ACUTE DISSEMINATED ENCEPHALOMYELITIS FOLLOWING INFECTION WITH *MYCOPLASMA PNEUMONIAE* AND *BURKHOLDERIA PSEUDOMALLEI*: A CASE REPORT

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Abstract. Acute disseminated encephalomyelitis (ADEM) is an immune-mediated, monophasic demyelinating disease that predominantly occurs in children with post-viral infection or post-vaccination setting but rarely after infection with *Mycoplasma, Burkholderia, Chlamydia, Legionella, Campylobacter* or *Streptococcus*. We present here a case of a 5-year-old girl with a history of cough for 2 months, fever and altered consciousness. She was treated with 2 courses of oral antibiotics prior to admission. An initial cerebrospinal fluid specimen obtained showed lymphocytic infiltration suggesting resolved pneumonia complicated with meningoencephalitis. She was initially treated with a 3-week course of intravenous azithromycin for *Mycoplasma. pneumoniae* infection as serum mycoplasma antibody titer was elevated. A subsequent alteration in sensorium warranted a magnetic resonance imaging of the brain, which was consistent with ADEM and steroid therapy was instituted. However, there were persistent fever and thrombocytosis; laboratory testing at this point revealed elevated *Burkholderia pseudomallei* IgM antibody titers. She received a total of 8 weeks of intravenous meropenam and trimethoprim/sulfamethoxazole followed by an additional 6 months of oral trimethoprim/sulfamethoxazole. She recovered completely without any residual symptoms. Patients who present with neurological symptoms with a history of recent infection with *M. pneumoniae* and/or *B. pseudomallei* should be evaluated for the presence of ADEM and treated accordingly.

Keywords: Acute disseminated encephalomyelitis (ADEM), *Burkholderia pseudomallei*, *Mycoplasma pneumoniae*

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INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated demyelinating disorder with an incidence of 0.64 per 100,000 patients per year (Torisu *et al*, 2010). Central nervous system (CNS) complications associated with *Mycoplasma pneumoniae* (MP) infection are reported in up to 0.01% of cases (Dawson *et al*, 2016) but with *Burkholderia pseudomallei*, CNS complications are rare. The clinical manifestations of *Mycoplasma* and *Burkholderia* infections (melioidosis) are heterogeneous. The onset of ADEM is usually sudden and patients may present with non-specific prodromal symptoms, such as fever, malaise, myalgia, headache, nausea or vomiting (Esposito *et al*, 2015). Encephalopathic signs due to ADEM, including restlessness, lethargy, hallucinations, confusion and altered sensorium, begin 4-21 days after the onset of prodromal symptoms (Tenembaum *et al*, 2007). Subjects with ADEM may have focal or multifocal neurological signs, such as hemiparesis, paraparesis and cranial nerve palsies, and have a higher risk of mortality and morbidity (Cole *et al*, 2019; Nishiyama *et al*, 2019).

There are no evidence-based recommendations for the treatment of patients with ADEM due to *Mycoplasma* or *Burkholderia*. Understanding the pathophysiology of ADEM associated with *Mycoplasma* and *Burkholderia* infections may inform future treatment and improve patient outcomes.

Case report

A previously well 5-year-old girl presented to our hospital with a high-grade fever for 10 days and a non-productive cough for 2 months. This was associated with post-prandial vomiting and poor oral intake. Prior to her admission, she had received a one-week course of oral amoxicillin followed by a five-day course of azithromycin from her general practitioner. She had a poor appetite but no other constitutional symptoms. She had no history of a recent head trauma or fall. She had no contact with pets or ingestion of unpasteurized milk.

The patient and all her family members had cough during the previous 2 months prior to admission. The family members were screened for tuberculosis (TB) by chest radiography and with the Mantoux test: the results of which were all negative. Although the symptoms resolved in the other family members, the patient's cough persisted.

The patient's past history was significant for a left temporo-parietal skull fracture with small epidural hemorrhage following a fall at age 11 months which was treated conservatively. The patient had no history of seizures after the fracture and she met all her developmental milestones normally.

During hospitalization, the patient had an episode of right-sided facial twitching and lip smacking with no limb involvement that lasted less than 5 minutes and resolved spontaneously. This episode was followed by post-ictal drowsiness.

On examination at admission, the patient was fretful but alert. Her temperature was 38.5°C, her pulse rate was 100 beats per minute, her blood pressure was 100/60 mmHg, her respiratory rate was 26 breaths per minute and her oxygen saturation on room air was 100%. Her cranial nerve examination, including fundoscopy, was normal; she had no nuchal rigidity. Neurologically, she had normal muscle tone but was hyperreflexic on both upper and lower extremities. She had non-sustained clonus and her Babinski examination was positive in the right lower limb. Her respiratory examination revealed normal breath sounds bilaterally. She had no lymphadenopathy or hepatosplenomegaly.

Her initial complete blood count revealed leukocytosis (white blood cell counts of 26.6×10^9 per liter) and was predominantly neutrophilic (75% neutrophils). She had thrombocytosis (platelet count of 673×10^9 per liter), an elevated C-reactive protein (CRP) of 17.2 mg/dl) and an elevated erythrocyte sedimentation rate (ESR) of 30 mm/hour. Her glucose and urea levels, electrolytes and liver function testing were all normal. Her chest radiograph was also normal.

Her cerebrospinal fluid (CSF) revealed leukocytosis with predominant lymphocytes (105 white blood cells/mm^3 with majority lymphocytes). The protein and glucose levels in the CSF were initially normal and the latex agglutination test was negative for *Haemophilus influenzae* Type b, *Streptococcus pneumoniae*, *Streptococcus* group B and *Neisseria meningitidis* groups A, B, C and Y.

Contrast-enhanced computed tomography (CECT) of brain was performed the following day which showed marked diffuse leptomeningeal enhancement suggestive of meningitis with no evidence of a focal brain lesion (Fig 1).

She was empirically treated with intravenous ceftriaxone and acyclovir but continued to have high-grade fever and upper motor neuron signs (hypereflexia, clonus and Babinski in the right lower limb). Her blood, CSF and urine cultures came back negative. After 7 days of hospitalization, her antibiotics were thus escalated to intravenous meropenam and azithromycin. Her serum mycoplasma IgM titer was tested and came back as >1:320. This titer eventually was reduced to 1:80 after completion of therapy.

However, on Day 12 of admission, her mood was labile and she became increasingly drowsy as well as refused to ambulate. Magnetic resonance imaging (MRI) of the brain demonstrated disseminated bilateral asymmetrical subcortical white matter hyperintensities at both cerebral hemispheres, corpus callosum and right thalami, consistent with changes of ADEM (Figs 2a and 2b). She was treated with intravenous methylprednisolone immediately after her MRI for 5 days followed by a tapering dose of prednisolone which resulted in marked improvement in terms of mobility and interaction with her parents. Despite an improvement noted, there was persistent, intermittent low-grade fever and thrombocytosis

(platelet of 640-670×10^9 per liter).

A repeat CECT of the brain showed residual leptomeningeal enhancement; an alternative diagnosis was sought. A gamma quantiferon test for tuberculosis was performed, which was negative. A Mantoux test was negative. A gastric lavage and CSF examination for acid fast bacilli (AFB) smears were negative. A polymerase chain reaction test and culture for tuberculosis were both negative. A CSF sample for herpes simplex virus (HSV) types 1 and 2 and adenovirus were negative. Anti-N methyl D-aspartate test and Leptospira IgM screen were negative. An autoimmune screen, echocardiogram and ultrasound of the abdomen were all normal.

On Day 21 of hospitalization, *B. pseudomallei* antibody titer test showed a titer of 1:640 and intravenous trimethoprim/sulfamethoxazole (TMP/SX) was added to meropenam therapy. Her fever resolved one week after the initiation of TMP/SX. A repeat CECT brain normalized 5 weeks after the patient became afebrile. A repeat CSF examination at that time revealed polymorphic pleocytosis of 30 cells/mm^3 and a low CSF glucose level of 2.7 mmol/l. The patient received a total of 8 weeks of intravenous meropenam and TMP/SX till the repeat CSF finding was normalized.

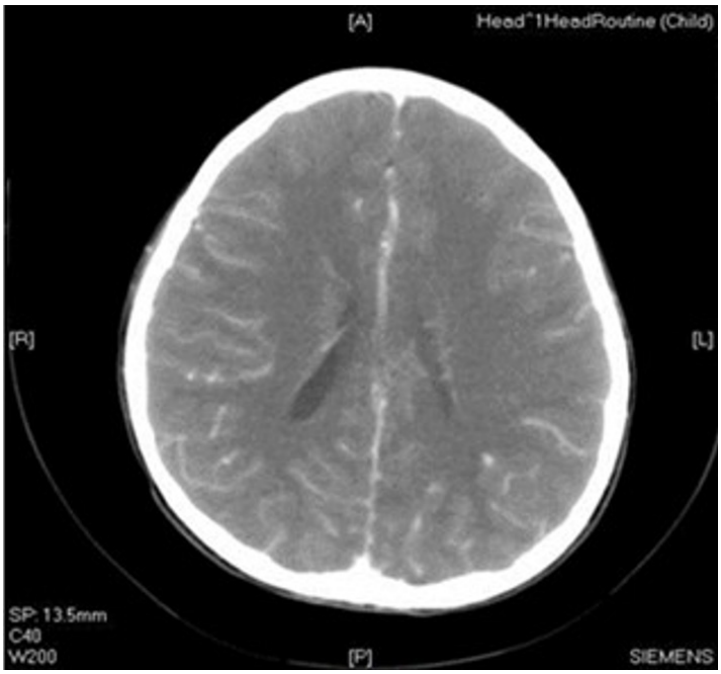

Fig 1 - Contrast Enhanced Computed Tomography (CECT) brain (axial CT at level of body of lateral ventricles) at day one of admission showing marked diffuse leptomeningeal enhancement

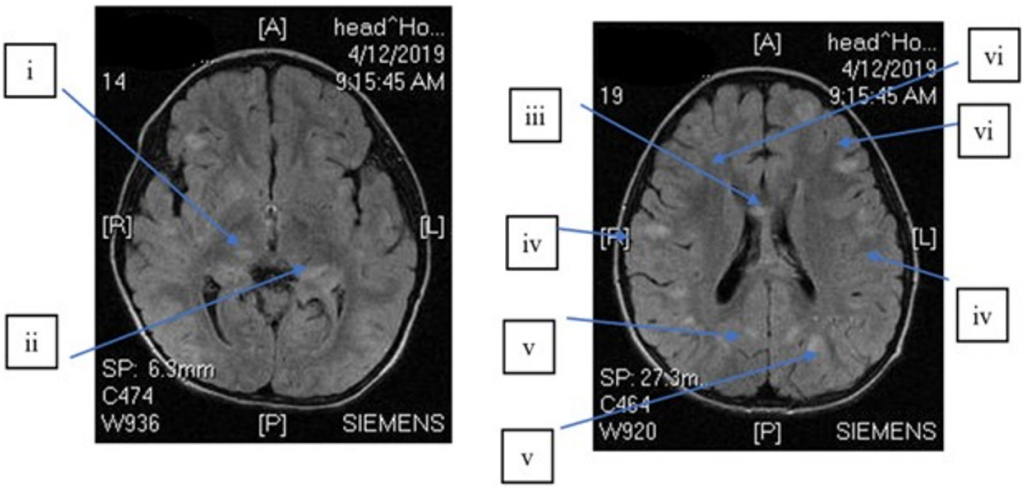

Fig 2 - MRI T2/FLAIR of the brain shows disseminated asymmetrical white matter hyperintensities

(2a) i: Right thalami; ii: Left hippocampi

(2b) iii: Corpus callosum; iv: Bilateral subcortical temporal lobes; v: Bilateral subcortical occipital lobes; vi: Bilateral subcortical frontal lobes

She was discharged after 11 weeks of hospitalization with a 6-month course of eradication therapy with oral TMP/SX. Within 24 hours after discharge, she was readmitted with chorea on exertion. Apart from chorea, the remaining neurological examination was unremarkable. She was diagnosed with having post-infectious chorea which resolved spontaneously after 2 days. A repeat MRI of the brain was performed 2 months after discharge which showed resolution of the subcortical white matter lesions. She remained asymptomatic after completion of the 6-month course of TMP/SX.

DISCUSSION

The patient had ADEM diagnosed based on her febrile encephalopathic presenting features, coupled with an initial lymphocytic CSF result and a compatible MRI findings of bilateral diffuse, asymmetrical subcortical white matter hyperintensities in the brain (Cole *et al*, 2019; Esposito *et al*, 2015). However, the CSF findings, clinical course of fever and thrombocytosis, and the treatment response despite on standard steroid therapy for ADEM, were not consistent with the classical presentation. In this case, we postulated the patient had a

dual infection with *M. pneumoniae* and *B. pseudomallei* (melioidosis), since the serology for both infections were positive and she improved with treatment for both these infections and this dual infection could have triggered ADEM.

M. pneumoniae generally causes respiratory infections but there are several case reports in the literature where ADEM occurred due to *M. pneumoniae* infection (Dawson *et al*, 2016; Laila *et al*, 2018). The exact pathogenesis of ADEM associated with *M. pneumoniae* infection may be an autoimmune disorder where the anti-*M. pneumoniae* antibodies invade the myelin (D'Alonzo *et al*, 2018). In our patient, we could not obtain a PCR test for *M. pneumoniae* from the CSF but we hypothesized *M. pneumoniae* infection could have caused her ADEM. The *M. pneumoniae* antibody seroconversion, its association with symptoms of prolonged cough, the absence of other abnormal respiratory findings and the presence of encephalitis suggest *M. pneumoniae* infection as an etiology for ADEM in this patient.

The persisting abnormal findings on CSF examination and the positive serology for *B. pseudomallei* suggest this patient also had neuromelioidosis. A similar case of melioidosis of the brain confirmed by brain biopsy was reported previously (Ekka *et al*, 2017). Melioidosis is difficult to diagnose. The gold standard for diagnosing melioidosis is having a positive culture for *B. pseudomallei*, which has a low sensitivity and low negative predictive value (Limmathurotsakul *et al*, 2007). Serology for melioidosis provides additional supporting evidence for a diagnosis but the results must be interpreted in the context of the clinical course and response to treatment.

The features of central nervous system infection in children can be subtle, variable, non-specific or even absent (Kim, 2010) as was the case in this patient. This is especially true among individuals with atypical presentations or prolonged fever where establishing the diagnosis can be challenging and dual infections must be suspected in these cases. The role of antibiotics is unclear among patients with a central nervous system infection due to *M. pneumoniae*. Systemic antibiotic is mandatory as associated encephalopathy results in increased morbidity and mortality (D'Alonzo *et al*, 2018). A macrolide antimicrobial is the drug of choice for patients with a central nervous system infection caused by *M. pneumoniae* due to its safety profile, cost effectiveness and strong immune-modulatory effects (D'Alonzo *et al*, 2018). Melioidosis of the central nervous system should be treated with an 8-week intensive regimen with meropenam or ceftazidime along with TMP/SX, doxycycline or amoxicillin-clavulanate, followed by a 6-month course of TMP/SX (Dance, 2014; Limmathurotsakul *et al*, 2007; Pitman *et al*, 2015).

This case highlights the importance of checking serology testing to diagnose melioidosis and *M. pneumoniae* infection in patients with suspected infection but with a negative culture and for those who were previously treated with antibiotics.

Serology testing is especially useful in limited resource settings where PCR facilities are not readily available or the exorbitant cost in testing. A high index of suspicion is necessary in melioidosis endemic areas. Melioidosis of the central nervous system should be considered in the differential diagnosis of a patient who presents with prolonged fever and meningitis. *M. pneumoniae* infection of the central nervous system should be considered in the differential diagnosis of a patient with prolonged respiratory symptoms and a negative workup for tuberculosis.

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CONFLICT OF INTEREST DISCLOSURE

The authors declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

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