Case Report

Scrub typhus manifesting with intracerebral hemorrhage: Case report and review of literature

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Abstract

Scrub typhus (ST), hitherto absent from many parts of India, is now recently being recognized as a significant cause of morbidity and mortality throughout the country. Its diverse clinical presentations, low of the index of suspicion by the treating physician, and lack of diagnostic testing in many parts of the country result in delayed treatment, leading to a host of complications. We here report such a complication, where ST manifested with a large intracerebral hemorrhage, of which, to the best of our knowledge, only nine cases have been reported in the English language worldwide. Family physicians, who are the often first point of contact for treatment of febrile illness, as ST typically manifests, need to be aware of this entity to prevent such catastrophic consequences.

Keywords: Intracerebral hemorrhage, intracranial bleed, *Orientia tsutsugamushi*, scrub typhus, stroke

Introduction

We here present a case of scrub typhus (ST) manifesting with a large intracerebral hemorrhage, of which, to the best of our knowledge, only nine cases have been reported in the English language worldwide.[1-8] Most of these were secondary to deranged coagulation profile, disseminated intravascular coagulation (DIC) and/or hemophagocytic lymphohistiocytosis (HLH), which were absent in this case.

As part of changing epidemiology of infectious diseases in India, ST is an increasingly important cause of morbidity and mortality, often secondary to late diagnosis. Its diverse clinical presentations, lack of diagnostic testing in most rural areas, and low index of suspicion are the likely causes of its usual delayed diagnosis.[2,4] The latter cause is perhaps courtesy of its rapid rise due to which a considerable number of clinicians lack awareness of the same. Additionally, ST can lead to a host of neuropsychiatric manifestations, if untreated, including meningitis, encephalitis, cerebellitis, cranial nerve palsies, demyelination, subdural hematomas etc.[9] Pathania *et al.*, in this very journal, have recently compared all studies in India looking at the clinico-epidemiological profile of ST cases, where they found the presence of characteristic eschar being reported in 11–46% of cases, renal failure in 4–51%, and mortality rate ranging from 2% to 21%. They strongly recommended for inclusion of ST as a differential in a case of fever of unknown origin, in India, especially in rural settings.[10]

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Case Report

A 28-year-old man had been brought to a private hospital in northern India with a 2-week history of altered sensorium, fever, headache, cough, and diarrhea, now accompanied by new-onset dyspnea and was admitted for febrile illness workup. At the time of admission, his GCS had been 15/15, pulse 120 beats/minute, blood pressure 130/80, respiratory rate 42/minute, with pulse oximetry 96% on room air, bilateral chest congestion, and arterial blood gas indicating pH 7.27, p_AO_2 81.3 mmHg, p_ACO_2 33.3 mmHg, bicarbonate 14.8 mmol/L, and a base excess 10.8 units. Other investigations had showed Na^+ 136 mmol/L,

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K^+ 3.4 mmol/L, hemoglobin 10.6 g/dL, total leucocyte count (TLC) 21,100 cells/mm^3, platelet count 1.04 lakhs/mm^3, serum bilirubin 0.9 mg/dL, aspartate aminotransferase (AST) 97.16 IU/L, alanine aminotransferase (ALT) 72.28 IU/L, blood urea nitrogen (BUN) 25.27 mg/dL, serum creatinine 2.1 mg/dL, serum albumin 2.53 mg/dL, international normalized ratio (INR) 2.1, procalcitonin 2.54 ng/mL, creatinine kinase-MB 2.05 IU/L, and myoglobin 135.7 ng/mL. Abdominal ultrasonography (USG) had revealed hepatosplenomegaly with mild ascites, with 2D-echocardiography demonstrating a left ventricular ejection fraction of 61%. The patient had been intubated and shifted to ICU. He had then developed acute respiratory distress syndrome (ARDS), stage-3 acute kidney injury (AKI) requiring four hemodialyses, and septic shock. Disseminated intravascular coagulation (DIC), however, was not present. He had then been diagnosed with multi-organ dysfunction syndrome (MODS) for which the hospital did an extensive workup, but could not locate the etiology. After a week of mechanical ventilation, correction of hemodynamic status, and broad-spectrum antimicrobial administration, the patient had stabilized enough to have an MRI of the brain performed. Unfortunately, it revealed a resolving intracerebral hematoma in the left temporal lobe [Figure 1], although the patient had no history of hypertension nor had any abnormal coagulation studies and/or platelet counts, throughout this illness. Upon this discovery, the private hospital promptly referred the patient to a higher center. At our institution, we continued ventilatory support, intensive monitoring, neuroprotective strategies, mannitol, and wide-spectrum antimicrobial administration, while investigating with a broad differential. As part of the institutional protocol for workup of complicated febrile illness, a broad panel of serologic testing was done, which found him found positive only for anti-ST IgM antibody. He was negative for HIV, hepatitis B surface antigen, hepatitis C, anti-Japanese encephalitis IgM antibody, real-time PCR for HSV-1, anti-chikungunya IgM antibody, anti-dengue IgM antibody, and malaria rapid test. On lumbar puncture, the CSF sample was xanthochromic, having 10–15 erythrocytes/high power field (HPF), CSF glucose of 80 mg/dL (corresponding serum glucose of 124 mg/dL), protein 462 mg/dL, cell count of 60/mm^3 with 95% lymphocytes, and negative Gram staining, and Ziehl-Neelsen staining.

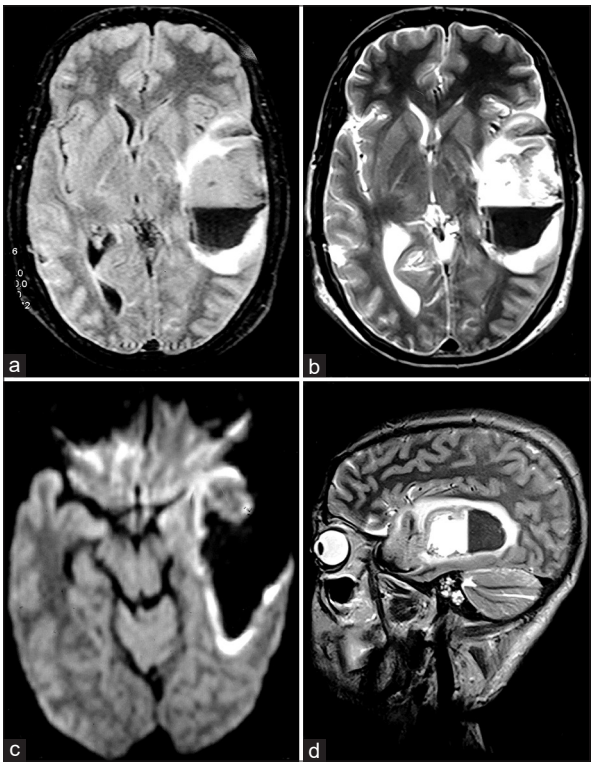

Figure 1: Resolving intracerebral hemorrhage in left temporal lobe seen on (a) axial FLAIR imaging, (b) axial T2-weighted image, (c) axial diffusion-weighted imaging, and (d) left parasagittal T2-weighted imaging

However, despite administering intravenous doxycycline, progressive multi-organ dysfunction syndrome (MODS) brought about his death after five days of ICU stay, primarily due to worsening renal function and severe respiratory acidosis.

Discussion

At our public referral hospital, we regularly receive referred patients with such "pyrexia of unknown origin (PUO)" with extensive workup having occurred outside yet a lack of diagnosis. From 2015, after the introduction of the inexpensive and rapid ST serology kit in India, we have found, like many other north Indian academic medical institutions, a considerable number of PUO cases to have been positive for ST, as in this case. Unfortunately, most ST patients that are referred to us are found to not have been ever worked-up for ST. We are also finding significant neurological complications of ST, which can occur in 14–83% of cases,[9] and which unfortunately are preventable with opportune treatment. This is due to the delayed administration of doxycycline, as in this case, which resulted from not having been tested for ST.

A comprehensive review of the MEDLINE database and searching of reference lists suggests that only nine such cases have been reported prior to the literature in the English language, whose salient features have been summarized in Table 1. However, we do acknowledge that given ST is rampant in Asia, such cases may also have been reported in Chinese, Korean, or Japanese languages, which we were unable to account for due to logistical challenges. In this case, intracerebral hemorrhage, with normal coagulation studies and normotension, may have been due to either uremic platelet dysfunction or due to pre-existing cerebral aneurysms. While the patient had expired prior to performing any angiographic study, poor autopsy protocols at our institution, as is common in India, also resulted in failure to identify any aneurysms. In comparison, most prior case reports had reported a state of deranged coagulation profile, DIC, and/or HLH.

For family physicians in India, ST now should be considered an important contributor to the changing landscape of infectious diseases. Presenting nonspecifically, it can wreak havoc if not tested for and thereby not diagnosed early. Such testing will occur routinely when ST is kept as a differential for workup

Table 1: Prior reported cases of scrub typhus with intracerebral hemorrhage in the English language and the current case

Author (Year)	Age (years), sex of patient	Eschar present (yes/no)	Location of intracerebral hemorrhage	Antimicrobial given	Associated complications
Yang *et al.*[1] (2005)	56, M	Yes, left scrotum	Left thalamic area	Tetracycline	DIC, thrombocytopenia
Lin *et al.*[2] (2013)	34, F	No	Unreported	Mino-cycline	HLH, DIC, multi-organ failure, death
Chung *et al.*[3] (2013)	53, F	Yes, left axilla	Right cerebral hemisphere	Rifampin	None (patient cured)
Kim *et al.*[4] (2014)	53, F	Yes, right ear	Right cerebellum	Doxycycline	Subarachnoid and intraventricular hemorrhage
Sood *et al.*[5] (2015)	18, F	Yes, right pubic region	Micro-hemorrhages in corpus callosum, subcortical white matter	Azithromycin	Loss of consciousness
Neyaz *et al.*[6] (2016)	55, M	No	Right frontal opercular region	Doxycycline	Refractory septic shock, ARDS, DIC, multi-organ failure
Kalita *et al.*[7] (2017)	Unreported (case was a part of large descriptive ICU study of infectious encephalopathy/encephalitis)				
Tuteja *et al.*[8] (2018)	53, F	No	Frontal lobar region	Doxycycline + azithromycin	Subarachnoid hemorrhage, severe thrombocytopenia
Tuteja *et al.*[8] (2018)	26, M	No	Left frontoparietal lobe	Doxycycline + azithromycin	Intraventricular hemorrhage
Current case	28, M	No	Left temporal lobe	Doxycycline	Subarachnoid hemorrhage, multi-organ failure, death

HLH: hemophagocytic lymphohistiocytosis; DIC: disseminated intravascular coagulation; M: male; F: female

of undifferentiated acute febrile illness. General practitioners and private hospitals urgently need to be made aware of the significance of early and affordable serological testing to prevent complications of ST.[9] It is also to be recognized that IgM ELISA-based testing and SD Bioline rapid testing have been found to have over a 97% correlation in India.[10]

Statement of human rights

All ethical procedures were duly followed and informed consent was taken. The patient cannot be identified by any part of the text or image.

Acknowledgments

Nil.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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