A rare case of rickettsial fever with isolated third cranial nerve palsy causing hemophagocytic lymphohistiocytosis

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ABSTRACT

Rickettsial infections are being increasingly diagnosed in the Indian subcontinent with the advent of affordable and sensitive diagnostic techniques. Rickettsial infections are sometimes complicated by the development of secondary hemophagocytic lymphohistiocytosis (HLH) which is life-threatening unless identified early and treated. Here, we describe a case of rickettsial fever in a 41-year-old male who presented with fever, skin rash, and neurological obtundation, complicated by both third cranial nerve palsy and HLH. The patient showed a good recovery in sensorium with intravenous doxycycline and dexamethasone, although the oculomotor nerve palsy persisted for about two months after discharge. This case highlights the need to initiate treatment for rickettsial fever and HLH on clinical grounds before waiting for confirmation by laboratory tests.

Key words: Hemophagocytic lymphohistiocytosis, Rickettsial fever, Rickettsiosis

CASE REPORT

A 41-year-old man, with no co-morbidities, from a rural area, presented with a history of fever, headache, generalized weakness for 1 week, blurred vision, and left-sided ptosis for 1 day followed by one episode of generalized tonic-clonic seizure 3 h prior to admission.

On examination, his heart rate was 104 beats/min, respiratory rate was 28 breaths/min, blood pressure was 108/70 mm Hg, and the temperature was 101°F. He was neurologically obtunded with a Glasgow coma scale score of E2V2M4, hence, was intubated for airway protection and admitted to the intensive care unit (ICU). Maculopapular rashes were noted all over the trunk and limbs. Ophthalmological examination revealed left eyelid edema, conjunctival edema, normal pupils, and fundus with left-sided pseudo-ptosis (Fig. 1a). There was restricted adduction, elevation, and depression of the left eye indicating left third cranial nerve palsy (Fig. 1b), along with loss of pupillary constriction in response to light (Fig. 1c).

Abdominal ultrasonogram revealed mild hepatosplenomegaly. There was no lymphadenopathy or eschar and brain imaging was normal. A provisional diagnosis of tropical fever with encephalopathy and oculomotor nerve palsy was made in view of the highly suggestive skin rash and obtundation, and work-up for dengue, leptospira, malaria and rickettsiae was initiated along with the other routine investigations. Intravenous doxycycline 100 mg twice daily for 7 days for rickettsial fever was started empirically from day 1, along with ceftriaxone 2 g twice daily and vancomycin 1 g twice daily, to cover meningitis and other sources of sepsis.
The initial laboratory tests showed a total leukocyte count of 11,700 cells/mm$^3$, hemoglobin 12.3 g/dl, platelet count of 21,000/mm$^3$, and total bilirubin of 4.93 mg/dl with a direct bilirubin of 3.85 mg/dl. Liver enzymes, as well as, renal function tests were normal. Dengue serology, Weil-Felix test, leptospira immunoglobulin-M, quantitative buffy coat for malaria and blood, and urine cultures were negative. Cerebrospinal fluid analysis was deferred in view of thrombocytopenia. The polymerase chain reaction (PCR) test for rickettsiae result which took 3 days was positive and other antibiotics were stopped.

On day 4 of ICU stay, he developed a high-grade fever with a further drop in platelet counts and hemoglobin to 9000/mm$^3$ and 8.5 g/dl, respectively, with no overt signs of bleeding. Blood, urine, and deep endotracheal secretion cultures were repeated and he was empirically initiated on intravenous piperacillin-tazobactam 4.5 g 6th hourly and transfused one unit of single donor platelets. Peripheral blood smear showed bicytopenia (normocytic normochromic anemia and thrombocytopenia), hence a workup for hemophagocytic lymphohistiocytosis (HLH) was initiated. Serum ferritin was 5984.9 µg/l, triglycerides 563 mg/dl, and fibrinogen 76 mg/dl (normal cut-off levels shown in Table 1). The culture reports were negative after 2 days. Bone marrow examination was deferred in view of thrombocytopenia. He was initiated on intravenous dexamethasone 10 mg/m$^2$ once daily from day 5 of the ICU stay. His sensorium recovered soon and he was successfully extubated on day 7 of ICU stay, and discharged from hospital after 5 days with oral dexamethasone. The third nerve palsy persisted at the time of discharge but showed a gradual improvement over the next 2 months (Fig. 2) along with normalization of laboratory parameters. Dexamethasone was tapered and stopped after a total duration of 8 weeks.

**DISCUSSION**

Rickettsiae are transmitted to humans by the bite of infected arthropod vectors such as lice, fleas, ticks, and mites or exposure to infected animals followed by contamination of the bite wound by the infected saliva, or feces [1]. On entering the bloodstream, they mainly invade the vascular endothelium and reticuloendothelial cells. The resulting vasculitis leads to skin rash, microvascular leakage, tissue hypoperfusion, and systemic complications such as cerebral edema and meningoencephalitis [1,5].

There have been two other cases of rickettsial infection with isolated third cranial nerve palsy reported [5,8]. Similar to our case, these two patients presented with fever, rash, and unilateral left oculomotor nerve palsy, but eschar was absent. However, none of the patients had altered mentation and both showed an improvement in the palsy within 1 month as compared to 2 months in our case.

The pathogenesis of cranial neuropathy associated with rickettsiae is unclear but has been attributed to the vasculitis of the vasa nervorum as well as tick paralysis caused by paralytic toxins identified in the saliva of ticks [5,6]. Another theory is the multiplication of the rickettsial pathogen at the site of tick bite and subsequent direct invasion of nearby nerves, leading to nerve ischemia and neuronal apoptotic cell death.
The Weil-Felix test for diagnosis of rickettsial infections is now rarely used outside of resource-limited settings due to its poor sensitivity and specificity, as shown in the previous studies [1,4,9]. Immunofluorescence assay is regarded as the gold standard but is restricted by its cost. Rapid diagnostic tests for scrub typhus are affordable and can be used as point of care tests but show varying sensitivity and specificity. Enzyme-linked immunosorbent assay to detect IgM antibodies has high sensitivity and specificity of 96.3% and 99%, respectively, but is impeded by the 5–6 days delay that IgM antibodies take to form, after the onset of illness. PCR can detect the pathogen early but should be done before treatment is started, as its sensitivity decreases with treatment.

The antibiotics of choice for rickettsioses are the tetracyclines, primarily doxycycline, 100 mg twice daily for a duration of 7 days or until 2 days after apyrexia is obtained, given either orally or intravenously [1,3]. If started early, doxycycline can quicken recovery from cranial nerve palsy and prevent long-term axonal degeneration [6]. Rifampicin, though more effective than tetracyclines, is restricted to resistant strains.

The patient in our study was clinically suspected to have HLH on the basis of persisting high-grade fever in the absence of infection, along with splenomegaly, bicytopenia, hyperferritinemia, hypertriglyceridemia, and hypofibrinogenemia, which fulfilled the Histioocyte Society definition of HLH (Table 1) [10]. HLH is a hyperinflammatory disorder and may be primary (inherited) or secondary, due to neoplastic, infectious, or rheumatological diseases [2,10]. It should be suspected in cases with unexplained high fever, hepatosplenomegaly, jaundice, generalized lymphadenopathy, and cytopenias [2,11,12]. Neurological symptoms may overlap those found in rickettsial infections, including seizures, cranial neuropathies, and altered mentation. Another diagnostic criterion is the finding of numerous engulfed cells within macrophages (histiocytes) on bone marrow biopsy, giving rise to the term hemophagocytosis [13]. However, this has poor sensitivity as the majority of initial biopsies are shown to be negative. In normal conditions, inflammatory stimuli trigger the release of cytokines from cytotoxic T-lymphocytes (CTLs), which stimulate macrophages, natural killer (NK) cells, and CTLs to proliferate with the release of cytolytic enzymes that lyse the target cells and terminate the antigenic stimulus [14]. In HLH, the NK cells and CTLs are dysfunctional and the antigenic stimulus persists, leading to uncontrolled hypercytokinemia with sustained macrophage activation and tissue infiltration. Early institution of therapy is critical to control this hypercytokinemia, which may otherwise result in end-organ failure and death, hence it is not necessary to fulfill all eight diagnostic criteria.

Treatment encompasses treating any underlying condition along with administration of intravenous dexamethasone 5–10 mg/m², tapered and stopped over 8 weeks [15]. The additional therapies for HLH include etoposide 150 mg/m², cyclosporine-A 3 mg/kg twice daily, and intravenous immunoglobulin 1.6 g/kg over 2–3 days. Intrathecal methotrexate or stem cell transplant are indicated in refractory cases.

CONCLUSION

This case report highlights the need to be vigilant for the signs and symptoms of rickettsial fever and HLH and institute early treatment, as confirmation by laboratory tests may be delayed. Infectious agents should be eradicated promptly, along with administering supportive care.

REFERENCES