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Case Report

An unusual cause of shock in pediatrics

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The Case

Miss Anju (name changed for privacy), five and half years old developmentally normal girl hailing from Puducherry presented to the Pediatric Emergency Department with high grade pyrexia of 7 days duration. On the fifth day of fever, she developed a macular rash which started over the face and spread to involve the rest of the body over a period of a few hours. Puffiness of face and abdominal distension had developed over the last 2 days along with decreased urine output. She had history of seizures since 2 years of age and was on regular therapy with Valproate sodium 20 mg/kg/day.

In our High Dependency Unit, she was noted to be drowsy, but responsive to call. Her axillary temperature read 101.5 degrees Fahrenheit. Her radial pulse rate was 140/minute with diminished pulse volume. Brachial blood pressure was 88/70 mm Hg and Hess test was negative. Her respiratory rate was 32 per minute. Her eyes were congested. She had a macular confluent rash involving the face, trunk and extremities. Her abdomen was distended. Her liver was firm, palpable 6 centimeters below the right costal margin, with a span of 10 centimeters. Her spleen was not enlarged. However shifting dullness was positive. There were no basal crackles, cardiovascular examination was unremarkable except for tachycardia.

An emergency platelet count was 30,000 per cu.mm, PCV 27%, and Hb 9.0 g/dl, ESR 70 mm/hr. Her renal function tests and electrolytes were normal. Her liver function tests showed low serum albumin (1.7 g/dl) and total protein (5.4 g/dl), and an elevated Aspartate transaminase (81 IU/L). An uncentrifuged urine examination revealed 4 RBCs/hpf with no proteinuria. A bedside chest radiograph was unremarkable.

She was started on broad spectrum antibiotic (Ceftriaxone) with antipyretics and intravenous fluids. She was given a normal saline bolus for shock and thereafter started on maintenance intravenous fluids. However her respiratory distress worsened within 6 hours, with a rate of 56 per minute. Her pulse rate was 172/minute and she remained febrile. Her blood pressure was104/66 mm Hg. Her JVP was elevated 4 centimeters above the sternal angle, and her liver was palpable 7 cm below the right costal margin. She was noted to have basal crackles and a faint S3 gallop. An EKG revealed low voltage complexes. She was given Frusemide 1 mg/kg and she was put on two-third maintenance intravenous fluids.

The gallop rhythm disappeared in 1 hour, and her chest was clear in another 2 hours. Her

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respiratory distress also improved. Her rash disappeared in 36 hours.

Further investigations showed Hb 8.2 g/dl, WBC count 3,600 per cu.mm, with 76% polymorphs, 18% lymphocytes, and platelet count of 38,000 per cu.mm. The peripheral smear revealed normochromic, normocytic anemia and toxic granules in neutrophils. Her blood and urine cultures were sterile. Thick smear examination for malarial parasite was negative on three consecutive days. An indirect Coomb's test for HRP-2 antigen was negative Her ESR was 70 mm/hour, CRP 12 µg/ml, total CPK 684 U/L, CPK-MB 10 U/L. A repeat chest radiograph was affirmative of fluid overload. Her echocardiograph confirmed mild pericardial effusion; however there was no evidence of cardiac tamponade and her ejection fraction was 62%. Her Widal was negative; anti Dengue serology was negative for IgG and IgM. A leptospira microscopic agglutination test was also negative.

However, she continued to have daily spikes of fever. Her antibiotics were changed to Ceftazidime with Amikacin on day 4. By day 3, her spleen was palpable 1 centimeter below her costal margin. She developed extensive subconjunctival hemorrhage in her right eye on day 4. Fever persisted.

In view of persisting fever, a bone marrow study was obtained. It revealed increased activity with normoblastic eythropoiesis and increased macrophages. The myeloid – erythroid ratio was 1:1, and there were no abnormal cells. Her marrow culture was noted to be sterile.

A Weil – Felix test was done as part of workup for pyrexia of unknown origin and the report was as follows: OX – 19: less than 20, OX – K: 80 and OX – K: 640. The titers were suggestive of scrub typhus. She was started on Doxycycline 2.2 mg/kg twice daily. She became afebrile in another 48 hours. Her subconjunctival hematoma resolved over 10 days. She was discharged to follow up on day 13 of admission.

Discussion

Introduction: Scrub typhus is caused by O.tsusugamushi , a rickettsia. It is prevalent in rural areas where there is abundant scrub vegetation-hence the name. (1,2). This disease is distributed in the the so-called tsutsugamushi triangle, lying between Australia, Russia and Japan (1) which includes mainly the Indian subcontinent, western Russia, China and the far east. The disease is endemic in parts of eastern, southern and south-eastern Asia, including India, especially in the foothills of the Himalayas. Nearly 1 million people may be annually infected (1).

Epidemiology: This disease scourged through the second World War and resulted in high morbidity and mortality (1-5). The disease was lesser known in the southern states of the country, where it has recently gained importance (6, 7). The mites normally infest rodents and are transmitted to man accidentally, when the latter tries to encroach onto the rodent habituating grounds or onto areas where mites are abundant called 'mite islands'. Diverse habitats like sandy beaches, equatorial rain forests, rice fields and even sandy deserts (4). So much so that the term Scrub typhus has been considered as a misnomer of late, and chigger-borne rickettsiosis has been suggested instead, due to this vast range of its habitat (4). Seasonal preponderance towards autumn and spring has been noted (1).

Etiology: This organism is maintained in nature by transovarial transmission in trombiculid mites, mainly of the genus Leptotrombidium. After hatching, the infected larvae inoculate the organisms into the skin while feeding on the animal host (1-5). The bacterium exhibits antigenic heterogeneicity and cross reactivity, the major serotypes (based on the 56 kDa protein) being Gilliam, Karp, Kato, Boryon, kawazaki and the recently identified Lichtfield strain (1,3,8, 9). In O. tsutsugamushi, an in-depth genetic analysis showed that high level of gene loss has taken place like in other obligate intracellular bacteria, but massive amplification of various mobile

elements has also taken place, which has induced intensive genome shuffling and generated a large number of repeated genes (9). The exact importance of these details is not known, but they may play an important part in its pathogenesis.

Pathogenesis: The rickettsia enter the capillaries at the site of bite and invade the vascular endothelial cells. They remain unnoticed or progress to a potentially fatal disease usually involving the lungs. They enter endothelial cells and fibroblasts through the clathrin-mediated endocytic pathway and move from the endosome to the cytosol at the phagosome/lysosome stage (10). These organisms are obligate intracellular pathogens and proliferate within these endothelial cells spreading to the neighbouring cells in a centripetal manner producing a microfoci of infection (1,2,3,4,10). The foci spread to involve the arterioles and venules and eventually disseminate to all the organ systems. The infected cells may show distintegration of golgi apparatus and fragmentation of the plasma membrane resulting in the lysis of the cells. The damaged vascular endothelium is surrounded by an inflammation which results in vasculitis, which results in furthur damage. Direct injury to the vascular endothelium is a hallmark of the infection with all members of the family Rickettsiaceae (4,10).

There is a combined upregulation of IFN-Õ and IL-10. It exerts an inhibitory effect on the immune response that helps surviving in an intracellular environment, in a similar way as in *Legionella pneumophila* infection (11).

Clinical features: Since the organism can invade any organ, the symptoms and signs are non-specific. The illness ranges from being mild to self limiting, at times fatal if left untreated. It is unclear whether severity is contributed by traits of the infecting strain, the infecting bacterial dose, the patient's immune response, or other host properties. The incubation period usually ranges from 6 to 21 days (usually 7 days).The illness classically sets in with an eschar at the site of the chiggers' bite associated with regional lymphadenopathy and a maculopapular rash. These signs are usually absent and most often the patients complain of fever, myalgia, headache and vague gastrointestinal symptoms (1-10), occasionally hearing loss (12). In severe cases, encephalitis and/or interstitial pneumonitis may be present (1-4).

It is important to timely diagnose such infections and initiate appropriate therapy as there is usually an excellent response to treatment. In developing countries with limited diagnostic facilities, such patients with undifferentiated febrile illness having evidence of multiple system involvement often are missed, which is associated with higher morbidity and mortality.

Diagnosis: Diagnosis of rickettsial infections rests mainly on serology, as isolation is difficult. The various tests that are available include microimmunofluorescence, latex agglutination, indirect hemagglutination, immunoperoxidase assay, and enzyme-linked immunosorbent assay. Immunofluorescence assay (IFA) is the "gold standard" technique and is used as a reference technique in most laboratories. The sensitivity and specificity obtained by immunoperoxidase assay for the serodiagnosis of scrub typhus resemble those obtained by IFA. The commercially available dot blot immunoassay for the diagnosis of scrub typhus lacks both sensitivity and, especially, specificity. This test can be considered useful only as a first-line test, as an alternative to the Weil-Felix test, for the rapid diagnosis of acute cases of infection in areas with a high prevalence. The Weil-Felix (WF) test is based on the detection of antibodies to various *Proteus* species which contain antigens with cross-reacting epitopes to antigens from members of the Rickettsiae. The OX-K strain of *Proteus mirabilis* was demonstrated to agglutinate with sera from scrub typhus patients and was further used in the diagnosis of *O. tsutsugamushi*-related infections. The criterion for a positive result is either one determination of a titer of 1:320 or greater or a four fold rise in titer starting from 1:50. By the WF test, agglutinating antibodies are detectable after 5

to 10 days following the onset of symptoms, with the antibodies detected being mainly of the immunoglobulin M (IgM) type. However, the WF test may be positive without rising IgM antibody titers. The Weil Felix test is usually positive during the second week of illness, which means that a number of patients may remain undetected if not sampled at the appropriate time. The requirement of double serum specimens has limited its usage for diagnosis. The poor sensitivity of the WF test are now well demonstrated but a good correlation between the WF test and the immunofluorescence assay (IFA) is often observed (1,2,6,13,14). Recently, commercial rapid detection kits like Dip-STicks, scrub typhus RCT and scrub typhus IgM and IgG Rapid Immunochromatographic Assay (PanBio, Brisbane, Australia) and Multies Dip-S-Ticks Scrub Recombinant Assay (Integrated Diagnostics, Baltimore, Maryland, USA) have appeared in the market but because of their high cost these are yet to become popular(15).

Molecular methods like PCR (14) have been developed, but are of restricted access due to the expenses involved.

Treatment: The treatment of choice is tetracycline and its congeners like doxycycline. But, Rifampicin is seen to be more effective than doxycycline in areas where scrub typhus appears to respond poorly to standard anti-rickettsial drugs. Therefore it is suggested that clinicians should monitor the progress of patients in the light of reports of drug resistance. Regimens for severe disease need to be evaluated for example, comparing intravenous chloramphenicol with intravenous tetracycline (16). Recent studies have revealed the effectiveness of alternative antibiotics like Azithromycin particularly in areas where scrub typhus appears to response poorly to standard anti-rickettsial drugs(17).

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GENERAL ALGORITHM FOR SHOCK

0 – 5 minutes

- Assess "Appearance", (decreased responsiveness), "Work of breathing" and "Circulation" (mottling, pallor, cyanosis, diaphoresis).
- Airway, Breathing, Circulation (including CFT), Disability (AVPU, GCS, pupillary response, brain perfusion), Exposure (visual bleeding, etc).
- Begin high flow O_2 / establish & maintain airway.
- Iv / intraosseous access
- 20 ml/kg initial fluid bolus
- Consider intubation

5 – 15 minutes

- Fluid boluses of 20cc/kg upto & >60ml/kg*
- Monitor for features of fluid overload
- Correct hypoglycemia
- Correct hypocalcemia
- Start early antibiotic
- 2nd iv access – **start inotropes**
- Assess shock- if not reversed

15 – 60 minutes

- Fluid refractory shock- start inotrope-dopamine

Cold shock- dopamine, epinephrine

- Warm shock- norepinephrine

1 – 6 hrs

- PICU shift
- Crystalloids / packed cells
- Monitor CVP,MAP,
- Titrate fluids & inotropes to reach ScVO2>70

Beyond 6 hrs

- Recognise catecholamine resistant shock
- Consider hydrocortisone 50mg/ m2/dose
- If cold shock & BP normal: Consider vasodilator/PDE inhibitor
- If warm shock & BP low: Consider vasopressin

*Boluses to be given at 5 – 10 ml/kg for cardiogenic shock

NB: Specific management protocols for each type of shock and for specific conditions continue to apply.