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Case Report

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Meliodosis Presenting as Rhombencephalitis with Antiganglioside Antibody Positivity

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Abstract

Background: Neuromelioidosis is a rare infection caused by *Burkholderia pseudomallei* with a predilection for brainstem involvement. The association of anti-ganglioside antibody positivity with neuromeliodosis has not been reported in literature so far.

Methods: We present a case of a 53-year-old woman with neuromeliodosis presenting as rhombencephalitis, with lesions later extending *via* the white matter tracts along with secondary demyelination. Her evaluation showed a strong positivity for anti-ganglioside antibodies. She was treated with antibiotics and other supportive measures. During the initial clinical deterioration phase, plasma exchange was done. Later, in view of slow response, stereotactic brain biopsy was done and the culture specimen grew *Burkholderia psuedomallei*. The association of anti-ganglioside antibody positivity also supports the initial response to immune mediated therapy.

Conclusion: Neuromeliodosis has a predilection for brain stem involvement with a high propensity to involve and spread along the white matter tracts. The presence of high titres of antiganglioside antibody may give a clue when there is difficulty to isolate the organism from CSF. High index of suspicion is very important for a better outcome.

Keywords

Neuromeliodosis, Rhombencephalitis, Anti-ganglioside antibodies, GD1b, GM1, *Burkholderia pseudomallei*

Introduction

Melioidosis is an infectious disease caused by gram-negative bacterium, *Burkholderia pseudomallei*, an endemic disease in northern Australia, Thailand and South Asia. Almost every organ can be affected by the organism, but the central nervous system (CNS) melioidosis is very rare [1]. The causative organism is resistant to a range of antimicrobial agents and ineffective therapy can result in high case fatality [2]. We report a rare case of Neuromeliodosis presenting as rhombencephalitis with parainfectious demyelination and a strong positivity for anti-ganglioside antibodies.

Patient Description

A 53-year-old lady, living in an urban area, belonging to an upper middle

class family with no comorbidities presented with history of prolonged vaginal bleeding for 1-month, fever of 5-days duration followed by vomiting, vertigo, dysarthria and ataxia. There was no history of headache, cognitive issues, weight loss or any other constitutional symptoms in the recent past. She used to bake cakes, consequently handled raw eggs. There was no cutaneous wounds or injuries prior to the onset of her symptoms.

On admission, she was conscious and oriented, with dysarthria, right gaze evoked nystagmus, dysmetria and ataxia. The cerebrospinal fluid (CSF) study done showed 5 cells/mm^3, all neutrophils, normal sugar and protein levels. Her magnetic resonance imaging (MRI) of the brain with gadolinium contrast study showed ill-defined T2/FLAIR hyperintense lesion with mass effect in right middle cerebellar peduncle and adjacent cerebellar hemisphere with multiple ring enhancing components (Figure 1). MR contrast perfusion study showed hypoperfusion within the lesions suggestive of a benign or infective lesion. Hence, the possibility of rhombencephalitis, probably of an infectious etiology such as listeria/neuromeliodosis/tuberculosis, was considered. Her paraneoplastic work up including computed tomography (CT) chest and abdomen contrast study was negative. Endometrial biopsy done, in view of prolonged vaginal bleeding was non-contributory. Additionally, her serum was negative for paraneoplastic anti-neuronal antibody panel.

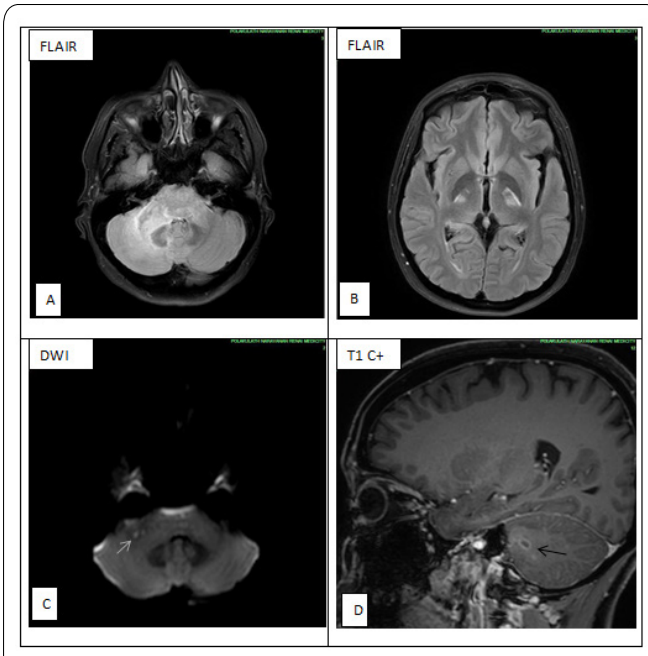

Figure 1: Initial magnetic resonance image of the brain: FLAIR axial images **A** and **B**- show hyperintense lesion in the right middle cerebellar peduncle, also involving the cerebellar hemisphere. In addition hyperintensity was seen extending supratentorially along bilateral corticospinal tracts. DWI axial images **C**- showed few small foci of diffusion restriction (white arrow). Small nodular and ring enhancing lesions were seen in post contrast T1 sequence **D**- sagittal image (black arrow).

She developed lower motor neuron type of facial weakness on the second day of admission with gaze palsy, slurred speech with drowsiness and swallowing difficulty. Her general condition deteriorated over next few days and she required mechanical ventilation on day 5 of admission. She was initially started on broad spectrum antibiotics to cover for suspected organisms along with antiviral drugs. She was running fever also. Her MRI brain was repeated following clinical deterioration showed multiple indistinct regions of T2 FLAIR hyperintensity with patchy diffusion restriction and post contrast enhancement in bilateral centrum semiovale, subcortical and deep white matter of both cerebral hemispheres, thalamus, internal capsule, brainstem and cerebellum. The possibility of rhombencephalitis with a para-infectious demyelination was considered. She was started on intra-venous immunoglobulin. However, her Glasgow coma scale (GCS) deteriorated and she showed decerebrate posturing. We presumed that, this could be due to an immune mediated process and after clinical discussion with our critical care specialist, the decision of plasmapheresis as a life saving measure was taken up, after getting consent from her family. The patient showed improvement in her sensorium after the second cycle of plasma exchange, hence the decision to continue it for five cycles was taken, the end of which tracheostomy was done to wean off from ventillator.

Her evaluation for an infectious etiology was negative including CSF polymerase chain reaction (PCR) test for bacteria including *Burkholderia psuedomallei*, listeria and mycobacterium tuberculosis, fungi and viruses. Blood and CSF cultures were sterile. In view of the improvement following plasma exchange, she was evaluated for causes for demyelinating diseases. Her serum aquaporin4 antibody, myelin oligodendrocyte glycoprotein antibody, CSF and serum angiotensin converting enzyme (ACE), serum HLAB51 were negative. Her serum anti-ganglioside antibody panel done by indirect ELISA method was negative for GQ1b, while it was strongly positive for GD1b and GMI IgG antibodies. Her viral markers were negative. She was treated with broad spectrum antibiotics (meropenam, ampicillin, ceftazidime). Acyclovir was stopped after 2-weeks. She was given steroids under the cover of antibiotics, in view of the initial improvement with immunotherapy as well as the associated parainfectious demyelination, which was later stopped.

After 3-weeks of treatment, the repeat MRI brain showed symmetrical hyperintensities involving bilateral periventricular and juxtacortical white matter, posterior limb of internal capsule with an interval increase in size and enhancement (Figure 2). The MR spectroscopy showed nonspecific findings of mild elevation of choline, reduction of NAA along with a small lipid peak. No significant increase in perfusion was noted. Her repeat CSF study showed 170 cells, 73% lymphocytes and elevated protein with low sugars. The most probable diagnosis based on clinical and radiological picture was Neuromeliodosis. However, a CSF PCR for *Burkholderia psuedomallei* was negative and culture was sterile. Although a stereotactic brain biopsy was planned then, for further characterization of her illness, her relatives did not give consent for the same.

She showed further deterioration with bilateral limb weakness (right side grade 1/5, left 2/5 power) and recurrent

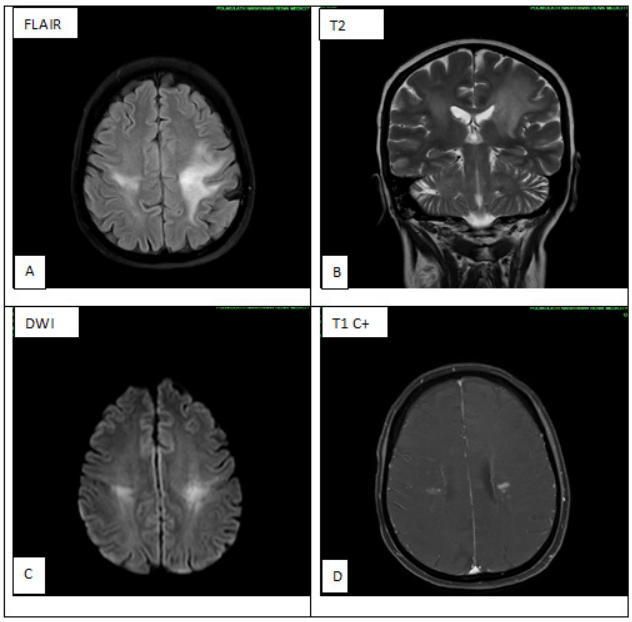

Figure 2: Follow up MR image of brain done after 4 weeks. FLAIR axial **A**- and T2 coronal images **B**- show increase in the extent of supratentorial white matter lesions. Diffusion weighted axial image **C**- shows moderate diffusion restriction over the corresponding areas. Post contrast axial sequence **D**- showing bilateral nodular and linear foci of enhancement.

right focal seizures, needing four antiepileptic drugs for adequate control. In view of the initial response to plasma exchange, intravenous immunoglobulin was given, considering the immune-mediated pathophysiology which was supported by the high antibody titres of anti-ganglioside antibodies. She was continued on antibiotics including intravenous ceftazidime, ampicillin and oral cotrimoxazole. After 7-weeks of treatment, repeat MRI brain was taken, which showed no reduction in the brain lesions (Figure 3). Her general condition remained the same, without any further deterioration. A stereotactic brain biopsy was done from another tertiary care centre after 60 days of the illness and the biopsy histopathology was non-

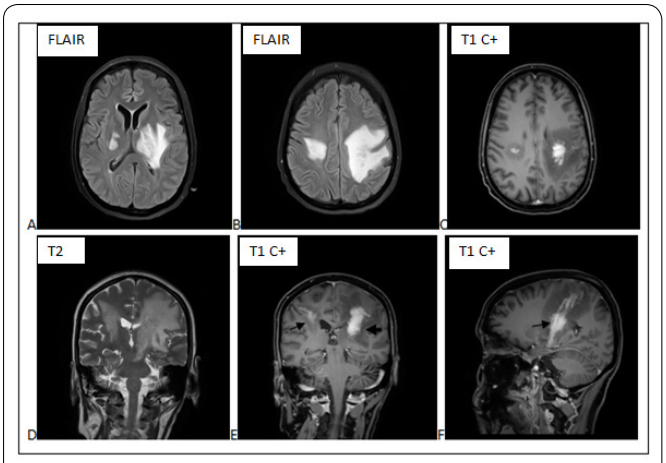

Figure 3: Follow up magnetic resonance images of brain after 7 weeks, T2FLAIR axial sequences **A** and **B**- T2 weighted coronal image **D**- showing increase in the hyperintense lesion over bilateral subcortical white matter (left > right). Post contrast T1 axial **C**- coronal E- and sagittal **F**- showing contrast enhancing lesion over bilateral white matter tracts (black arrows).

contributory. The biopsy specimen was cultured, which grew *Burkholderia psuedomallei* after 7-days. After obtaining the final diagnosis of Neuromeliodosis, ampicillin was stopped and continued on intravenous ceftazidime (2 gm iv q6h) and oral cotrimoxazole. She showed gradual improvement, tracheostomy closed, was tolerating oral feeds, speech improved, left side power better (grade 4/5) with gradual recovery of right upper and lower limb (grade 3/5).

Discussion

We present a rare case of Meliodosis, also known as Whitmore's disease, with CNS involvement, *Burkholderia pseudomallei* growth was confirmed in the culture sample of brain biopsy obtained from the patient. Our patient also showed an unusual elevation of anti-ganglioside antibodies (GD1b and GM1) in serum.

Burkholderia pseudomallei is a motile gram negative bacterium which causes Meliodosis, an endemic disease in northern Australia, Thailand, South Asia including China and is rarely encountered in the Indian subcontinent, reported mainly from Southern part of India [3, 4]. It is often found in contaminated water and soil and spreads to humans and animals through direct contact with the contaminated source [1, 2]. Diabetes mellitus is the most common risk factor for meliodosis. Only 1.5 to 5% cases have been reported to have neurological involvement. Meliodosis is acquired by inhalation, ingestion and inoculation.

Neuromeliodosis is a heterogeneous condition that present with encephalomyelitis, brain abscess, isolated meningitis or extra-axial collection [2]. Encephalitic syndrome without myelitis is the most common presentation. Fever, focal neurological deficits, especially cranial nerve palsies are the most prominent feature. CNS lesions are mainly (48%) located in the brainstem. In the brainstem encephalitic variant, the cranial nerves mainly, abducens, facial, glossopharyngeal and vagus nerves are affected. The bacteria enters the CNS mainly by hematogenous spread and can cross the blood-brain barrier and blood-CSF barrier [5]. In the encephalomyelitic presentation, another pathway for the entry of the organism is by direct brainstem invasion through the nasal passage and cranial nerves [6]. *Listeria monocytogenes*, herpes simplex virus type 1, and *Mycobacterium tuberculosis* are other common infectious causes for brainstem encephalitis [7].

Actin based motility mechanisms have been described as the major method of intracerebral spread of the pathogen along white matter tracts [8]. The bacteria are oriented longitudinally along the axonal axis and the affected fibres show degenerative changes, including axonal swelling and vacuolation. The fibres show complete disintegration in advanced stages and the swollen axons still remain surrounded by an intact myelin sheath, which restricts the bacteria to a certain degree along the axon [9]. This may explain the spread of the microorganism along CNS white-matter fibre tracts and the large extent of the abcesses through CNS [10].

The CSF profile of CNS melioidosis, usually shows

pleocytosis with mononuclear cells predominance that is comparable to tuberculous or viral meningitis, usually with normal sugars and elevated protein. But, tuberculous meningitis typically shows a higher CSF protein concentration with a lower CSF glucose level. In one-third of CNS meliodosis cases, a polymorphonuclear cell predominance is often seen. The peculiarity of neuromeliodosis is the absence of CSF spillage of organism, as the organism is largely confined to the white matter fibre tracts, hence isolation of organism from CSF may not always be possible, as in our patient.

Contrast-enhanced MRI is the most sensitive neuroimaging study for CNS melioidosis. Brainstem lesions are seen to be prominent in the encephalomyelitis type. Classical MRI features include calvarial osteomyelitis, leptomeningeal enhancement, ring enhancing lesions, edema, abscesses and predilection for involvement of brainstem [10]. Neuromelioidosis has great propensity to involve and spread along the white matter tracts across the projection and commissural fibres which results in bilateral and asymmetric distribution of lesions [10, 11]. Dissemination through white matter tracts lead to involvement of both the supra and infratentorial structures as well as the spinal cord and hence, the difficulty to completely eradicate the organism which result in a poorer clinical outcome. Similar pattern of spread is described with organisms like *Borrelia burgdorferi*, *Listeria monocytogenes* and *Shigella flexneri*. Parenchymal lesions may involve adjacent subdural or epidural spaces, skull and extracranial structures [10]. This invasive behaviour may mimic tuberculosis, invasive fungal infection and malignant neoplasms.

Culture from the infected tissue is the gold standard for the diagnosis of melioidosis [12]. Although it is 100% specific, sensitivity may be as low as 60% [12]. The source biopsy encompasses 1) brain tissue 2) pus from the brain or subdural collection or epidural abscess and 3) CSF. But, it is very difficult to obtain the specimen from some pathogenic location such as the brainstem. Hence, diagnosis is usually made by the presentation of the compatible CNS diseases which is supported by positive cultures from other specimens. The blood culture yields a positive result in the highest sensitivity with 52 percent. Culture in the Ashdown's medium, a gentamicin containing liquid transport broth grows *B. pseudomallei* [13].

According to the 2010 consensus recommendations, ceftazidime and meropenem are the drugs of choice for intensive-phase therapy, while trimethoprim/sulfamethoxazole is the first-line drug for eradication-phase therapy [14]. Antibiotics like chloramphenicol and doxycycline are also used in intensive-phase therapy in some neuromelioidosis cases; however, they are not effective and thus should be avoided. Neuromeliodosis requires prolonged treatment, with eight weeks and six to twelve months for intensive and eradication-phase therapy, respectively [15].

To the best of our knowledge, anti GD1b and GM1 antibody positivity with neuromeliodosis has not reported so far in the literature. There are few case reports on the association of Guillian Barre syndrome with *B. pseudomallei* infection [13, 16, 17]. The results of attachment inhibition studies suggested that *B. psuedomallei* binds to the asialo-ganglioside GM1, GM2 receptors [18]. In our patient also, the antibodies to ganglioside GD1b and GM1 were strongly positive. This could probably be explained by the peculiar binding of the bacterium to the ganglioside receptors and an exotoxin mediated molecular mimicry. The presence of such high titre for antibody could also be a probable explanation for initial improvement following immunotherapy especially during the initial rapid deteriorative immune mediated phase of the infection as in our patient.

Antiganglioside antibody production as a result of molecular mimicry was well documented following viruses [e.g., cytomegalovirus (CMV), Epstein-Barr virus (EBV), infuenza virus, hepatitis E virus and Zika virus] and bacterial infections (e.g., *Campylobacter jejuni*, *Mycoplasma pneumoniae*) [19, 20]. There have been associations of several other infectious diseases with the presence of CSF antiganglioside antibodies and demyelinating white matter lesions in the brain [21]. Similarly acute paralytic disease like GBS has been associated with several infectious diseases including the most recent COVID-19 pandemic [22].

Bicekerstaff brain stem encephalitis (BBE), a rare neurological disorder associated with ophthalmoplegia, ataxia and altered sensorium and is known to be associated with GQ1b positivity in 66% of cases, also reported with GD1a, GD1b and GM1 positivity [23]. According to the literature, T2-high-signal lesions have been reported in the upper mesencephalon, cerebellum, thalamus or brainstem in patients with BBE [24]. Our case cannot be taken as a typical case of BBE. Though Bickerstaff encephalitis is known to cause supratentorial involvement, in this case the lesion is seen to extend along the cortico spinal tract with evidence of demyelination. The clinical and radiological picture doesn't match with a typical BBE in this case. All the more, the response to immunotherapy was only partial in our case, in contrast to BBE which usually shows a more robust response and near complete resolution of lesions. Hence, this may be taken as a new entity which present with parainfectious demyelination with GD1b and GM1 positivity secondary to Neuromeliodosis, responding only partially to immunotherapy. The radiological lesions in this case worsened even after immunotherapy, probably due to persistent infection and only the immunological phenomenon could be treated with intravenous immunoglobulin. Early isolation of organism helps in early initiation of specific antibiotic therapy that can save the patient from imminent deterioration in health.

Conclusion

Neuromeliodosis is a rare neuroinfection with a predilection for brain stem involvement. To the best of our knowledge, this is the first report where the association of antiganglioside antibody with CNS meliodosis has been noted. The presence of high titre of anti-ganglioside antibody whether can be taken as a clue for neuromeliodosis, especially when there is difficulty in going ahead with brain biopsy,

needs further data. The possible role of an immunotherapy also needs consideration based on further evidence, as there is an associated immune mediated deteriorative phase during the course of the infection.

Learning Points

• Neuromeliodosis is a rare neuroinfection with a predilection for brain stem involvement with a high propensity to involve and spread along the white matter tracts.

• The absence of CSF spillage of the organism, as it is mainly confined to the white matter fibre tracts makes it difficult to isolate it from CSF.

• A low threshold of suspicion should be applied in cases, where magnetic resonance imaging show enhancing brainstem lesions with spread along the white matter tracts.

Author Contributions

NB: Study design, concept, data acquisition, literature search, manuscript drafting and editing and will act as guarantor of the article. MG: Design, concept, literature search, manuscript drafting and critical review. PM: Concept, data acquisition, manuscript drafting and critical review. AKD: Concept, design and critical review DKB: Concept, data acquisition, manuscript editing and critical review. MS: Concept, patient care and critical review of manuscript.

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Conflicts of Interest

There are no conflicts of interest.

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