Four cases of scrub typhus possibly 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 world¹. 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 process². 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.

Repeat blood counts showed persistence of polymorphonuclear leukocytosis 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 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. Approximately 4% of hospitalised patients have a fatal outcome. Scrub typhus causing leucocytoclastic vasculitis and pan-digital gangrene has been reported in adults. Retinal vasculitis in children has also been reported. KD following Rocky Mountain spotted fever has been reported in a 4 year old girl. 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.

The aetiology of KD is still controversial and infections, including bacterial, viral (most common), chlamydia, mycoplasma and rickettsial organisms 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.

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. 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.

References
1. Taubert KA. Epidemiology of Kawasaki disease in the United States and worldwide. Prog Pediatric Cardiol 1997; 6:181-5. https://doi.org/10.1016/S10589813(97)00188-4
2. Kusuda T, Nakashima Y, Murata K, Kanno S, Nishio H et al. Kawasaki disease –specific molecules in the sera are linked to microbe-associated molecular patterns
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in the biofilms. PLoS One 2014; 9(1): e113054. https://doi.org/10.1371/journal.pone.0113054 PMid: 25411968 PMCid: PMC4239021

3. Hornick RB. Rickettsial Diseases. Bennette JC, Plum F. Cecil Textbook of Medicine. 21st ed. 1911-12

4. Sothayanom P, Chierakul W, Wuthiekanum V et al. Rapid diagnosis of scrub typhus in rural Thailand using polymerase chain reaction. American Journal of Tropical Medicine and Hygiene 2006; 75(6): 101-2.

5. Praveen Kumar AS, Prasad AM, Gumpenny L, Sidadappa R. Leucocytoclastic vasculitis and polyarthralgia in scrub typhus: An unusual presentation. International Journal of Medicine and Public Health 2013; 3:352-4. https://doi.org/10.4103/2230-8598.123530

6. Suja L, Krishnamoorthy S, Sathiyan S, Srinivasan S. Scrub typhus vasculitis causing pan digital gangrene. International Journal of Case Reports and Images 2015; 6(7):416-21.

7. Kalal BS, Pranaik P, Nagaraj S, Rego S, Shet A. Scrub typhus and spotted fever among hospitalised children in South India: Clinical profile and serological epidemiology. Indian Journal of Medical Microbiology 2016; 34:293-8. https://doi.org/10.4103/0255-0857.188315 PMid: 27514949

8. Bal AK, Kairys SW. Kawasaki disease following Rocky Mountain spotted fever: a case report. Journal of Medical Case Reports 2009; 3: 7320. https://doi.org/10.4076/1752-1947-3-7320 PMid: 19830185 PMCid: PMC2737781

9. Krishnan R, Pillai RK, Elizabeth KE, Shanavas A, Bindushima S. Paediatric scrub typhus in South Kerala: An emerging public health problem. Clinical Epidemiology Global Health 2016; 4(2): 89-94. https://doi.org/10.1016/j.cejgh.2016.03.003

10. Uchiyama T, Kato H. The pathogenesis of KD and superantigens. Japanese Journal of Infectious Disease 1999; 52:141-5. PMid:10592892

11. Yanagawa H, Nakamura Y, Ojima T, Tanihara S. Changes in epidemic patterns of KD in Japan. Pediatric Infectious Disease Journal 1999; 18:64-6. https://doi.org/10.1097/000064541999010 00-00015 PMid: 9951983

12. Tsaka K, Hamashima Y. Studies on rickettsia-like body in Kawasaki disease. Attempts of the isolation and characterisation. Acta Pathol Jpn 1978; 28:235-45