Case Reports

Four cases of scrub typhus probably complicated by Kawasaki Disease

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Introduction
Kawasaki disease (KD) is an acute systemic vasculitis and is the commonest cause of acquired heart disease in children in the developed world[1]. The exact cause of KD is still unknown. There is a strong possibility that certain infections, in the background of susceptible genetic factors may trigger the inflammatory process[2]. Here we report 4 cases of scrub typhus complicated by KD. All 4 cases presented from August-September 2017.

Case 1
A 5 month old boy presented with high grade fever for 10 days. There was a history of a maculopapular rash on the 3rd day of fever which spontaneously subsided on the 7th day. The child was very irritable with mild pallor and had inflammation of the BCG scar. There was hepatosplenomegaly without significant lymphadenopathy. The white blood cell (WBC) count was 17,800/cu mm (N70%, L28%, E1%, B1%). The erythrocyte sedimentation rate (ESR) was 10mm in the first hour and the C-reactive protein (CRP) was 149 mg/dl. The liver function tests (LFTs) were normal except for hypoalbuminaemia (serum albumin 2g/dl). Blood and urine cultures were sterile.

Broad spectrum antibiotics (intravenous ceftriaxone and vancomycin) were started. Echocardiographic screening was normal. Scrub typhus IgM enzyme linked immunosorbent assay (ELISA) was 1.2. Azithromycin was started. However, even after 48 hours the child continued to be febrile and irritable. Cerebrospinal fluid (CSF) study was normal.

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Repeat blood counts showed persistence of polymorphonuclear leucocytosis with rising ESR (40mm) and CRP (160mg/dl). Repeat echocardiogram done on the 14th day of illness showed dilatation of coronaries (LMCA Z score +3.86, LAD +2.79). Intravenous immunoglobulin (IVIG) 2g/kg was started along with aspirin. The child became afebrile within 24 hours and was discharged on aspirin 3mg/kg/day.

Case 2
A 5 month old boy was admitted with a history of high grade fever for 10 days. On the 7th day of fever he developed a maculopapular rash over trunk, face and abdomen. On examination, the infant had a toxic look and was very irritable with a bulged anterior fontanelle. He had oral mucositis, scrotal desquamation and hepatosplenomegaly without any significant lymphadenopathy. Laboratory results revealed anaemia and polymorphonuclear leucocytosis with high CRP and ESR. Blood culture was sterile. CSF showed aseptic meningitis (cells 75, all lymphocytes, protein 95mg/dl, sugar 55mg/dl). It was sterile.

Therapy was started with ceftriaxone and vancomycin. Weil Felix OXK was +1:160, Scrub typhus IgM (ELISA) was +1.822. Thereafter doxycycline was added. Despite this therapy patient continued to be febrile and irritable with a progressive dip in haemoglobin and rising CRP and ESR. Echocardiogram revealed dilatation of coronaries (Z score LMCA+ 2.5, RCA+ 2.67). IVIG 2g/kg was given with aspirin, to which he responded.

Case 3
A 1 year old girl was admitted with a history of upper respiratory tract infection for which she had been receiving oral antibiotics. However, the fever continued and at the time of admission she was very irritable with hepatosplenomegaly. There was an eschar over her left groin. She was started on IV ceftriaxone and since scrub typhus IgM was positive, oral doxycycline was also started. She became afebrile after 48 hours but acute phase reactants (CRP, ESR) continued to rise. Echocardiogram revealed dilatation of coronaries (Z score LMCA +3.57, proximal RCA +3.47).

IVIG and aspirin were given to which she responded.

Case 4

A 4 month old boy presented with a history of fever for 2 weeks with features of a lower respiratory tract infection. On examination, he was very restless, had a maculopapular rash, oedema of extremities and hepatosplenomegaly. All her inflammatory markers were raised (Table 1). There was hyponatraemia with sterile pyuria. In spite of broad spectrum antibiotics, the febrile spikes continued. Scrub IgM (ELISA) was +2. Azithromycin did not show any response. Echocardiogram on 4th day of admission revealed coronary dilatation (Z score LAD +3.48) with mild pericardial effusion. She responded to IVIG 2g/kg.

Laboratory data of the 4 patients on admission

Laboratory test	Case 1	Case 2	Case 3	Case 4
Haemoglobin (g/dl)	10	9	9.7	8.4
White blood cell count (per cu mm)	17,800	33,600	25,300	31,800
Neutrophils (%)	70	25	36	33
Platelet count (per cu mm)	4,500,000	230,000	320,000	135,000
C-reactive protein (mg/dl)	149	149	33.2	77
Erythrocyte sedimentation rate (mm 1st hr)	10	45	80	52
Aspartate aminotransferase (IU/dl)	41	90	66	65
Albumin (g/dl)	2	2.6	3	2.7
Sodium (meq/l)	128	138	138	135
Sterile pyuria	absent	present	absent	present

Discussion

Scrub typhus is a mite borne infection caused by *Orientia tsutsugamashi* and the vectors are larval trombiculid mites called chiggers[3]. Approximately 4% of hospitalised patients have a fatal outcome[4]. Scrub typhus causing leucocytoclastic vasculitis[5] and pan-digital gangrene[6] has been reported in adults. Retinal vasculitis in children has also been reported[7]. KD following Rocky Mountain spotted fever has been reported in a 4 year old girl[8]. Coronary dilatation has been reported in one child in a study of the clinico-epidemiological profile of paediatric patients with scrub typhus in Southern Kerala[9].

The aetiology of KD is still controversial and infections, including bacterial, viral (most common), chlamydia, mycoplasma and rickettsial organisms[10] may be one of the predisposing factors. The infectious aetiology of KD may be suggested by temporal clustering and marked seasonality along with geographic and family clustering[11].

All our 4 patients presented with fever, rash and hepatosplenomegaly. Serology showed IgM (ELISA) positive for scrub typhus. One of them had features of meningitis (CSF IgM for scrub typhus could not be done). The striking similarity in all the cases was persistence of fever, extreme irritability in the background of elevated inflammatory markers and non-response to doxycycline/azithromycin (which prompted us to exclude KD).

All 4 cases presented from August-September 2017. The close clustering and temporal association of scrub typhus with KD may be due to:

- Nonspecific serological response to scrub typhus in a patient with KD.
- Scrub typhus leading to vasculitis
- Scrub typhus leading to KD as a super antigen interacting with the immune system.

Coincidental occurrence of scrub typhus and KD, though unlikely, cannot be ruled out because seroconversion could not be done in our patients. Both KD and scrub typhus are associated with vasculitis involving small and medium sized vessels. Rickettsial-like bodies have been found in peripheral blood and biopsy specimens from the skin and lymph nodes of patients with KD[12]. It could be possible that these patients had vasculitis due to scrub typhus and their clinical conditions improved after a combination of IVIG and doxycycline. This suggests that IVIG may have some benefits in vasculitis associated with infections such as scrub typhus.

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