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Infection related glomerulonephritis due to scrub typhus in paediatric population: A case series and literature review

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ABSTRACT

Background: Infection-related glomerulonephritis (IGRN) is an immune-complex mediated renal injury occurring simultaneously with the infection. Till date, though rare, all the reported cases of IRGN were caused by either *Streptococcus* spp. or *Staphylococcus* spp. Emerging suggestive risk factors for IRGN were diabetes mellitus, malignancy, HIV infection, and alcoholism. IRGN following *Rickettsial* infection, its disease course, and fatality are unknown. **Aims and Objectives:** In the pediatric population most of the cases are diagnosed as post-infection glomerulonephritis that occurred after a latent period. Here we have presented five typical cases of IRGN with its complication caused by atypical organism. From both points of view, the case series is rare and unique. **Materials and Methods:** The authors report five cases of IRGN in scrub typhus infection that illustrate the difficulty of its diagnosis and do a brief review of the literature on this topic. **Results:** All the five cases were presented with fever, without any Eschar except one. Moreover, they presented with bizarre renal symptoms confounding diagnosis. All the cases had neutropenia and lymphocytosis that was the sole finding to point toward scrub typhus. But none of our cases had developed acute kidney injury as such. **Conclusion:** Scrub typhus is an acute febrile illness. Hence, patients with nephritic presentation should be evaluated for Scrub typhus infection if associated with long-term unresolving fever.

Key words: Glomerulonephritis; Hematuria; Hypertension; Infections; Scrub typhus

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INTRODUCTION

Scrub typhus is an age-old disease. During World War II, Scrub typhus caused considerable morbidity and mortality among troops deployed In Southeast Asia. However, there has been a considerable decline in the incidence of scrub typhus in the later decades.[1] Scrub typhus is a Rickettsial febrile illness caused by *Orientia tsutsugamushi* (*Rickettsia tsutsugamushi*). It is spread by tick bite and an Eschar is produced at the bite site, in 45–55% of cases.[2] Scrub typhus is characterized by focal or disseminated vasculitis and perivasculitis involving the liver, spleen, heart, lungs, and nervous system and may present as non-specific febrile illness or multi-organ involvement.[3] The prevalence and outcome of kidney involvement, especially AKI, in scrub typhus are not known.[4] Immune complex-mediated glomerulonephritis in Rickettsial infection are hardly reported cases in pediatric patients. Importance of keeping scrub typhus in mind as an etiology for infection-associated acute kidney injury in tropical countries. Scrub typhus can cause nephrotic syndrome-like features like malaria does.[5]

The authors report five cases of infection-related glomerulonephritis (IRGN) in scrub typhus infection that illustrates the difficulty of its diagnosis and do a brief review of the literature on this topic.

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CASE REPORT

Case 1

A 6 ½ years old boy presented with moderate fever and generalized swelling for 3 weeks. Swelling had started in the periorbital region 3 weeks back. Gradually, he developed swelling of both lower limbs and scrotum associated with decreased urine output for the past 5 days, for which the parents sought for medical treatment. He had a history of high-grade fever with rashes at an initial 2–3 days of illness. During admission, the boy was alert, conscious, afebrile, and anicteric. He had moderate pallor and generalized pitting edema. His pulse rate was 84/min but blood pressure (BP) was 130/70 mm of Hg. There were significantly enlarged lymph nodes in the cervical region only. Per abdominal examination revealed firm, non-tender, and mild hepatomegaly with positive shifting dullness.

Our provisional diagnosis was nephrito-nephrotic syndrome (kidney disorder that causes the body to pass too much protein in urine). Later the workup was done. Complete hemogram showed hemoglobin (Hb)–8.49 g/dl; total leukocyte count (TLC) - 7600/μl; Differential leukocyte count – $N^{26}L^{58}$ $M^{13}E^{2}$ B^{1}, Platelet count- 1.02 lakhs/μl. Packed cell volume was 24.8% and there were no abnormal cells. (Table 1)

C-reactive protein (CRP) - 14.6 mg/L; Serum cholesterol- 100 mg/dl; Serum Na+ - 134.2 meq/L, K+ - 3.78meq/L, Urea – 14, Creatinine-0.51; Liver function test – total bilirubin- 0.68 mg/dl, direct bilirubin- 0.12 mg/dl, serum glutamic pyruvic transaminase (SGPT)- 56U/L, serum glutamic oxaloacetic transaminase (SGOT)- 48U/L, total protein- 3.1 g/dl, albumin- 1.9 g/dl. Serum cholesterol -140 mg/dl; Urine routine examination report was- protein ++, red blood cells – plenty, Serum anti streptolysin O titre was <200 U/ml; epithelial cells – nil. Ultra sound of abdomen revealed moderate ascites and bilateral pleural effusion. (Table 1)

The reports made a dilemma of diagnosis but excluded acute kidney injury. As the urine culture report was pending, the patient was treated with intravenous ceftriaxone presuming as a case of urinary tract infection. Later on, the culture report showed no growth. The swelling was increasing and there was low-grade persistant fever. So further work up was done to rule out any atypical infection. Enzyme-linked immunosorbent assay for Scrub typhus revealed strongly positive Immunoglobulin (Ig)M titer.

Patient was put on oral azithromycin (10 mg/kg/day; once daily dosage) and after 3 days of treatment the fever subsided and after 5 days of treatment edema was started subsiding. BP became normal without any anti-hypertensive medication. Edema disappeared completely after 10 days of starting oral azithromycin. Hypertension set at the 95th percentile of their age, sex, and height.

Age	SBP	DBP
3–5 years	95–107	60–71
6–9 years	95–110	60–73

SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Case 2

A 5-year-old boy presented with high-grade fever for 2 weeks with decreased urine output, with high colored urine and facial puffiness for the past 5–6 days. During admission the patient had high-grade fever, bilateral pedal edema and facial edema, BP was 110/74 mm of Hg, and soft mild hepatomegaly. We started treatment with broad-spectrum antibiotics and blood samples was sent for investigation. By the 3rd day of admission, the child had developed severe headache followed by vomiting and the BP was 136/84 mm of Hg. The BP was controlled conservatively by oral anti-hypertensives. In the meantime the investigational reports came, showing Hb -8.8 g%, TLC - 10500/cmm, differential leucocyte count (DLC) – $N^{23.5}$ $L^{70.5}$ $M^{4.7}$ $B^{0.5}$ $E^{0.08}$ Platelets - 1.9 lakhs/μl. CRP - 110.5 mg/l; Widal test was positive in 1:80 dilution; malaria antigen was negative; urine routine examination- appearance normal, protein ++, red blood cells 18-20/high power field, no epithelial cast, no bacteria; urine culture was negative so also the blood culture. The edema was gradually increasing and the BP become uncontrollable with only oral calcium channel blockers (CCB). We started angiotensin-converting enzyme inhibitors (ACEI) orally along with CCBs. Later the report showed urea- 56 mg/dl, creatinine-1.07 mg/dl, Na+ - 140.1 mmol/l, K+ -3.6 mmol/l; in liver function test total serum bilirubin - 0.71 mg/dl, direct bilirubin - 0.23, SGOT - 72 U/l, SGPT - 65 U/l, total protein - 6.7 g/dl, Albumin - 3.6 g/dl, serum cholesterol - 90 mg/dl. Ultrasound of the abdomen showed raised cortical echogenicity in both kidneys. (Table 1)

After 14 days of treatment there was no improvement of symptoms, rather the condition deteriorated by means of persisting fever, generalized edema, and gross haematuria. Kidney biopsy was done and revealed Minimal Change Disease. Then oral azithromycin was started and blood for scrub typhus IgM was sent as the patient came from a scrub typhus endemic region. The scrub typhus IgM was positive. After 6 days of treatment with azithromycin the patient became afebrile and both BP and hematuria were controlled by 14 days after starting treatment with azithromycin. During post-discharge follow-up after 4 weeks, BP and clinical condition were normal and there was no microscopic hematuria.

Table 1: Tabular presentation of findings of the cases is given below

Findings of the cases	Case 1	Case 2	Case 3	Case 4	Case 5
Age	6 years 6 months	5 years	4 years	1 year	4 year
Sex	Boy	Boy	Girl	Girl	Girl
Duration and intensity of fever	>3 weeks, moderate grade	>2 weeks, high grade	10 days, moderate grade	8 days, high grade	7 days, moderate grade
Lymphadenopathy	Cervical, non-significant	No	No	Cervical, significant	No
Hepatomegaly	Mild, firm	Just palpable	No	No	Firm , mild
Ascites	Shifting dullness	No	No	No	No
Pleural effusion	Bilateral , mild	No	No	No	No
Spleenomegaly	No	No	No	No	No
Eschar	No	No	No	No	Yes
Pallor	Moderate	Moderate	Moderate	Mild	Mild
Facial Puffiness	Yes	Yes	Yes	Yes	Yes
Edema	Generalised	Pedal and facial	Facial	Yes	Yes
Pulse Rate	84/min	78/min	96/min	138/min	104/min
Blood Pressure	130/70 mm of Hg	136/84 mm of Hg	128/72 mm of Hg	98/64 mm of Hg	126/70
Hematuria	Microscopic	Microscopic	Gross	Microscopic	Microscopic
Proteinuria	++	++	++	++	++
Urea	14	56	46	33.3	36
Creatinine	0.51	1.07	0.8	0.47	1.02
Sodium (mmol/l)	134.2	140.1	136.6	143	138.7
Potassium (mmol/l)	3.78	3.6	4.32	3.72	4.2
Hemoglobin (g%)	8.49	8.6	8.5	9.4	10.7
Total Leukocyte Count (per cmm)	7600	10500	12900	21600	19800
Neutrophils (%)	26	23.5	12.9	27.9	21.8
Lymohocytes (%)	58	70.5	76.5	56.2	72.8
Serum Albumin (g/dl)	1.9	3.6	2.4	3.2	3.9
Serum Cholesterol (mg/dl)	140	90	110	126	115
CRP (mg/l)	14.6	110.5	14.5	76.4	43.6
Anti Streptolysin O (IU/l)	<200	<200	<200	<200	<200
Defervescence after treatment (in days)	3	6	5	2	2
Anti-hypertensive drugs required	No	CCB and ACEI	CCB	CCB	CCB

CRP: C-reactive protein, CCB: Calcium channel blockers, ACEI: Angiotensin converting enzyme inhibitors

Case 3

This case was almost similar to the second case, 4 years old grade 1 malnourished girl child having Gr-1 malnutrition was brought with fever for 10 days and red color urine for 3 days. She also had a history of recurrent upper respiratory tract infection. During admission she had moderate pallor, periorbital edema and BP was 106/48 mm of Hg. Initially, she was treated as a case of urinary tract infection. The investigation reports were Hb - 8.5 g%, TLC - 12900/cmm, DLC - $N^{12.9}$ $L^{76.5}$ $M^{9.4}$ $E^{0.6}$ $B^{0.6}$ platelets - 1.67 lac/cmm. CRP - 14.5 mg/l; urine microscopic finding was plenty of red blood cells, urine culture showed no growth, Serum urea – 46 mg/dl, creatinine - 0.8 mg/dl. After 5 days of treatment, the patient experienced 1 episode of generalized tonic clonic convulsion. The convulsion controlled with short-acting benzodiazepines. During convulsion the BP was 136/72 mm of Hg and capillary blood glucose was 124 mg/dl, serum Na^+ -136.6 mmol/l, K^+ - 4.32 mmol/l, (i) Ca^{++} - 4.41 mg/l. Though there was no sign of meningeal irritation cerebrospinal fluid study was done to rule out meningitis. Further evaluation was done including Widal test, malaria antigen test, leptospira IgM antibody, dengue IgM antibody, and Scrub typhus IgM antibody test. All of them were negative except scrub typhus Ig M test which was positive. Brain imaging showed hyperintensity in the occipital cortex suggestive of hypertensive encephalopathy. This patient with scrub typhus presented with hematuria, and with hypertension with its complication, like a case of nephritic syndrome. After treatment with oral azithromycin fever resolved by the 5th day and on follow-up, there was no hypertension and/or hematuria. (Table 1)

Case 4

A 1-year-old girl presented to outpatient department with a history of fever for 8 days, associated with edema which

started in the face and gradually progressed to bilateral pedal edema. Her parents also gave a history of scanty urine output for the last 48 h. General examination revealed significant cervical lymphadenopathy bilaterally. IgM for scrub typhus was positive. Blood tests revealed a total count of 21600/mm^3 DLC N27.9, L 56.2, E 15.9, M0, B0, Hb – 9.4 g/dl. Serum urea and creatinine were normal 33.3 mg/dl and 0.47 mg/dl, respectively. Serum cholesterol was normal. (Table 1)

She was started on oral Azithromycin (@ 10 mg/kg/day). Fever subsided after 48 h and urine output improved over the same duration. Edema had completely subsided by day 6 of treatment. The patient was discharged without any residual complaints after 7 days of antibiotic.

Case 5

A 4-year-old boy with bodyweight of 13 kg was admitted with a history of fever for 7 days along with complaints of reduced urine output, painful micturition with increased frequency and high colored urine for nearly the same duration of time and reduced appetite. There was no history of any bleeding from any other orifices. Both parents were agricultural workers and the family lived quite close to the rice fields. On physical examination, a typical eschar was seen near the left flank on the back along with facial puffiness. IgM Scrub typhus was positive (titer 0.7). Blood counts revealed neutrophilic leukocytosis with a total count of 19800/mm^3 and thrombocytopenia (Platelets 16000/mm^3). Urinalysis revealed 2+ proteinuria, 10-12 pus cells, and 6–7 RBC's/hpf. Granular casts were also seen on microscopical examination (PIC). Serum values of urea, creatinine, and electrolytes were within normal limits. There was no associated hypertension. He was started on I.V Azithromycin for 7 days. The fever resolved within the first 48 h of therapy and there was improvement in appetite along with a reduction of facial puffiness. Urinary symptoms also abated in the next 2 days and repeat urinalysis done at 5 days of hospital stay was normal. The patient was discharged after 7 days without any complications. (Table 1)

DISCUSSION

Renal involvement in scrub typhus infection is not uncommon. Patients usually present as acute kidney injury in a background of acute febrile illness. The urinalysis with dipstick, positive albuminuria, and microscopic hematuria is most common.[6]

In this series, we have presented five cases having hematuria, hypertension, albuminuria, and edema along with fever suggestive of nephritic syndrome-like presentation. Rickettsial infection is also a rare cause of glomerulonephritis.[7] Several hypotheses have been proposed to explain the mechanism by which *O. tsutsugamushi* infection causes acute renal involvement. According to Dumler et al., prerenal azotemia is the main pathophysiology of renal failure caused by the decrease of effective renal blood flow due to increased vascular permeability in patients with murine Typhus accompanied by systemic vasculitis.[8]

In a recent study, Glassock et al.,[9] proposed a nomenclature for glomerulonephritis associated with infections, which were classified into two, post-infectious glomerulonephritis (PIGN) and IRGN. Our patients exhibited few clinical findings, such as fever, weight gain, and pedal edema simultaneously, without any latent period. Such clinical course is suggestive of IRGN, related to the primary infection. Direct renal parenchymal injury by the causative organism followed by immunocomplex-type glomerulonephritis, as suggested in parvovirus B19 IRGN might also be considered.[10]

In a study conducted by Bal et al., 48.7% of the cases with acute febrile illness in children 101°F) with cough, cervical lymphadenopathy, and puffiness of face were the most common clinical features.[11]

Post-streptococcal glomerulonephritis is the most common form of PIGN in children. It is known to have a favorable prognosis. In contrast to post-streptococcal glomerulonephritis, most other bacterial pathogens cause glomerulonephritis when the infection is still active, hence the term infection-associated glomerulonephritis or IRGN has been proposed.[12] In patients with *Staphylococcus*-associated glomerulonephritis, predisposing conditions like diabetes, alcoholism, cancer, malnutrition, or intravenous drug addiction are often found.[13]

All five cases were presented with fever, without any Eschar except one. Moreover, they presented with bizarre renal symptoms confounding diagnosis. All the cases had neutropenia and lymphocytosis that was the sole finding to point toward scrub typhus. But none of our cases had developed acute kidney injury as such. There is very few literature about the nephritic-like presentation, i.e., hematuria, hypertension and proteinuria in varied complications. One of our cases had also developed hypertensive encephalopathy that strongly prompts hypertension in those cases was not an observational bias. Scrub typhus is an acute febrile illness that is known to be endemic in the South East Asian countries and the Western Pacific region.[14] So patients with nephritic presentation should be evaluated for Scrub typhus infection if associated with long-term unresolving fever. Due to

under detection and empirical use of azithromycin before adequate evaluation, the actual disease burden remains underestimated.

CONCLUSION

- IRGN is a different entity from PIGN. IRGN occurs simultaneously along with the infection without any latent period, whereas PIGN occurs few days later after the formation of antibody against the causative organism
- In IRGN, there is direct renal injury by the organism as well as immune complex-mediated glomerulonephritis, mostly cresentic type. Common causative organisms for IRGN are *Staphylococcus*, *Streptococcus*, *Escherichia coli*, *Yersinia*, *Pseudomonas,* and viral agents such as Parvo virus B9
- Rickettsial infection can also cause IRGN rarely, especially in endemic area.

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ETHICAL APPROVAL

The study was approved by the institutional ethics committee.

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BKK- Concept and design of the study, prepared first draft of manuscript; **RG and AKR-** Interpreted the results; reviewed the literature and manuscript preparation; **BKK and AKR-** Concept, coordination, statistical analysis and interpretation, preparation of manuscript, and revision of the manuscript

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