from skin or liver) to identify the possible nidus of infection and guide systemic therapy accordingly. Identification of these infectious foci is particularly important in cases where vitreous cultures are negative. From our review, among ocular fluid/vitreous samples taken, only one patient had culture-positive B. pseudomallei isolated from the vitreous. The others were diagnosed based on high titres of melioidosis serology from blood or urine (the titre ranging from 1:320 till 1:5 122). In our case series, the second patient was treated for melioidosis endogenous endophthalmitis based on the clinical findings and the high seropositivity (1:640) even though his ocular culture was negative. In contrast, our first patient did not undergo any vitreous or aqueous fluid sampling as she responded well with the initial treatment of topical and systemic antibiotics after her blood serology came back positive for melioidosis.

There might be a correlation between the serology titres and the severity of the ocular disease manifestation. In our case series, Case 1 subject had one of the lowest melioidosis serology titres (1:320) as compared to the rest. Consequently, the ocular manifestation of endogenous endophthalmitis was relatively mild in her. Only medical therapy was necessary in her case and she managed to regain her vision to 6/18 after completion of treatment. She was among the two patients who achieved a good visual outcome in this review. From our review of the eight subjects, the initial treatment was intravitreal antibiotics (2 patients), pars plana vitrectomy (2
patients), intravenous antibiotics only (3 patients). Enucleation was done for one patient as the initial treatment, while another patient had enucleation done after developing a painful blind eye about a week after being allowed home. Most of the visual outcome were poor despite a standard recommended treatment being given. In view of highly virulent B. pseudomallei, ocular melioidosis frequently end up with devastating complications such as cataract development, retinal detachment, intraocular abscess, suprachoroidal haemorrhage and vitreous haemorrhage[4]. Recurrent or persistent intraocular infection may require multiple intravitreal antibiotics injection and surgery.

B. pseudomallei is generally susceptible to trimethoprim-sulfamethoxazole, broad-spectrum cephalosporins, and carbapenems. Treatment is divided into acute and eradication phase. In acute phase, parenteral drugs are given for more than 10 d to prevent death from overwhelming sepsis whereas in eradication phase, oral drugs are given to prevent relapses. Eradication therapy recommendations are usually to complete the oral antimicrobial for a total of 20 weeks. Intravenous ceftazidime is the first line treatment in acute phase whereas carbapenems are reserved for severe infections or treatment resistant cases. The second line therapy is amoxicillin/clavulanic acid (co-amoxiclav). Oral antimicrobial therapy of choice is trimethoprim-sulfamethoxazole (co-trimoxazole) and co-amoxiclav[15]. Centres of disease control and prevention recommend that to treat melioidosis, generally start with intravenous antimicrobial therapy for 10-14 d, followed by 3-6 months of oral antimicrobial therapy[16]. In our first patient, she had completed the acute phase treatment for one week duration whereas the second patient completed for two weeks. Both completed the eradication phase of four months duration.

For an effective eradication of the intraocular organism in endophthalmitis, early and complete vitrectomy is highly recommended[17]. The vitreous humour is a nutrient-rich reservoir which is ideal for the replication and proliferation of microorganisms. The intravitreal microorganism causes severe inflammation in various ways. Firstly, the eye’s inflammatory response towards the foreign pathogen may lead to poor vision due to cystoid macular oedema and epimacular membrane formation. Secondly, the endotoxin and exotoxin secreted by the microorganism are usually accumulated and sequestrated within the vitreous cavity, leading to widespread retinal necrosis (as seen in our second patient). Most of the cases with melioidosis-related endophthalmitis and panophthalmitis required surgical intervention such as pars plana vitrectomy and enucleation[3]. Complete and early vitrectomy for endophthalmitis will dramatically reduce the inflammatory debris load in the vitreous cavity and provide a large specimen for diagnostic evaluation. Vitrectomy also allows direct inspection of the retina by removing the non-transparent medium. This might help to increases the access of intravitreally administered antibiotic to the retina as well[16]. The indication for early vitrectomy is by the clinical appearance and course instead of presenting visual acuity. In patients with poor red reflex and rapid deterioration, early vitrectomy may be indicated to prevent further damage to the intraocular structures, leading to irreversible visual loss. Debulking the infectious and inflammatory debris in the eye also hasten the clearance of the offending pathogen, thus may lead to the reduction in the risk for enucleation or evisceration[17]. The visual prognosis of endophthalmitis is generally poor. However, in the two cases described above, they had widely contrasting outcomes. The main predicting factor is the severity of ocular findings upon presentation. Both patients presented with poor vision but the unfortunate boy in the second case with RAPD positive ended up with a poorer visual outcome (developed retinal ischemia with retinal detachment) even though a more aggressive treatment was given.

4. Conclusion

Diagnosis can be challenging in ocular culture negative melioidosis endogenous endophthalmitis. A high index of suspicion is crucial in this subgroup of patients especially in endemic areas, as late or suboptimal treatment may lead to potentially life- or sight-threatening complications. Early empirical antibiotic treatment should be commenced promptly in suspicious cases even though the treatment outcome might vary.

Conflict of interest statement

The authors report no conflict of interest.

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