International Journal of Contemporary Pediatrics
Das S et al. Int J Contemp Pediatr. 2020 Aug;7(8):1812-1815
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: http://dx.doi.org/10.18203/2349-3291.ijcp20203185

Case Report

Scrub typhus leading to focal segmental glomerulosclerosis in a child due to genetic predisposition

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Received: 22 May 2020
Accepted: 29 June 2020

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ABSTRACT

Scrub typhus is a multisystem disease, caused by genera orientia tsutsugamushi and is currently endemic in India. In children, the disease may vary from a mild to a severe form. Complications include encephalitis, myocarditis, disseminated intravascular coagulation, acute kidney injury, atypical pneumonia, etc. The pathophysiologic mechanisms of renal involvement in scrub typhus include prerenal failure, septic shock, vasculitis, acute tubular injury and direct renal invasion by rickettsia. Here, authors present the case of a previously well 5-year old female child who was admitted to our hospital with a history of high-grade fever and pain abdomen. IgM scrub typhus turned out to be positive and she was adequately treated with doxycycline. She turned afebrile but then gradually developed anasarca, hematuria, proteinuria and persistent stage 2 hypertension. Kidney biopsy was done which revealed focal segmental glomerulosclerosis (FSGS). Further workup of the patient by whole exome sequencing revealed missense mutations in TBX18, INF2 and NPHS1 genes. Mutations in INF2 gene is a recently discovered cause of autosomal dominant FSGS. In our case, the scrub typhus mediated kidney injury probably acted as a trigger in unmasking FSGS in the already genetically susceptible child.

Keywords: Focal segmental glomerulosclerosis, Genetic mutations, INF2 mutation, Scrub typhus

INTRODUCTION

Scrub typhus is a vector borne zoonosis which is caused by a gram-negative pleomorphic coccobacilli and obligate intracellular parasite called Orientia Tsutsugamushi. It is spread by the bite of trombiculid mite. Patients usually present with anorexia, headache and very high-grade fever and chills. There may also be pain abdomen, a maculopapular rash and generalised lymphadenopathy.[1] Scrub typhus can affect all of the organ systems and is notorious for the development of serious complications like atypical pneumonia, acute renal failure, acute respiratory distress syndrome, myocarditis and septic shock, encephalitis and encephalomyelitis.[2,3] Renal complications of scrub typhus have been frequently reported. An Indian study found renal abnormalities in almost 82% of patients presenting with scrub typhus with evidence of acute kidney injury (AKI) in 53% patients.[4] Nephrotic syndrome has also been reported.[5] However, Focal Segmental Glomerulosclerosis (FSGS) occurring after scrub typhus infection has not been previously reported in literature. FSGS is a diverse syndrome which arises due to podocyte injury, the sources of which are varied (circulating factors, genetic abnormalities, medication and viral infection).[6] In the present case, a genetically susceptible individual developed FSGS, with scrub typhus associated renal invasion being the cause of podocyte injury.

CASE REPORT

A five-years old female child was admitted to our hospital with complaints of high-grade fever and pain abdomen along with headache and malaise for the last 7 days. She was born as a full-term neonate and did not have a significant birth history. On examination, she was irritable, had a temperature of 103ºF, a maculopapular rash throughout her trunk, cervical lymphadenopathy and a tender abdomen with mild hepatomegaly. Scrub typhus IgM ELISA turned out to be reactive.

Other diseases like dengue, kalazar, malaria, leptospira were ruled out. Intital urine examination was normal. Patient was given doxycycline for 5 days, after which she turned afebrile. But then she gradually developed anasarca (puffiness of face, bilateral pleural effusion, pericardial effusion, ascites and bipedal edema), tender hepatomegaly, bilateral wheeze and basal crepitations in chest and stage 2 hypertension.

The platelet count was found to be decreased, triglycerides slightly raised and albumin reduced. Anti-nuclear antibodies (ANA) showed a titre of 1:160, which could be due to the severe nature of the infection and systemic lupus erythematosus was ruled out by a negative anti ds-DNA report. Hepatitis B and C were also ruled out (Table 1).

Table 1: Reports of baseline blood investigations and other tests done to rule out specific diseases.

Test	Result
Hemoglobin	8.9 g/dl
Total WBC count	11,700/cumm
Platelets	24,000/cumm
Urea	48 mg/dl
Creatinine	0.6 mg/dl
Triglycerides	306 mg/dl
Albumin	2.5 gm/dl
Ferritin	776 ng/ml
ICTC	Non-reactive
Anti-nuclear antibodies	3+ homogeneous
Anti ds-DNA	<10 IU/ml
HBsAg	Non-reactive
Anti-HCV Antibody	Non-reactive

Echocardiography showed severe pericardial effusion with pulmonary arterial hypertension. Chest X-ray showed bilateral massive pleural effusion. Pleural fluid and ascitic fluid analysis did not reveal anything significant. Computed tomography scan of whole abdomen showed enlarged kidneys with globular shape and rounded margin.

Excretion of contrast was delayed. Mantoux test and CBNAAT report were negative. Patient was initially managed for heart failure with milrinone infusion. However, hypertension was consistently between stage 1 and stage 2, even with two different anti-hypertensive drugs. Single measurement of 24-hour urinary protein showed non-nephrotic range proteinuria. However, urine albumin creatinine ratio was highly raised suggesting macroalbuminuria with 20-25 red blood cells per high power field (Table 2).

Table 2: Results of urine examination.

Test	Result
Urine albumin creatinine ratio	906.8mcg/mg creatinine
Albumin	2+
Pus cell	3-4/hpf
Red blood cell	20-25/hpf
Granular casts	2-5/lpf
24-hour urinary protein	Non-nephrotic range proteinuria

Repeat urine examinations also showed that patient continued to have persistent microscopic haematuria. These findings strengthened the suspicion of a renal pathology.

Finally, renal biopsy was done. Renal biopsy revealed focal segmental glomerulosclerosis (FSGS) with acute tubular injury (Table 3).

Table 3: Result of renal biopsy.

Test	Result
Light microscopy findings-	Total 8 glomeruli seen. 3 glomeruli segementally sclerosed with adhesion. Rest 5 show mild mesangial matrix expansion with focal hypercellularity. Tubules- Acute tubular injury with RBC casts. Intratubular polymorphonuclear cells noted
Immunoflou -rescence	IgM shows podocytic uptake. IgG, IgA, C1q, kappa, lambda show no immune deposits
Final diagnosis	Focal Segmental glomerulosclerosis without tubulointerestitial chronicity
	Acute tubular injury
	Focal pyelonephritic changes

Edema was managed by pleural and ascitic fluid drainage and blood pressure was controlled by furosemide, spironolactone, amlodipine and labetalol. Since FSGS in association with scrub typhus has not been previously reported, whole exome sequencing was done to search for genetic causes. e. pertensive drugs.

Three missense mutations were found, all of which are responsible for causing kidney diseases (Table 4).

After resolution of her presenting symptoms, patient was discharged on the above four anti-hypertensives, and asked to come for follow up after a month. On follow up

examination, patient was found to be doing well. Blood pressure was within normal limits and there were no further complaints. Patient was instructed to come for regular follow ups thereon.

Table 4: Result of whole exome sequencing to search for genetic mutations causing focal segmental glomerulosclerosis.

Gene (Transcript)	Location	Zygosity	Inheritence	Classification
TBX18	Exon 8	Heterozygous	Autosomal dominant	Uncertain significance
INF2	Exon 8	Heterozygous	Autosomal dominant	Uncertain significance
NPHS1	Exon 18	Heterozygous	Autosomal recessive	Uncertain significance

DISCUSSION

Rikettsial infections are prevalent throughout the world. In India, scrub typhus has been commonly reported from the southern part, although there have been reports of several outbreaks occurring in the sub-himalayan region.[7] In children, scrub typhus disease may vary from being a mild to a very severe form. An eschar may not be present in all cases. Scrub typhus should be suspected in all cases presenting with high grade fever, rash, lymphadenopathy and hepatosplenomegaly. Complications of this disease range from encephalitis, myocarditis, disseminated intravascular coagulation (DIC), AKI, atypical pneumonia, etc. There is paucity of studies regarding complications of scrub typhus in children. A study from South India showed high incidence of AKI in children suffering from scrub typhus.[8] Renal involvement is believed to be a part of the multiorgan dysfunction syndrome in severe disease. The mechanisms may be reduced renal perfusion due to hypovolemia, increased vascular permeability, acute tubular necrosis, vasculitis, thrombotic microangiopathy and also direct renal invasion by O. Tsusugamushi.[9,10] Nephrotic syndrome has been shown in association with scrub typhus although it is very rare, especially in children. Recognised secondary causes of FSGS in children are mainly viral infections like hepatitis B, hepatitis C, HIV, cytomegalovirus, parvovirus B19 and Epstein Barr virus. Malaria, leptospira are also rare causes. In this case, there was no eschar. Scrub typhus IgM ELISA was sent on the basis of high index of suspicion which came out to be positive. The child was treated adequately with doxycycline. In spite of that, she soon developed anasarca, proteinuria, hematuria and stage 2 hypertension due to which kidney biopsy was performed which revealed FSGS. Viral causes of FSGS, malaria and leptospira were already ruled out by appropriate tests. The child did not have any risk factors for adaptive FSGS like congenital cyanotic heart disease, sickle cell anemia, obesity, sleep apnoea and high-protein diet.[11-14] Whole exome sequencing was done which revealed heterozygous missense mutations in TBX18, INF2 and NPHS1 genes. TBX18 gene mutation is associated with congenital anomalies of kidney and urinary tract and bilateral multicystic dysplastic kidney while NPHS1 gene mutation is associated with congenital nephrotic syndrome. Recent studies have shown that mutations in INF2 (inverted formin 2) gene is associated with familial forms of FSGS and it is the most common cause of autosomal dominant FSGS.[15-17] FSGS can be precipitated by any form of podocyte injury. Podocyte depletion arising from an inability to replicate results in a podocyte catastrophe.[18] To balance this deficit, podocytes compensate by hypertrophy to cover more of the glomerular capillary surface area. In glomerular diseases, glomerular hypertrophy occurs with progressive nephron loss, leading to increased pressure in the remaining glomeruli. In our case, scrub typhus mediated renal invasion probably led to podocyte depletion, which unlike other post-infectious injury, did not recover due to the underlying genetic predisposition. The parents of the child were counselled about the prognosis of the disease and requested to come for regular follow ups.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Das S, Pandey R, Roy S. Scrub typhus leading to focal segmental glomerulosclerosis in a child due to genetic predisposition. Int J Contemp Pediatr 2020;7:1812-5.