HOSTED BY
ELSEVIER

Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Disease

journal homepage: www.elsevier.com/locate/apjtd

Document heading doi: 10.1016/S2222-1808(14)60793-3

Anti-neutrophilic cytoplasmic antibody-positive cutaneous leucocytoclastic vasculitis due to scrub typhus

Suman Suryanarayana Karanth[1*], Krishna Chaitanya Marupudi[1], Anurag Gupta[2], Mukhyaprana Prabhu[1]

[1]*Department of Medicine, KMC Manipal, Manipal University, Manipal, Karnataka, India*

[2]*Fortis Memorial Research Institute, Gurgaon, Haryana, India*

PEER REVIEW

Peer reviewer

Dr. Terry A. Klein, Vector-borne Disease Surveillance Program Manager, Public Health Command Region-Pacific, 65th Medical Brigade, Unit 15281, Box 754, Seoul, Korea.
Tel: +822-7917-1749
E-mail: terry.a.klein2.civ@mail.mil
Co-reviewers: Dr. Vasudeva Acharya, Manipal, India. Dr. H Manjunatha Hande, Manipal, India.

Comments

This is an important case report study that highlights syndromic complications due to infections with scrub typhus.
Details on Page 336

ABSTRACT

Leucocytoclastic vasculitis (LCV) is a small-vessel vasculitis affecting the postcapillary venules presenting as papules, purpura and maculopapular rash, occurring as a primary disorder or secondary to malignancies, drugs, infections and connective tissue diseases. The causative agents implicated are *Streptococcus* spp., *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Mycobacterium lepromatosis*, and viruses, *e.g.*, hepatitis, influenza and HIV. Scrub typhus has rarely been associated with LCV. We reported a rare case of anti-neutrophilic cytoplasmic antibody-positive LCV due to scrub typhus in a 56 year old male who presented with fever and purpuric lesions and was successfully treated with oral steroids.

KEYWORDS
Vasculitis, Scrub typhus, LCV

1. Introduction

Scrub typhus is an acute febrile illness caused by *Orientia tsutsugamushi* (*O. tsutsugamushi*) which is transmitted by the bite of the thromboculid larval mites (chiggers). Its presentation ranges from asymptomatic or mild illness to multi-organ involvement including death[1]. Typical clinical picture consists of fever, myalgia, rash, lymphadenopathy and an eschar at the chigger mite bite site. Complications of scrub typhus include pneumonia, acute respiratory distress syndrome, myocarditis and meningoencephalitis[2]. While the occurrence of vasculitis has been documented in literature[3], scrub typhus causing anti-neutrophilic cytoplasmic antibody (ANCA)-positive leucocytoclastic vasculitis (LCV) has rarely been reported. We discussed the first case of LCV caused by scrub typhus in India.

*Corresponding author: Dr. Suman Suryanarayana Karanth, Department of Medicine, KMC Manipal, Manipal University, Manipal, Karnataka, India.
Tel: 8826663867
E-mail: drsumansk@gmail.com

Article history:
Received 18 Aug 2014
Received in revised form 23 Aug, 2nd revised form 25 Aug, 3rd revised form 9 Sep 2014
Accepted 4 Oct 2014
Available online 6 Feb 2015

2. Case Report

A 56-year-old male presented to our emergency department with a 7-day history of high-grade intermittent fever without chills. This was followed by the appearance of palpable purpura over the bilateral lower limbs. He suffered from arthralgia and myalgia, but denied complains of itching, jaundice, arthritis, abdominal pain, cough, haemoptysis, hematuria, hematochezia, photosensitivity, parasthesias or weakness. He resided in a scrub typhus endemic area where he was an agriculturist involved in harvesting crops. There was no history of recent travel or unprotected sexual exposure, illicit drug use or blood transfusions.

On examination, he was febrile (37.78 ℃), and tachycardia, mild icterus and mild hepatomegaly was noted. An eschar over the patient's left axilla and bilateral non-blanching palpable purpura without any skin necrosis or ulcers was observed. There was no joint effusion, dryness of eye or neurological deficits. The cardiac and respiratory system examinations were within normal limits. Investigations revealed elevated white blood cell counts and erythrocyte sedimentation rate (haemoglobin: 13.6 g/dL, total white cell count: 13 500 cells/microl, platelet count: 142 000 cells/microl, erythrocyte sedimentation rate: 100 mm/h). Liver function tests were suggestive of mild direct hyperbilirubinemia and elevated liver enzymes (total bilirubin: 3 mg/dL, direct bilirubin: 1.8 mg/dL, serum glutamic oxaloacetic transaminase: 129 IU/L, serum glutamic pyruvic transaminase: 81 IU/L, alkaline phosphatase: 300 IU/L). Urine microscopic examination, prothrombin and activited partial thomboplastin time, chest roentgenography and serum protein electrophoresis were normal. In tests for HIV, hepatitis B and C and *Leptospira* IgM enzyme-linked immunosorbent assay were negative. Blood and urine cultures were sterile. Weil-Felix (titres of OX 19 1: 640), which is indicative of a rickettsial infection, and scrub IgM enzyme-linked immunosorbent assay were positive. Anti-neutrophilic cytoplasmic antibody to myeloperoxidase was positive. Anti-nuclear antibody, anti-dsDNA, anti-Ro, anti-La, anti-streptolysin O and rheumatoid factor were negative. C-reactive protein was elevated (45 mg/dL) while complement levels (C3, C4) were normal. Skin biopsy was performed which showed infiltration of predominantly neutrophils, in addition to fibrinoid necrosis of the vessel wall in the dermis with C3 deposits on immunofluorescence. A diagnosis of LCV probably due to scrub typhus was made.

Patient received oral doxycycline (100 mg twice daily) for 14 d and 60 mg/day (1 mg/kg body weight) of oral prednisolone for 7 d for the purpuric rashes. The patient was afebrile within 3 d of antibiotic therapy and the purpuric lesions improved over the next 4 d without residual scarring.

3. Discussion

LCV is a small-vessel vasculitis mediated via immune complex deposition, with the cardinal feature being the involvement of postcapillary venules. The inflammatory infiltrate is predominantly neutrophils that adhere to the activated endothelial cells, consequently releasing lytic enzymes and producing fibrinoid necrosis in blood vessel wall followed by hemorrhage[4]. Myriad of presentations can vary from limited involvement of the skin in the form of palpable purpura, nodules, maculopapular rashes or skin ulcerations to systemic involvement in the form of renal failure, pericarditis and pleuritis[5].

LCV can occur as a primary disorder or secondary to malignancies, drugs, infections and connective tissue diseases. Some of the implicated drugs are non-steroidal anti-inflammatory drugs, antibiotics, anticonvulsants, antiarrhythmics and methotrexate. LCV symptoms usually occur within a week of exposure and have a self-limiting course following discontinuation of causative drugs[4]. Infectious agents include: *Streptococcus* spp., *Mycobacterium tuberculosis*, *Mycobacterium leprae*, *Mycobacterium lepromatosis* (leprosy), and viruses (*e.g.*, hepatitis, influenza, cytomegalovirus and HIV[5]. Postulated mechanisms by which infections trigger vasculitic process include direct invasion by the pathogen and immune complex mediated damage of endothelial cells[6].

The histological picture of LCV is similar irrespective of the causative aetiology. Classically, fibrinoid necrosis with infiltration of neutrophils, and endothelial swelling and damage, involving the postcapillary venule within the superficial dermis can be seen. The role of cell-mediated immune mechanisms are supported by the abundance of $CD3^+$, $CD4^+$ and $CD1a^+$ cells in the lesions. Immunofluorescence studies reveal a predominance of C3 and IgM in early lesions and fibrinogen and C3 in late lesions[5].

Scrub typhus has rarely been reported to cause LCV. Endothelial cell destruction followed by perivascular infiltration of leucocytes leading to thrombosis of the blood vessel is a known mechanism of pathogenesis in scrub typhus[7]. A total of three cases of LCV have been reported where *O. tsutsugamushi* was the causative agent[8-10]. Only one patient presented with

ANCA-positive LCV similar to our case and was treated with pulse dose of methylprednisolone (1 g/day), in addition to course of doxycycline for scrub typhus[10]. The skin lesions in the remaining two patients recovered spontaneously[8,9]. Some of the recommended therapies for LCV are corticosteroids, colchicine, dapsone, cyclophosphamide, intravenous immune globulin and plasma exchange[4]. Our patient benefitted from a short course of oral steroids at the dose of 1 mg/kg for 1 week period. We discontinued steroids as there was improvement in the skin lesions. Our case differed from the patient described by Kang *et al*[10], since our patient did not present with any neurological manifestations. The prognosis of LCV mainly depends on the extent of systemic involvement. Though the presence of ANCA positivity in cutaneous LCV helps diagnose systemic vasculitis, its mere presence is not predictive of a future systemic involvement[11]. To our best knowledge, this is the first case of ANCA-positive LCV produced by an infection with *O. tsutsugamushi* (scrub typhus) in India and only the second such case in the literature.

Conflict of interest statement

We declare that we have no conflict of interest.

Comments

Background

This is a report of an uncommon medical syndrome attributed to scrub typhus infection. While LCV is infrequently associated with scrub typhus infections, the information provided has significant medical implications when considering vector-borne infectious diseases and administration of drugs.

Research frontiers

This is a report of an uncommon medical syndrome attributed to a scrub typhus infection. Medical professionals must consider this syndrome during the diagnosis of scrub typhus cases.

Related reports

There is only one other report of cutaneous LCV attributed to a scrub typhus infection.

Innovations & breakthroughs

This is a case report that describes an uncommon clinic case of cutaneous LCV attributed to a scrub typhus infection. The report highlights medical considerations when diagnosing scrub typhus.

Applications

This case report, which describes an uncommon clinic case of cutaneous LCV, is useful for medical providers in their diagnosis of scrub typhus in endemic areas, including syndromic complications.

Peer review

This is an important case report study that highlights syndromic complications due to infections with scrub typhus.

References

[1] Cowan GO. Rickettsial infections. In: Cook GC, Zumla AI, editors. *Manson's tropical diseases*. 21st ed. Philadelphia: Saunders; 2003, p. 891-906.

[2] Chrispal A, Boorugu H, Gopinath KG, Prakash JA, Chandy S, Abraham OC, et al. Scrub typhus: an unrecognised threat in South India-clinical profile and predictors of mortality. *Trop Doct* 2010; **40**: 129-133.

[3] Singh P. Scrub typhus, a case report: military and regional significance. *Med J Armed Forces India* 2004; **60**: 89-90

[4] Daniel CL. Leukocytoclastic vasculitis and Henoch-Scholein purpura. In: Koopman WJ, Moreland LW, editors. *Arthritis and allied conditions; a textbook of rheumatology.* 15th ed. New York: Lippincott Williams & Wilkins; 2005, p. 1793-1797.

[5] Calonje E, Brenn T, Lazar A, McKee PH, editors. *McKee's pathology of the skin*. Philadelphia: Saunders; 2012.

[6] Silva ME, Cherry JD, Wilton RJ, Ghafouri NM, Bruckner DA, Miller MJ. Acute fever and petechial rash associated with influenza A virus infection. *Clin Infect Dis* 1999; **29**: 453-454.

[7] Settle EB, Pinkerton H, Corbett AJ. A pathologic study of tsutsugamushi disease (scrub typhus) with notes on clinicopathologic correlation. *J Lab Clin Med* 1945; **30**: 639-661.

[8] Tseng SM, Hsiao YP, Shih HJ, Hsu YH, Yang JH. *Orientia tsutsugamushi*-induced leukocytoclastic vasculitis-a case report. *Dermatol Sin* 2007; **25**: 142-146.

[9] Praveen Kumar AS, Prasad AM, Gumpeny L, Siddappa R. Leukocytoclastic vasculitis and polyarthralgia in scrub typhus: an unusual presentation. *Int J Med Public Health* 2013; **3**: 352-354.

[10] Kang Y, Jang HW, Han SH, Jeong SJ, Ku NS, Baek JH, et al. [ANCA-associated vasculitis after scrub typhus]. *Infect Chemother* 2011; **43**(1): 82-85. Korean.

[11] Sais G, Vidaller A, Jucglà A, Servitje O, Condom E, Peyri J. Prognostic factors in leucocytoclastic vasculitis: a clinicopathologic study of 160 patients. *Arch Dermatol* 1998; **134**: 309-315.