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Case Report

Malignant mediterranean spotted fever in the setting of diabetes mellitus: An uncommon cutaneous entity

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ABSTRACT

In this era of immune suppression and potential biological warfare, we need to be aware of cutaneous manifestations of relatively uncommon bacterium, their atypical variants, and the early treatment protocols. We present atypical presentation of Indian possible tick typhus diagnosed clinically and confirmed both by biopsy of the lesion and serological tests.

Key words: Fièvre boutonneuse, malignant Mediterranean spotted fever, rickettsia, Wohlbach's nodule

INTRODUCTION

Rickettsia, a concept that developed over a period of time, has seen significant taxonomic re-classification with the advent of modern molecular technologies. These are obligate, intracellular, gram-negative cocco-bacilli, 0.3-1.0 µm, composed of RNA and DNA and reproducing through binary fission. With up to 21 species of rickettsia known to be causing human disease and Center for Disease Control (CDC) listing *R. rickettsiae*, *R. prowazekii*, and *C. burnetii* as Category B on the list of potential weapons of biological warfare, the less fatal *R. conorii* and *R. typhii* can also cause significant morbidity if genetically engineered or mutated strains emerge. Our case additionally highlights the significance of such infections occurring in immune-compromised individuals who may present with atypical presentations due to altered immune response and further may present difficulties in diagnosis.

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CASE REPORT

A 55-year-old male diabetic patient presented with fever, intense headache, chills, arthralgia, myalgia, nausea, vomiting, headache, and rash on back, buttocks, abdomen, genitalia, and proximal extremities in the outpatient department of medicine was referred to dermatology department for rash [Figures 1 and 2]. There was a typical history of being in contact with dog, and he also had complaint of being bitten by an unknown insect with formation of crusted lesions at these sites 15 days back. The character of the rash was polymorphic with numerous

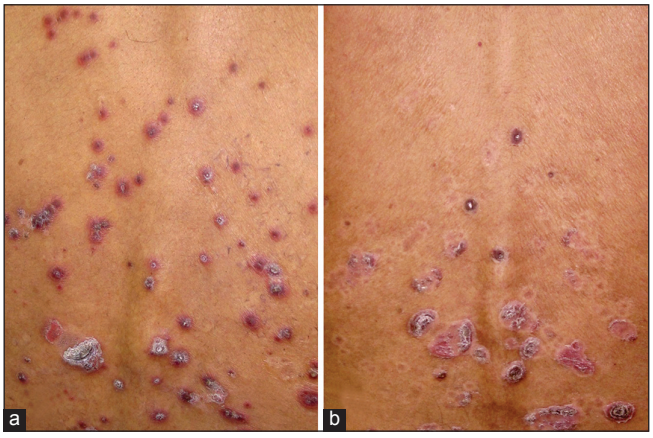

Figure 1. Panel A– Multiple variously sized macular, papulo-vesicular, crusted lesions in various stages of evolution on back. Panel B– Follow up of the patient on fifth day showing healing with erythema and hypopigmentation of smaller lesions and shedding of crusts of bigger lesions

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macular, papular, papulo-vesicular, variously sized, centrally crusted, erythematous lesions in various stages of evolution. The patient had a pulse rate of 52 per minute, which was confirmed on ECG. No cardiac cause of bradycardia was located. The first clinical differential was thought of as Kaposi's varicelliform eruption, and Tzanck test was done. Surprisingly, no acantholysis or multinucleate giant cells were seen. But, with relevant history and seeing the minimal response to conventional antibiotics (Ceftriaxone with Gentamycin i.v.) after 3 days, a presumptive diagnosis of rickettsia was made, although the lesions were atypical. He was put on Doxycycline 100 mg bid for five days.

Since facilities of rickettsial diagnosis are available at limited centers, the sample was sent to National Center for Disease Control, Delhi for confirmation of diagnosis. The serum sample was positive for IgM and IgG antibodies to Indian tick typhus (*R.conorii*) by ELISA test. Weil Felix test reaction was positive with titer >1:160 to Proteus OX2 antigen. As regards to hematological parameters, his hemoglobin level was 124 g/L, total leukocyte count 15.9 × 10^9/L, differential leukocyte count neutrophils 8.9 × 10^9/L, lymphocytes 5.3 × 10^9/L, eosinophils 1.1 × 10^9/L, monocytes 0.6 × 10^9/L, ESR 32 mm in first hour (Westergren's method), thrombocyte count 80 × 10^9/L, blood urea 8.2 mmol/L, serum creatinine 186 mmol/L, serum sodium 128 mmol/L, plasma glucose fasting 8.14 mmol/L, plasma glucose post-prandial 16.1 mmol/L, serum bilirubin 15.4 μmol/L, SGOT 48 U/L, SGPT 56 U/L. His other investigations as ultrasound abdomen, X-ray chest, RA factor, ASO titers, CRP, VDRL in dilution were all either normal or non-reactive.

The histopathology was done [Figure 3], and it showed eschar formation, breach in epidermis, focal occlusive end-angiitis of small venules, and arterioles with prominent perivascular infiltrate predominantly lymphocytic in nature (Wohlbach's nodule).

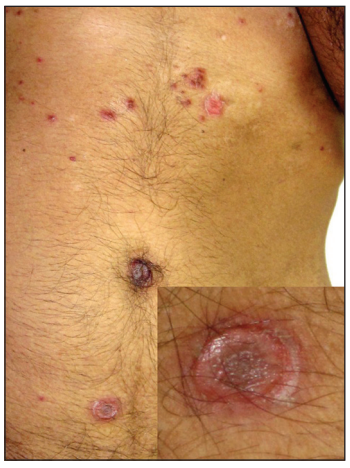

Figure 2. Lesions on abdomen and chest region of the patient. Inset: Close up view of seemingly targetoid lesion

The patient was put on doxycycline 200 mg/day for further 7 days, and he improved both in cutaneous lesions and systemic signs and symptoms.

DISCUSSION

Mediterranean spotted fever (MSF) (Fièvre boutonneuse) is the prototype of non-Rocky Mountain Spotted fever group (RMSF) group. Unusual rickettsial strains related to *R. conorii* have been put in 'R. conorii complex,' which include the Indian tick typhus rickettsia, Astrakhan fever rickettsia, and the Israeli spotted fever rickettsia. The Indian tick typhus strain (ATCC VR-597) was isolated from *Rhipicephalus sanguineus* tick by C.B. Philip in 1950. The prevailing vector is the brown dog tick, *Rhipicephalus sanguineus* also *R. pumilio*, with the reservoirs of infection being domestic dogs, rabbits, and rodents. It does not lead to infection in dogs with maximum cases being reported in spring and summer seasons. As per observations of Colomba C *et al*.,[1] the ticks modify their feeding habits by becoming hunters in warm periods and address more readily to humans. This in turn may lead to more lesions with ulcerations.[2]

Many cases have been reported from Indian subcontinent, but none has been of 'Malignant Mediterranean Fever,' which is the first of its kind from India.

In our case, the lesions were more crusted in nature with few macular lesions and it was perhaps due to late presentation. Tache noire is a typical red papular lesion with necrosis in center and is seen in upto 72% cases with *R. conorii* infection.[3]

Malignant in rickettsial disease means severe form associated with neurological complications, chronic liver disease, alcoholism, diabetes mellitus, glucose 6 phosphatase deficiency, end-stage renal disease, and cardiac disease. The

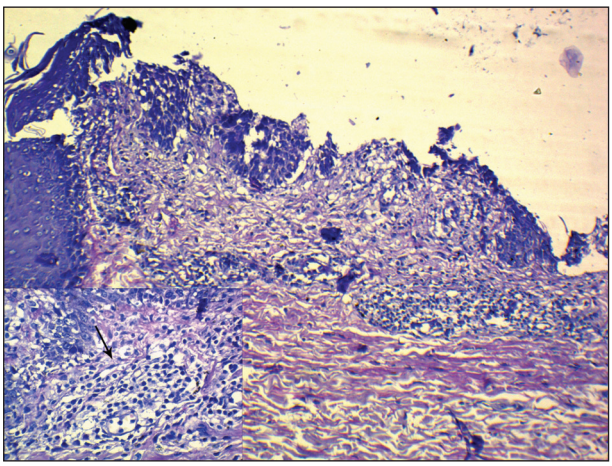

Figure 3. Showing breach in epidermis, eschar tissue, end-angiitis of small venules and arterioles with predominantly lymphocytic infiltrate (H and E 4 × 10). Inset: Close-up view of typical Wohlbach's nodule (H and E 10 × 10). Arrow indicates the Wohlbach's nodule

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malignant form is diagnosed when patients present with at least two laboratory findings and two clinical symptoms of the following criteria:

Laboratory findings: Thrombocytopenia $<100 \times 10^9$/L, renal failure (creatinine level > 150 mmol/L, hyponatremia <130 mmol/L, hypocalcemia <2.1 mmol/L, hypoxemia (arterial oxygen pressure <10.5 kPa). Clinical symptoms: Purpuric rash, stupor, pneumonia, bradycardia, coma, jaundice, gastrointestinal bleeding, arthargia, orchitis, conjunctival hyperemia, meningism, meningitis, and local lymphadenopathy.

Pathologically, in skin biopsy samples, endothelial cell swelling, platelet aggregation and perivascular polymorphonuclear leukocytes, and mononuclear cells are seen. This results in focal occlusive end-angiitis of small venules and arterioles. This is the typical Typhus or Wohlbach's nodule described by Wohlbach.[4]

The presence of rickettsia in India has been documented in Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Rajasthan, Assam, West Bengal, Maharashtra, Kerala, and Tamil Nadu.[5-9]

The differential diagnoses to be considered in such cases are malignant syphilis, pityriasis lichenoides et varioliformis acuta, varicella zoster, leuocytoclastic vasculitis etc. Since VDRL was non-reactive and also the infiltrate was also not wedge-shaped or very dense at the dermo-epidermal junction, we could rule out these disorders.

As with other rickettsiae, attempts to isolate the organism are biohazardous and unnecessary. PCR may be used; however, it remains less available and more expensive than serology. Serologic testing using specific methods (e.g. immunofluorescence antibody test, indirect immunoperoxidase test, enzyme immunoassay) is superior to the Weil-Felix reaction. However, these tests are cumbersome and only available in a few special laboratories. Comparative evaluation of Weil-Felix test and IgM ELISA for diagnosis of Scrub Typhus carried out at National Center for Disease Control, India, showed that Weil Felix test is equally sensitive with specificity of 89%.[10]

Successful therapeutic agents include doxycycline (100 mg bid orally for 1-5 days) and chloramphenicol (500 mg qid orally for 7-10 days).[11]

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