

## Polyarthritis and massive small bowel bleed: An unusual combination in scrub typhus

Nayyar Iqbal<sup>1</sup>, Solomon Titus<sup>2</sup>, Aneesh Basheer<sup>1</sup>, Sanjoy George<sup>1</sup>, Sudhagar Mookkappan<sup>1</sup>, Shashikala Nair<sup>3</sup>, Thomas Alexander<sup>4</sup>, Anita Ramdas<sup>5</sup>, Sivakumar Periyasamy<sup>1</sup>, Patricia Anitha<sup>3</sup>, Reba Kanungo<sup>3</sup>

1. Department of General Medicine, Pondicherry Institute of Medical Sciences, Pondicherry, India
2. Department of General Surgery, Pondicherry Institute of Medical Sciences, Pondicherry, India
3. Department of Microbiology, Pondicherry Institute of Medical Sciences, Pondicherry, India
4. Department of Gastroenterology, Pondicherry Institute of Medical Sciences, Pondicherry, India
5. Department of Pathology, Pondicherry Institute of Medical Sciences, Pondicherry, India

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### CASE STUDY

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#### Corresponding Author:

Dr Nayyar Iqbal  
Assistant Professor  
Department of General Medicine  
Pondicherry Institute of Medical Sciences  
Ganapathichettikulam, Puducherry, India, 605014  
Email: [drinayyar@gmail.com](mailto:drinayyar@gmail.com)

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### ABSTRACT

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Scrub typhus is an acute febrile illness caused by the intracellular parasite *Orientia tsutsugamushi*. Although most cases present with mild symptoms and signs and recover spontaneously, some cases can be severe with multi-organ dysfunction and a protracted course, which may be fatal if left untreated. Apart from fever and constitutional symptoms, atypical presentations allow this disease to mimic several common conditions. We report a case of scrub typhus in an 18-year-old male who presented with severe polyarthritis involving all large joints and a massive lower gastrointestinal bleed from ulcers in the terminal ileum, secondary to vasculitis in the small bowel. This combination of pathologies has not previously been reported in cases of scrub typhus. The patient improved following surgical intervention and specific anti-rickettsial therapy with azithromycin.

#### Key Words

Scrub typhus; polyarthritis; small bowel bleed

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### Implications for Practice:

#### 1. What is known about this subject?

Scrub typhus is an acute febrile illness caused by the intracellular parasite *Orientia tsutsugamushi*. It is endemic to Southeast Asia, and is transmitted by larval forms of mites called chiggers. In the last decade, it has emerged as one of the common causes of febrile illness in South India.

#### 2. What new information is offered in this case study?

Polyarthritis in scrub typhus has never previously been reported. Upper gastrointestinal bleeding is one of the manifestations of scrub typhus. Small bowel bleeds are very rare and only two cases have been previously reported.

#### 3. What are the implications for research, policy, or practice?

In cases of acute febrile illness with these rare manifestations, scrub typhus should also be considered as a differential diagnosis in endemic areas. Early recognition and timely surgical intervention is necessary to prevent severe illness and death.

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### Background

Scrub typhus is a zoonotic disease transmitted by the larval mites (chiggers) of the *Leptotrombidium deliense* group. The term "scrub" is used because of the vegetation that harbours the vector.<sup>1</sup> It is endemic to the part of the world known as the "tsutsugamushi triangle", which extends from Japan and far eastern Russia in the north, to northern Australia in the south, and to Pakistan in the west.<sup>2</sup>

Scrub typhus is prevalent in many parts of India with recent outbreaks reported from both north and south India,

including Pondicherry.<sup>3</sup> Outbreaks occur during the rainy season and in the cooler months in South India, though sporadic cases are reported throughout the year. In south India, as many as 40–50 per cent of cases of acute febrile illness have been attributed to scrub typhus.<sup>4</sup>

After mite acquisition, the clinical manifestations begin following an incubation period of 6–21 days. It is characterised by fever, headache, myalgia, cough, and diarrhoea. These symptoms may be followed by breathlessness, jaundice, and rash.<sup>5</sup> The pathognomonic features such as eschar and lymphadenopathy are seen in 50 per cent of patients.<sup>6</sup>

The course of this disease may be complicated by acute respiratory distress syndrome (ARDS), acute hepatitis, acute renal failure, meningoencephalitis, disseminated intravascular coagulation, shock, and myocarditis.<sup>7</sup> Gastrointestinal bleeding, a distinctly rare presentation of scrub typhus, manifests as haemetemesis and melena. It has been reported in 6–7 per cent of scrub typhus cases and the site of bleeding is mostly in the stomach.<sup>8</sup> Small bowel bleeding as a result of scrub typhus has been reported only twice.<sup>9,10</sup> Moreover, scrub typhus presenting as polyarthritis has not been reported so far. We report the first case of scrub typhus with polyarthritis as the presenting feature, complicated by massive small bowel bleeding.

### Case details

An 18-year-old male presented with a 10-day history of fever and acute onset of joint pain involving bilateral large joints over the previous week. He also described loose stools without mucus or blood over the previous four days. On examination, his pulse was 82 beats/minute and blood pressure was 110/70mmHg. He was febrile (38.3°C) with mild swelling, warmth and tenderness of bilateral shoulder, elbow, hip and ankle joints; there was pain and restricted active and passive movements in all these joints but no joint deformities or crepitus. There were no rashes, eschar, or lymphadenopathy. All other systemic examinations were normal. A provisional diagnosis of reactive arthritis was made. He was started on intravenous ceftriaxone empirically to cover enteric fever and non-steroidal anti-inflammatory drugs (NSAIDs) for arthritis pending investigations.

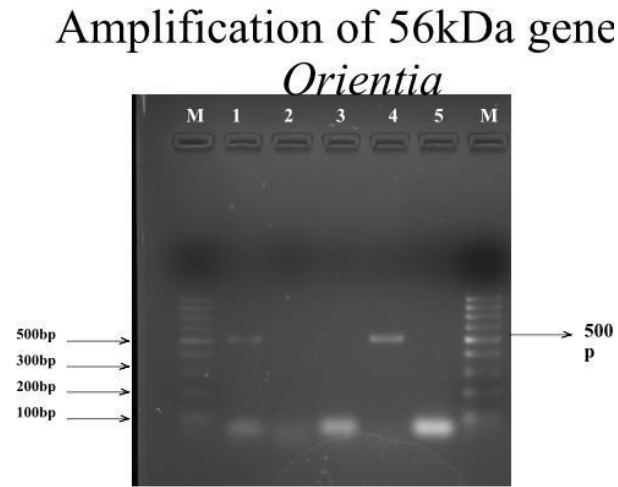
His initial investigations revealed leucocytosis (WBC–20,900/cu.mm) with neutrophilia (neutrophils–83 per cent), elevated erythrocyte sedimentation rate (ESR) (105mm/1<sup>st</sup> hr), positive C reactive protein (CRP) and hypoalbuminemia

(2.4gm/dl). Other haematological and biochemical tests were within normal limits (Table 1). As part of connective tissue workup, anti-nuclear antibody (ANA), anti-double stranded DNA (anti dsDNA), anti-streptolysin O (ASO) titre, rheumatoid factor (RA factor), anti-CCP antibody, p-ANCA, c-ANCA, levels of complements C3 and C4 were performed and were negative. Further workup, including Widal, Brucella agglutination test, serology for HIV, HBsAg, anti-HCV, Chikungunya antibody, Dengue NS1, IgM and IgG, Leptospira IgM, and malarial antigen tests, which were all negative. His urine, stool, and blood cultures were also negative. Chest, bilateral hip joint, and lumbar spine radiographs were all normal. Ultrasound examination of the affected joints did not show any effusion, however, ultrasound examination of the abdomen revealed hepatomegaly.

In spite of NSAIDs his fever persisted and the joint pain did not resolve. On day 12 of illness, he also indicated the onset of black-coloured stools. NSAIDs were therefore discontinued and an upper gastrointestinal endoscopy performed. It showed mild gastritis without any evidence of ulceration. A bone marrow biopsy and culture of the aspirate was performed and did not show any abnormality. A Mantoux test was also negative.

As Pondicherry is an endemic area for scrub typhus, a blood sample was sent for agglutination test (Weil-Felix) and IgM ELISA to *Orientia tsutsugamushi*. These tests turned out to be positive. Following this finding, azithromycin (500mg once daily) was initiated. To confirm the diagnosis, nested polymerase chain reaction (PCR) was performed on DNA extracted from the blood clot using a Blood-Genomic extraction kit (Sigma-Aldrich). The gene coding for 56kDa antigen of *Orientia tsutsugamushi* was detected by the nested PCR using primers previously described by Saisongorh et al.<sup>11</sup> The product was electrophoresed on 1.25 per cent agarose gel and visualised using Gel Doc (It<sup>2</sup> Imager, UVP LLC., London, United Kingdom). This PCR is specific for detecting the 56kDa gene of *Orientia tsutsugamushi* and the amplicon obtained was an expected 483 base pair product that was compared with standard molecular weight markers (Figure 1). Variations in this gene are responsible for antigenic and genetic diversity of *Orientia tsutsugamushi*. Using this set of primers for conserved region of the gene of this organism, variants can also be picked up.<sup>12</sup>

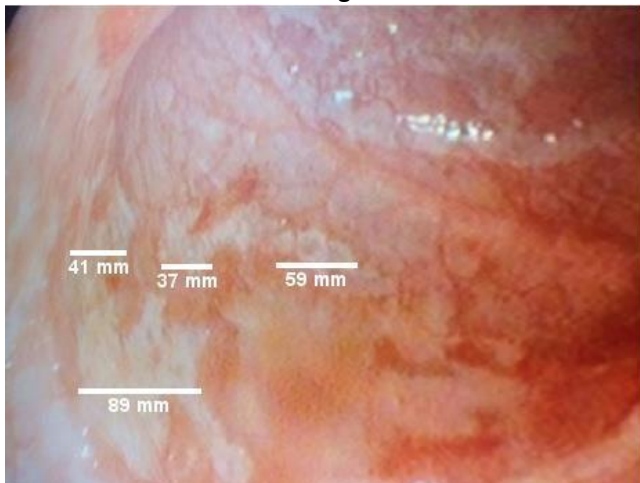
**Figure 1: Nested PCR for *Orientia tsutsugamushi* (for 56kDa antigen)**



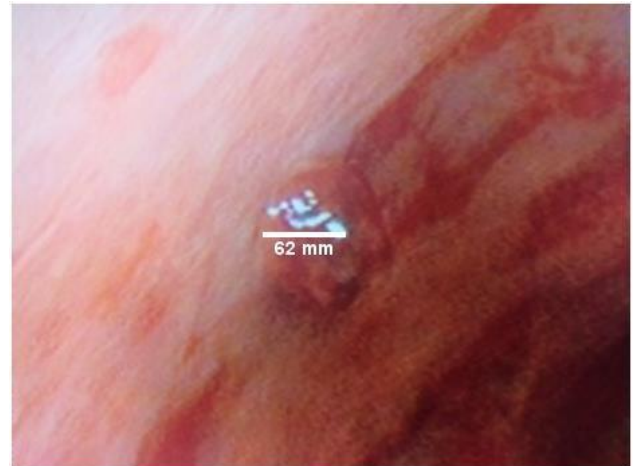
- Lane M: 100 bp molecular weight marker
- Lane 1: Positive control
- Lane 2& 3: Negative control
- Lane 4: Test sample

On day 14 of illness the patient had acute onset hematochezia and his haemoglobin dropped to 6.7gm/dl. An emergency colonoscopy was performed after stabilising the patient with a packed cell transfusion. Colonoscopy showed mild inflamed caecum and bleeding from the proximal bowel to the ileocaecal junction. Hence, an immediate laparotomy with per-operative enteroscopy was performed. This revealed actively bleeding ulcers in the terminal ileum (Figures 2a and 2b).

**Figure 2a: Per-operative enteroscopy showing multiple areas of erosions with bleeding**



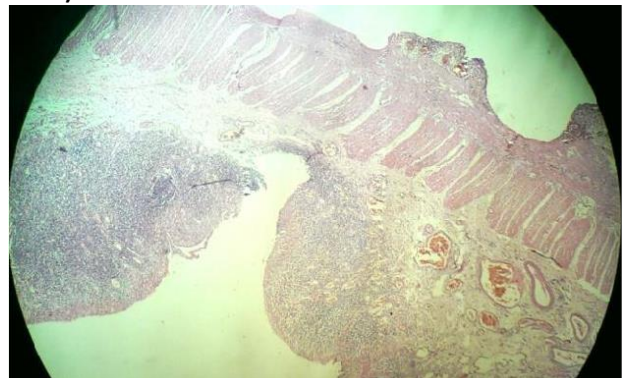
**Figure 2b: Per-operative enteroscopy showing a bleeding ulcer**



Hence, the distal one-third of the ileum and part of the ascending colon were resected and the ileum was anastomosed with the ascending colon. Postoperatively the patient had no further gastrointestinal bleeding and oral feeds were introduced on the third postoperative day. His haemoglobin gradually improved to 11gm/dl by the tenth postoperative day. After two weeks of treatment, initially with intravenous azithromycin followed by oral azithromycin, the patient recovered from all symptoms of joint pain, fever, and loose stools. His serum albumin improved to 3.2gm/dl.

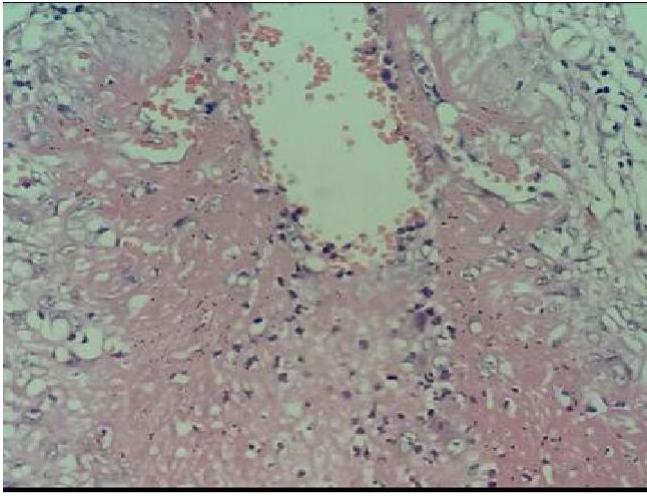
Histopathological examination of resected bowel showed multiple deep ulcers in the terminal ileum. Submucosal oedema and congestion was noted along with changes in the vessels and prominent perivascular acute inflammatory infiltrate encroaching the vessel wall suggestive of vasculitis. The vascular changes were more prominent along the sub-serosal vessels. There was no evidence to suggest inflammatory bowel disease or other infectious aetiology, including granulomatous infection. Patchy erosions and ulcers were seen in the caecum as well (Figures 3a and 3b).

**Figure 3a: Histopathology section from Ileum showing ulcer, submucosal oedema, and congestion (H&E stain, 100X)**





**Figure 3b: Histopathology section from resected bowel showing vascular changes with acute inflammation (H&E stain, 400X)**



## Discussion

Scrub typhus is a common differential diagnosis for undifferentiated fever in the tropics. It can have atypical presentations such as hypotension due to adrenal failure, severe bradycardia, meningitis, and pancreatitis.<sup>13,14</sup> Although the Australian Defence Force health report mentions joint pain as one of the constitutional symptoms of scrub typhus,<sup>15</sup> polyarthritis of all large joints has not been reported previously as a presenting feature. Another report mentions ankle joint arthritis in rickettsial infection diagnosed by Weil-Felix test;<sup>16</sup> however, a specific diagnosis of scrub typhus was not made in this case. We report the first case with severe polyarthritis in case of scrub typhus.

Diagnosis of scrub typhus is mainly by serological methods. However, with high specificity, nested PCR has a distinct advantage over Weil-Felix test and IgM ELISA where false-positive results may occur (sensitivity of 43.5 per cent and 86.5 per cent, respectively).<sup>17-19</sup> Nested PCR with sensitivity of 100 per cent and specificity of 82 per cent is a very useful technique to detect *Orientia tsutsugamushi* DNA, making it a novel tool for early diagnosis of scrub typhus.<sup>20</sup> PCR to detect the gene encoding 56 kDa antigen has been used by most workers as this gene is specific for *Orientia tsutsugamushi*.

The majority of scrub typhus cases have a benign course, especially if treatment is started early. However, some cases may be complicated by acute respiratory distress syndrome, renal failure, hepatitis, myocarditis, or multi-organ dysfunction. The mechanism for these complications are vascular injury due to vasculitis and perivasculitis in capillaries and small arteriole, which may be focal or

disseminated involving lung, heart, liver, spleen, intestine, and central nervous system.<sup>21</sup> Complications are likely to occur if diagnosis is delayed.<sup>22</sup> Among the uncommon complications, gastrointestinal bleed carries a relatively poor prognosis, especially in elderly patients.<sup>9</sup>

Upper gastrointestinal bleeding has been reported infrequently in the past in cases of scrub typhus.<sup>23,24</sup> The upper gastrointestinal involvement may range from petechiae and erosions to ulcers with active bleeding that may require endoscopic treatment.<sup>25</sup> Bae et al.<sup>9</sup> reported a similar case presentation in which the patient had massive small bowel bleeding; this case was also managed surgically with resection of the affected bowel.

Histopathological examination of the resected bowel showed increased perivascular infiltration with inflammatory cells, consistent with vasculitis. We also considered NSAID-induced ulceration and bleeding as one of the contributing factors, as our patient had received NSAIDs. Classically, ulcerative lesions due to NSAIDs involve mucosa and submucosa with submucosal edema and mild fibrosis without inflammatory infiltrates;<sup>26</sup> this was absent in this patient. Instead, there was transmural inflammation of the bowel. Another close differential diagnosis is inflammatory bowel disease, which was excluded due to absence of crypt distortion, crypt abscess, or granulomas on histopathology.<sup>27</sup>

Since vasculitis was demonstrated in the bowel, we believe polyarthritis could also be secondary to vasculitis involving the large joints, although this could not be conclusively established by histopathology. Azithromycin, apart from having an antimicrobial effect, also has immunomodulatory action<sup>28</sup> and this may have assisted in the improvement of the arthritic symptoms. According to published definitions of severity of scrub typhus,<sup>29,30</sup> our patient fulfilled all the criteria of severity. The prompt initiation of antibiotic and surgical intervention helped our patient to have a favourable outcome, similar to the case reported by Bae et al.<sup>9</sup>

## Conclusion

Scrub typhus can have various clinical presentations, including polyarthritis, while lower gastrointestinal bleeding can be a potentially fatal complication of scrub typhus. This case highlights a rare presentation that includes both symptoms. A high index of suspicion and confirmatory diagnosis, with appropriate surgical intervention, may lead to successful outcomes in such complex cases.

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### **PEER REVIEW**

Not commissioned. Externally peer reviewed.

### **CONFLICTS OF INTEREST**

Aneesh Basheer discloses that he is on the editorial board of the Australasian Medical Journal.

### **PATIENT CONSENT**

The authors, Iqbal N, Titus S, Basheer A, George S, Mookkappan S, Nair S, Alexander T, Ramdas A, Periyasamy S, Anitha P, Kanungo R, declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.

**Table 1: Serial haematological and biochemical parameters during hospital stay**

	Normal Values	Day 10 of illness	Day 14 of illness	Day 15 (Post-OP Day 1)	Day 24 of illness (Post-OP Day 10-Discharge)
Haemoglobin (gm/dl)	11-16.5	12.1	6.7	8.1	11
PCV (%)	35-50	37.3	19.2	23.4	33.6
WBC(cells/cu.mm)	4000-11,000	20,000	26,700	21,000	12,400
DLC (%)					
Neutrophil	40-70	83	80	80	78
Lymphocyte	20-40	10	18	06	20
Eosinophil	0-6	01	01	02	02
Platelet (cellsX10 <sup>9</sup> /)	1.5-4.5	2.1	3.9	2.8	2.9
Urea (mg/dl)	15-40	40	16	18	20
Creatinine (mg/dl)	0.7-1.4	0.8	0.5	0.6	0.6
AST (U/L)	Up to 40	15	20	32	35
ALT (U/L)	Up to 41	23	16	26	32
T. Protein (gm/dl)	6.6 - 8.7	5.9	3.9	3.9	6.1
S. Albumin (gm/dl)	3.97 - 4.95	2.4	1.7	1.8	3.2