

Case Report

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'Meliodiosis' complicated with guillain-barre syndrome: A case report

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Abstract

Melioidosis is a disease caused by gram negative bacteria called Burkholderia Pseudomallei. Development of Guillain Barre Syndrome (GBS) with this disease is very rare. We report a case of Melioidosis which got complicated with development of GBS. Laboratory detection of B. Pseudomallei by culture remains the mainstay to diagnosis. Early recognition and intensive treatment of this difficult to treat and highly resistant organism is necessary to prevent mortality. Meropenem is the drug of choice for intensive treatment followed by oral antibiotic treatment with trimethoprim and sulfamethoxazole during eradication phase. GBS is a post infectious autoimmune process which developed in patient having melioidosis with septicemia and confirmed with NCV studies. Treatment with immunoglobulins lead to the successful recovery of patient. The clinical manifestations of this disease are strongly similar with that of Tuberculosis and can mislead the diagnosis without strong microbiological evidence and laboratories unfamiliar with this bacterium.

Background

Melioidosis is disease caused by Burkholderia pseudomallei, which is a gram negative facultative intracellular bacterium. It is also called as Whitmore's disease which is predominantly found in tropical climate particularly in south east Asia, northern Australia, Sri Lanka [1-3]. Very few cases have been reported from India. It is being underdiagnosed and underreported in Indian subcontinent. Most of the cases have been found in wet monsoon season [4,5]. B. Pseudomallei is a BSL level III pathogen, and also a CAT B bioterrorism agent. The bacterium is mainly found in soil and water. Its modes of infection are percutaneous inoculation, inhalation, aspiration and sometimes acquired by ingestion. Presentation is extremely varied and high index of suspicion is needed in countries endemic in tuberculosis like India due to its similar clinical presentations [6]. Most common presentation of melioidosis is pneumonia in 50% cases [7] which may be with or without fulminant septicaemia, superficial skin and soft tissue abscesses, abscesses in various visceral organs like liver, kidney, prostate, spleen, muscles, lymph nodes and salivary gland involvement, septic arthritis [8]. It can affect

almost all systems. Neurological complications of melioidosis are very rare [1] and very few cases have been reported from India. The most common neurological manifestation was meningoencephalitis, other manifestations include brain abscess, meningitis, brain stem and cranial nerve involvements [9-13]. Neurological Melioidosis with GBS like illness have been reported [9-12] but only 2 have a level 1 diagnostic certainty according to Brighton criteria [8,9]. GBS is a post infectious polyradiculoneuropathy and many infections have been reported associated with it. Approximately 70% cases of GBS occur 1-3 weeks after an acute infectious process- usually respiratory or gastrointestinal infection. Development of GBS after B. Pseudomallei infection is very rare complication and we report a patient who presented with multifocal melioidosis disease with septicemia further developed GBS.

Case presentation

44-year-old male known diabetic for ten years presented to ER with case of high-grade fever, altered sensorium with delayed response and respiratory symptoms. Patient had history of travelling to western coastal regions of Maharashtra, India

and working in farm fields 15 days back when he started having dry cough with episode of fever for 2-3 days. He received symptomatic treatment and third generation cephalosporines from local physician, where fever subsided but cough was persistent with increased frequency especially in supine position with expectoration on and off.

On presentation patient had high grade fever with tachycardia with symptoms of respiratory insufficiency, hyperglycemia with normal anion gap, trace urinary ketones. On nervous system examination revealed altered sensorium with delayed response and power 4/5 in all four limbs with normal reflexes, rigidity on passive movements in lower limbs, neck stiffness+, frontal baldness- feature suggestive of? inherited myotonic dystrophy. On day 1 his total leukocyte count (7360/cmm), raised procalcitonin 2.2, c- reactive proteins 220, mildly raised liver enzymes with normal ammonia levels. Covid RT PCR test was negative on admission. Patient was treated with ceftriaxone, doxycycline, vancomycin, oseltamivir, Insulin, fluid resuscitation. Patient required noninvasive ventilatory support for initial two days. His MRI Brain showed chronic ischemic changes and was not conclusive for stroke or encephalitis. Chest x ray showed nodular densities in right midzone subsequently CT chest showed enlarged lymph nodes in right paratracheal, right hilar, precarinal and subcarinal regions, largest measuring 3.9 cm in right paratracheal region with significant central caseation, and right sided consolidation.

Patient had persistent fever and features of encephalopathy when febrile. Differential diagnosis of pyrexia of unknown origin, tuberculosis with TB meningitis and melioidosis with multifocal involvement was considered and needed to be ruled out.

On day 2 CSF analysis showed normal proteins of 51 mg/ dl, sugar 96.24 mg/dl and WBC 2 cells/cmm, with CSF ADA levels normal excluding the diagnosis of TB meningitis. CSF culture and multiplex PCR was negative and other causes of viral meningitis was ruled out. Work up for pyrexia of unknown origin done which was negative for all possible causes of tropical fever panel, malaria, dengue, Leptospira, salmonella, chikungunya, west Nile fever, India ink negative for cryptococcus and negative for IgM Rickettsia.

On day 3 CT guided biopsy of hilar lymph node was done and 3 cc yellowish pus was aspirated. PUS from lymph node was negative for TB PCR.

Patient continued to have high grade fever spikes with intermittent delirious episodes when febrile. On day 4 Antibiotics upgraded to inj Meropenem and Inj Aztreonam. Blood culture and pus sent from lymph node, both showed growth of 'Burkholderia pseudomallei'. Diagnosis was confirmed as per culture reports as disseminated Melioidosis with acute septicemia. After confirmation of melioidosis intravenous Meropenem 1 gm was continued. Patient's Urine culture showed associated urinary tract infection with pseudomonas aeruginosa CRE growth.

However, the disease process was complicated by bilateral lower limb weakness which had progressively increased over five days and difficulty in walking. Patient also gave history of leg pain five days back before admission and bilateral lower limb weakness.

On day 6 patient on evaluation had proximal + distal motor weakness with absent deep tendon reflexes. Acetylcholine receptor antibodies was negative. NCV studies conducted which showed bilateral motor axonal demyelinating neuropathy affecting both lower limbs. Possibility of post infectious Guillain barre syndrome was suspected based on high clinical suspicion of rapidly evolving symmetrical limb weakness, absent deep tendon reflexes, absent sensory signs, monophasic course with onset of symptoms within 28 days of infectious process supported by positive findings of NCV studies were consistent with GBS. Patient was immediately started on IV immunoglobulins therapy. IV immunoglobulins 0.4 mg/kg /day (30 gm/day) for five days was given. Recovery started within 2 to 3 days of receiving immunoglobulins. Patient's lower limb weakness improved to power 4/5 in all 4 limbs, was able to walk. Inj meropenem continued and eradication therapy started with tab cotrimoxazole for 12 weeks.

Discussion

Melioidosis is caused by gram negative facultative intracellular organism 'Burkholderia pseudomallei'. It has three different types of presentations 1. multifocal disease with septicemia is the most common type 2. localised disease involving particular organ with septicemia and 3. localised infection. Multiorgan infectious disease can present with a wide spectrum of clinical presentations. Melioidosis commonly presents as deep or superficial seated abscess formation, with septicemia and with or without features of pneumonia. The high risks patients include diabetes mellitus, pre-existing renal disease, thalassemia, occupational exposure with soil and water e.g., diabetic rice farmers. According to retrospective study conducted in coastal region of India, Pneumonia was the most common clinical presentation (32.6%), followed by musculoskeletal disease (20%), and melioidotic lymphadenopathy (7.4%) [4,5]. Median age of this disease found to be 42.5 years. Males constituted 75% of cases and 78.12% of cases were from rural areas. Fever was the most common symptom. Mainly found in coastal regions in India, Diabetes followed by alcoholism are the commonest risk factors [4,5].

Differential diagnosis was made as pyrexia of unknown origin, Tuberculosis with TB meningitis and Melioidosis under evaluation. High grade fever with respiratory symptoms of cough, breathlessness and CT findings of lymph node abscess was strongly fitting into diagnosis of tuberculosis. Patient also had neurological symptoms of delirium, encephalopathy hence initially thought to be pulmonary TB with lymph node abscess and TB meningitis. Symptoms of melioidosis and tuberculosis overlap each other making difficult in diagnosing melioidosis cases. However, CSF reports was negative for tuberculosis.

Patient is >40 yrs male with known diabetic for 8 years with recent exposure to soil and stagnant water in farms in rainy season at coastal regions of Maharashtra. The environmental factors such as close association with weather and rainfall are yet to be elucidated [14-16]. Deep seated lymph node abscess and features of pneumonia with sepsis with strong history of stagnant water exposure in fields made us to consider Melioidosis. Incubation period for melioidosis is average 9 days and anywhere between 1 to 21 days, diabetic males are predominantly affected [17]. Diabetes, as a strong risk factor suggest Function-

al neutrophil defect can be important factor in its pathogenesis. Skin inoculation is considered the main route of infection in agricultural workers in developing countries [18].

The pus culture from lymph node showed *B. Pseudomallei* and blood culture also showed the same. Hence clear diagnosis of multifocal melioidosis with acute septicemia was confirmed. The most common neurological manifestation in melioidosis is meningo encephalitis, next is brain abscess [13]. According to systematic review article most common complication is neurological complication [17] and so far, 2 cases have been mentioned in literature with GBS as a complication of Melioidosis with level 1 diagnostic certainty according to Brighton criteria [9,10]. Patient's disease process was complicated by bilateral lower limb weakness. Development of GBS is suspected based on clinical presentation and NCV studies conducted to support diagnosis.

GBS is an acute, frequently severe post infective polyradiculoneuropathy that is autoimmune in nature. Approximately 70% of cases of GBS occur 1-3 weeks after an acute infectious process, usually respiratory or gastrointestinal, commonly campylobacter jejuni (32%), cytomegalovirus (13%), EBV (10%) were significantly more frequent in GBS patients according to a case control study [14,15]. Other infections may be associated with GBS include H. Influenza, Varicella, Herpes, Mumps and mycoplasma. In >50 cases we do not have a known cause.

All forms of GBS are autoimmune diseases. Circumstantial evidence suggests that all GBS results from immune response to foreign antigens such as infectious agents. The immune response is misdirected to host nerve tissue through a resemblance of epitopes, a phenomenon called 'Molecular mimicry' [19]. The targets of such immune attack are thought to be gangliosides compounds which are present in large amount in peripheral nerve tissues. Here our patient developed rapidly evolving symmetrical ascending motor weakness in limbs, deep tendon reflexes were absent, there was no sensory involvement and variable autonomic dysfunction such as hypertension, weakness occurred within 28 days of infectious process, NCV studies showed bilateral motor axonal demyelinating neuropathy affecting both lower limbs, there is a presence of characteristic antecedent event. Considering all these possibilities of GBS secondary to melioidosis infection considered. The findings fulfill level 2 of Brighton diagnostic criteria for diagnostic certainty of Guillain Barre syndrome [20-23].

The disease could have been due to an Burkholderia exotoxin mediated neurological disease or the infection with *B. Pseudomallei* could have triggered an autoimmune process and molecular mimicry resulting in GBS. Is there any association between GBS developing in diabetic patients with gram negative septicemia is still area under research. Few cases of GBS with diabetic ketoacidosis have been described. Patient gave history of b/l lower limb pain with mild weakness 5 days before admission, initially suspected to be diabetic neuropathy related weakness by family doctor. Our patient was hyperglycemic on admission with normal anion gap. Two case reports [9,10] show melioidosis with development of GBS on a background of diabetes mellitus.

Bacteremic melioidosis has a poorer prognosis than non-bacteremic melioidosis. The presence of septic shock is a strong predictor of mortality [4]. Identification of *B. pseudomallei* in culture was a key diagnostic step in our patient. For hospital systems unfamiliar to identifying *B. pseudomallei*, or poor re-

sources a delay or misidentification of the pathogen as pseudomonas species are not uncommon [5]. These delays can be fatal, *Burkholderia pseudomallei* is highly resistant gram-negative organism which is resistant to many of the first line antibiotics used to treat gram negative septicemia. The resistance found to penicillin's, ampicillin, first and second generation cephalosporins, aminoglycoside -gentamycin, streptomycin, tobramycin, ceftriaxone and polymyxin. Treatment of melioidosis consists of two phases intensive treatment phase 1 and eradication phase 2. As our patient had active melioidosis, we used high dose of intravenous Meropenem as induction therapy. In recommendations by Timothy intravenous Meropenem, and revised Darwin treatment guidelines [20,21]. The key recommendations were use of the cephalosporin Ceftazidime or a carbapenem antibiotic for initial treatment of acute infection over 2-4 weeks and a combination of co-trimoxazole and doxycycline for eradication over a 12-20-week period. It is common practice to briefly overlap initial intravenous and eradication antibiotic therapy and assess tolerance of the oral eradication agents. A period of 12-20 weeks eradication therapy is now widely used with good evidence for efficacy [20-22]. Intravenous immunoglobulins and plasmapheresis are equally effective in GBS treatment. However, because of ease of administration immunoglobulins is preferred treatment. After 2 days of receiving immunoglobulins, patient's lower limb power improved rapidly by day 3 and fully recovered. The prompt suspicion of post infectious GBS and subsequent investigation and treatment lead to successful recovery in this patient.

Conclusion

Melioidosis should always be suspected in patients who has fever with deep seated abscess and history of diabetes, particularly middle-aged male with history working in stagnant water and farms. Association of cases increasingly found in monsoon season. Symptoms of pneumonia and lymph node abscess may misdirect to consider tuberculosis but culturing the pathogen is key factor in diagnosis and treating the cause. GBS is post infectious autoimmune in nature which can complicate Melioidosis, and it should be suspected in patient developing lower limb weakness. IV immunoglobulins seem to be effective treatment of GBS associated with Melioidosis. The case also illustrates that intensive intravenous meropenem in induction stage followed by cotrimoxazole as eradication treatment is effective in treating severe and complicated Melioidosis.

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