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Rickettsial Infections: A Clinician's Diagnostic Dilemma

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Abstract- Rickettsial diseases are arthropod borne zoonotic infections that are being increasingly recognized as one of the causes of pyrexia of unknown origin (PUO). These pathogens are gram-negative bacteria causing fever and rash, usually transmitted to humans by tick or flea bite. These infections must be differentiated from other febrile illnesses such as enteric fever, malaria, dengue, leptospirosis, and infectious mononucleosis. The common clinical presentation includes fever with chills and rigor, headache, vomiting, cough, conjunctival congestion and eschar. Presenting with varied and non-specific symptoms, ignorance, and low index of suspicion, they are often under-diagnosed due to the unavailability of the reliable diagnostic test. Weil- Felix test (WFT) is a non-specific heterophile tube agglutination test in which antibodies against rickettsiae are detected. If timely treatment with doxycycline is instituted the adverse consequences can be well averted.

Keywords: *rickettsia, rash, fever, weil-felix test.*

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Rickettsial Infections: A Clinician's Diagnostic Dilemma

Dr. Sriranjani Iyer [α], Dr. Harsh Rajeev Mehta [σ] & Dr. Sarojini P. Jadhav [ρ]

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I. Introduction

Rickettsial diseases are some of the most covert re-emerging infections of the present times. They are notoriously difficult to diagnose; untreated cases can have fatality rates as high as 30-35% but when diagnosed properly, they are often easily treated (1). High index of suspicion is the key to early diagnosis. Fever, rash, headache, myalgia, lymphadenopathy and eschar are various clinical features of these infections.

The greatest challenge to the clinician is the difficult diagnostic dilemma posed by these infections early in their clinical course when antibiotic therapy is most effective (4). For India, the reported numbers are an underestimate due to lack of community-based data and non-availability of confirmatory laboratory tests (5). Rickettsial disease in India is documented from Jammu and Kashmir, Himachal Pradesh, Uttaranchal, Rajasthan, Assam, West Bengal, Maharashtra, Kerala and Tamil Nadu (1, 6).

Rickettsial infections sometimes produce severe life-threatening manifestations and takes a fulminant course. Rickettsial infections are attributed to causing pyrexia of unknown origin (PUO) and thereby require to be differentiated from other febrile illnesses such as enteric fever, malaria, dengue, leptospirosis, and infectious mononucleosis (7). No single laboratory finding is specific for early diagnosis.

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Tests available to diagnose rickettsiosis are culture, serology including immunofluorescence, and molecular tests. Weil- Felix test (WFT) is a non-specific heterophile tube agglutination test in which antibodies against rickettsiae are detected using a heterophile Proteus antigen (8). Doxycycline is the drug of choice, and it can be used safely even in children below eight years of age.

We report two cases of fever with rash with a varied presentation, diagnosed to be rickettsial in origin after exclusion of other illnesses with pyrexia of unknown origin.

Case Report 1

A 6-year-old, previously healthy male child presented to the hospital with complaints of fever followed by rashes over lower extremities. He also complained of myalgia, arthralgia, and headache. Initially, these rashes were small erythematous, which soon developed into tender pustular eruptions over lower extremities, which were managed by incision and drainage. Pus from the lesion was sent for culture and antibiotic sensitivity. Pustular eruptions continued after that, and they quickly ulcerated. There was no reduction in fever spikes in the child with the maximum recorded temperature of 39.5 degree centigrade. It was associated with progressing myalgia and arthralgia. There were no pets in the family or the neighbourhood. He gives a history of playing in fields but does not recall any history of exposure to any animal or insect bite. There was no significant travel history.

Physical examination revealed a lethargic febrile child with multiple tender pustular eruptions (5-10 in number per limb), predominantly over the medial aspect of legs progressing upwards towards the trunk. These pustules showed an erythematous base. Old pustules converted into multiple undermined ulcers over the legs, with 2.5cm x 2.5cm being the largest. Inguinal lymphadenopathy over bilateral inguinal region was present with lymphnode being non-tender, enlarged, firm in consistency, 2cm x 1 cm in size, partially mobile with no superficial skin changes over the lymphnode.

The child was initially treated with empirical injectable antibiotics starting with amoxicillin and clavulanic acid, but his symptoms progressed gradually with time, with pustular eruptions progressing upwards from the lower extremities, with an increase in the number of pustules. Patient's unresponsiveness to

various intravenous higher antibiotics lead to a detailed approach to this case with discussion among pediatrician, surgeon, dermatologist as well as a microbiologist.

The patient's leukocyte count was elevated, starting from 24000 cells per cubic mm progressed to 42000 cells per cubic mm. Other laboratory values were within normal limits. Pus culture and sensitivity persistently showed no growth. Blood culture and sensitivity was also sent before the starting of empirical antibiotics, which showed no growth. Edge biopsy of the lesion was inconclusive once and a repeat biopsy report showed focal ulceration and necrosis of the epidermis.

As a diagnosis of exclusion, as suggested by the microbiologist, Weil- Felix test was done, which was positive for Ox 19-9 with a titre of 1:320. Patient was diagnosed to have a rickettsial infection and was started on Injectable Doxycycline. There was a resolution of all symptoms, including fever, pustules, eschars, myalgia, and arthralgia. All the symptoms resolved within 7-10 days, and all laboratory values came back to the normal range within ten days. He recovered well within ten days with an uneventful hospital stay and was discharged with a split skin graft over the raw area over the medial aspect of the left foot of previous ulceration but graft was rejected.

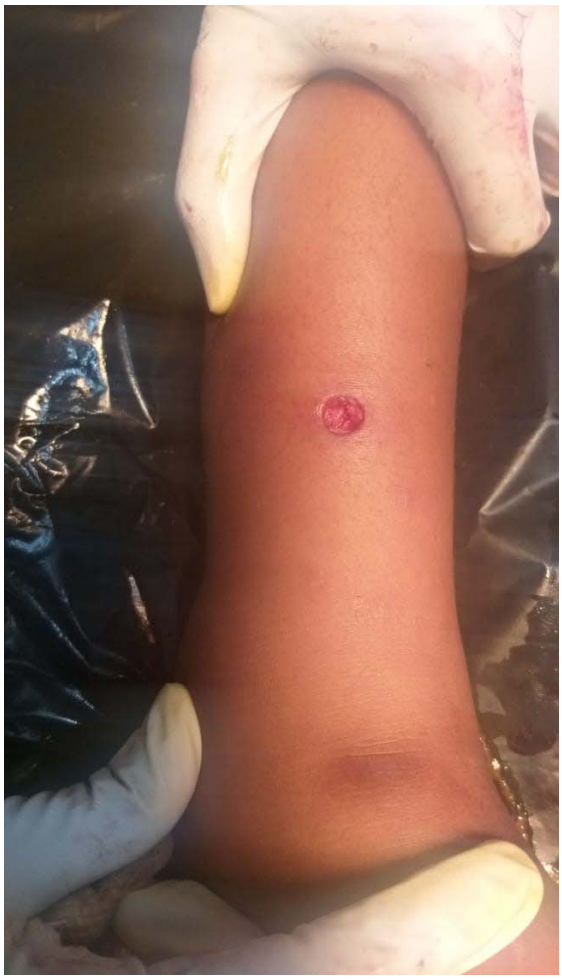


Figure 1: Initial Pustular lesion over leg after incision and drainage

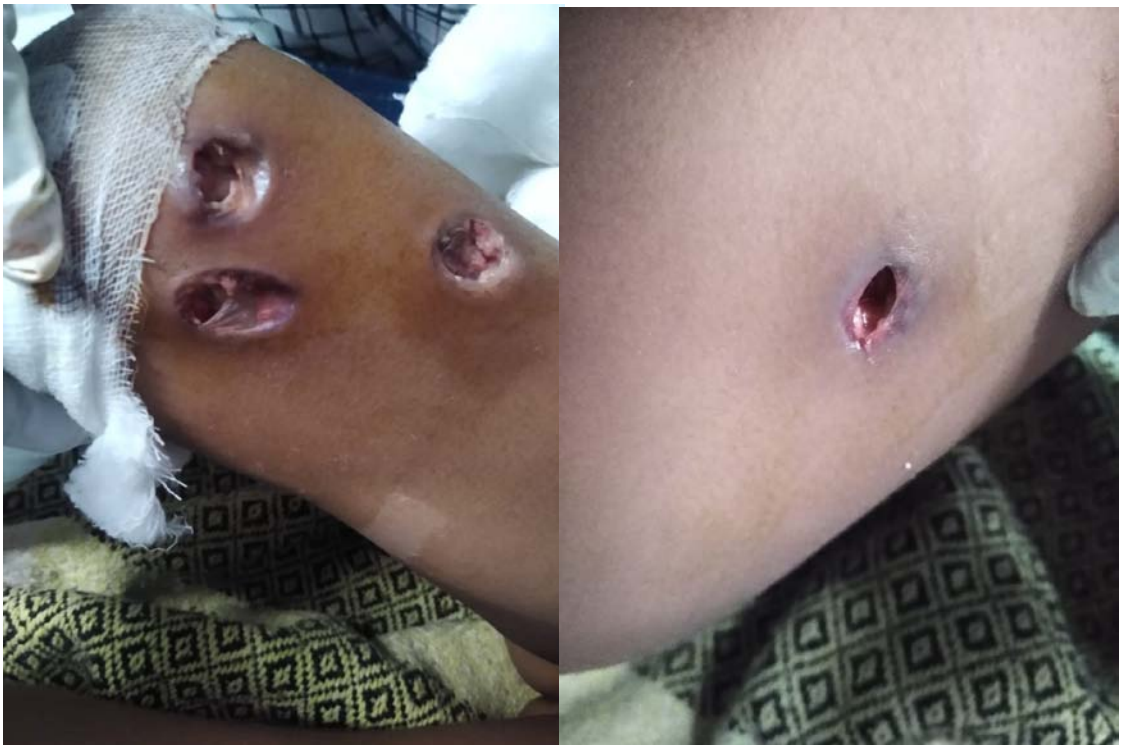
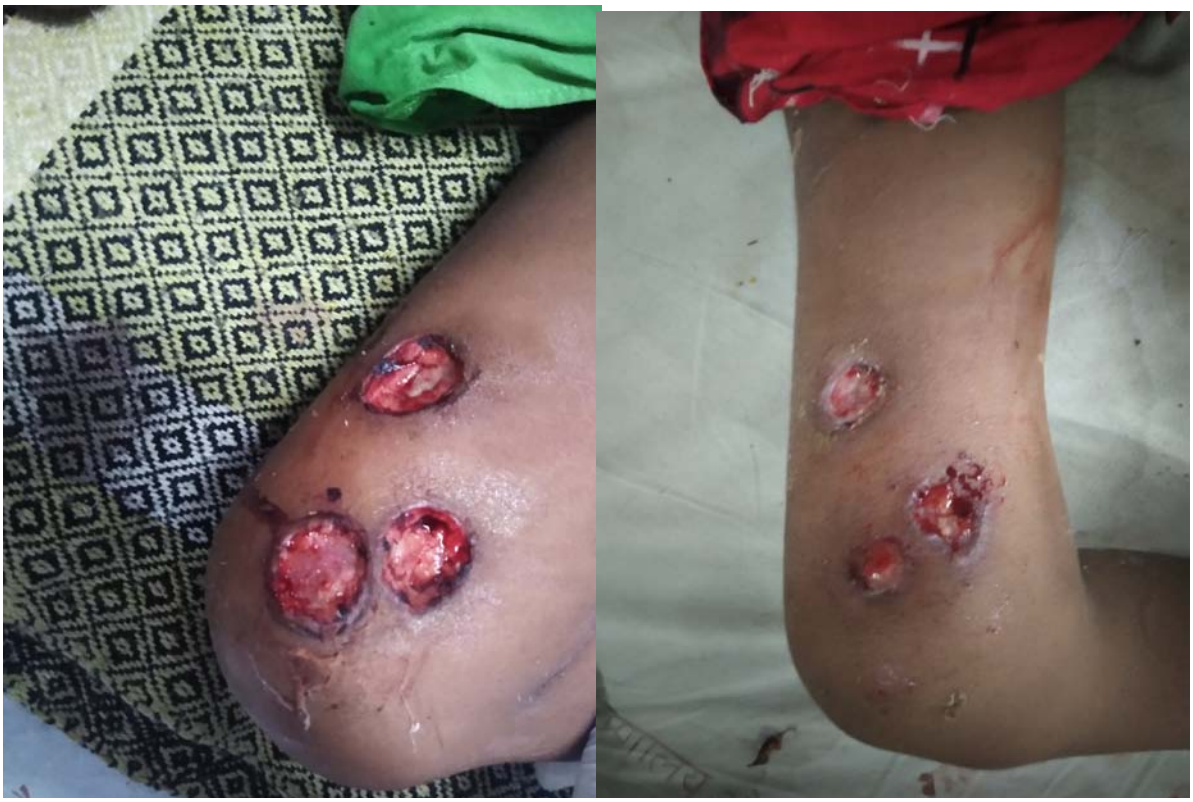


Figure 2 and 3: Multiple undermined ulcers over thigh with pus and slough covering the floor



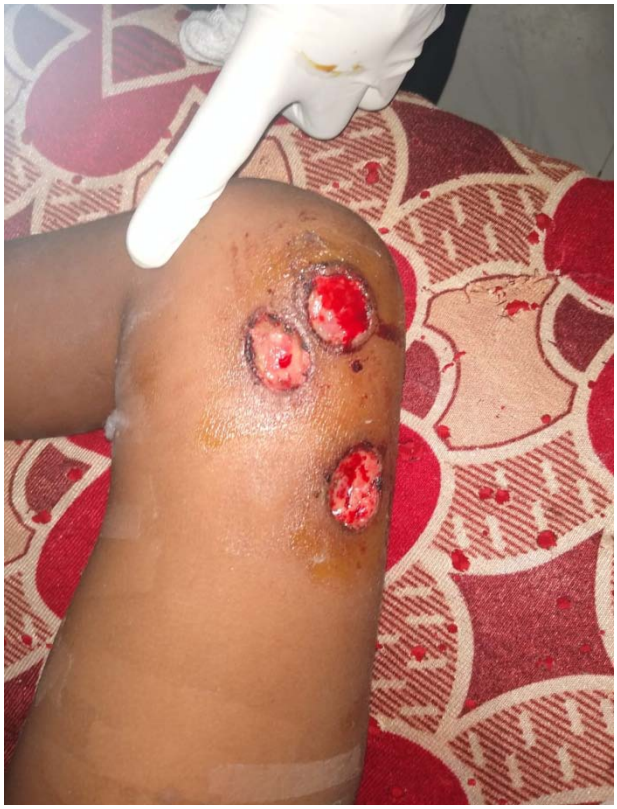


Figure 4, 5 and 6: Healing ulcers over thigh after the start of Doxycycline

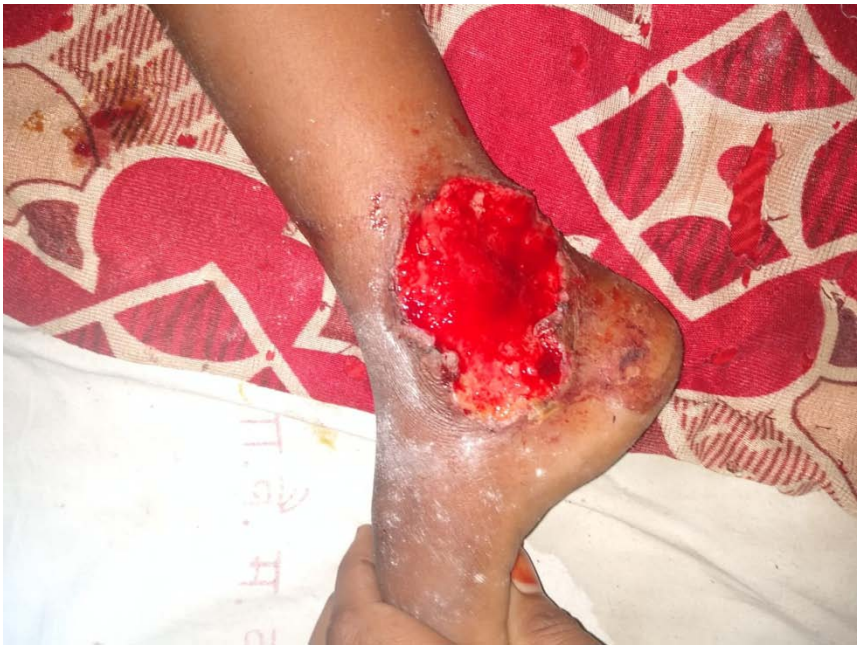


Figure 7: Healthy granulation over the medial aspect of right ankle

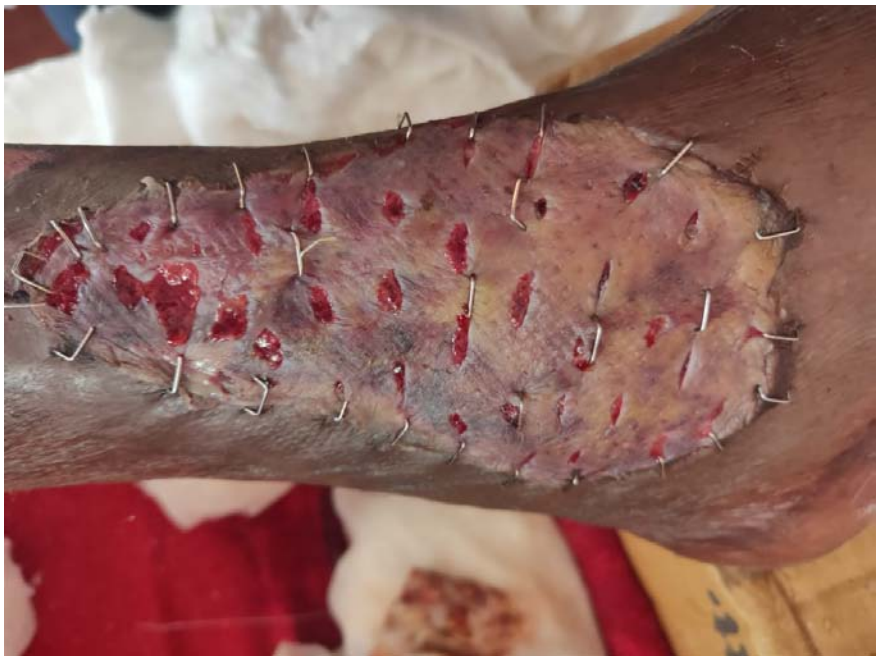


Figure 8: Split skin graft over the medial aspect of right ankle

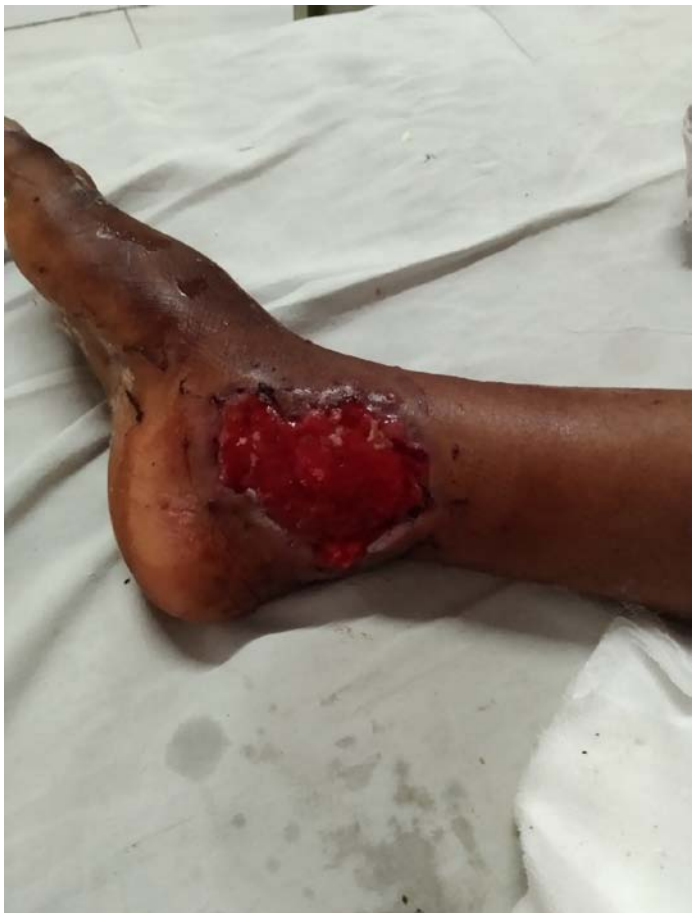


Figure 9: Ulcer over right ankle post graft rejection

Case Report 2

A 4-year-old female child was brought by parents to casualty with chief complaints of swelling over the right thigh since one month. There is a positive history of low-grade fever on and off with chills since 15 days. She had vague nonspecific symptoms. An irregular indurated swellingextending from medial aspect to posterior aspect of the right thigh of around 10

cm x 8cm in size was present, which was tender to touch with redness over the swelling.

Ultrasonography of right thigh was done, which showed an ill-defined heteroechoic collection with few dense internal echoes with no vascularity within it noted in the intramuscular plane in the right postero-medial thigh, with extensive fat stranding with diffuse subcutaneous edema giving cobble stone appearance suggestive of a non-tappable infective etiology.

The patient was taken for debridement under anaesthesia. Intraoperatively, 10ml caseous material was expressed out and sent for culture and sensitivity and CBNAAT testing. Indurated tissue specimen was sent for histopathology, which was suggestive of infected granulation tissue with exudates of neutrophils and lymphocytes. Pus culture sensitivity report showed Staphylococcus aureus sensitive to linezolid, cefoxitin, and clindamycin. CBNAAT report was negative for tuberculosis. She was treated with sensitive Intravenous antibiotics with regular dressings, but the wound over right thigh showed minimal improvement. Repeat debridement was done after 20 days, and wound swab culture was suggestive of Klebsiellapneumoniae sensitive to amikacin, cefepime, imipenem, and gentamicin. Patient was started on amikacinafter that, according to pediatric dosage. The exposed muscle showed induration and colour change and was sent for a muscle biopsy, which was suggestive of few gram-negative bacilli and pus cells.

Due to minimal improvement in the wound healing, a review opinion was taken after consulting with the panel of pathologist, microbiologist, surgeon, paediatrician and a Weil-Felix test was suggested. It was positive for OX-1, OX-2, with a titre of 1:160 for OX 19 and 1:160 for OX 2. The patient was treated for Rickettsia, and a course of Doxycycline was given for 14 days. Her wound was improving with a generalized improvement in the overall condition of the patient. All laboratory parameters came back to the normal range. The child was discharged, and daily dressings were advised. On Follow-up, the wound showed healthy granulation tissue. Fungal culture was present on KOH preparation. Swab culture on Saboraud's Dextrose Agar showed features suggestive of Trichosporon Infection. The patient was treated with Capsule Fluconazole 150mg for three weeks and had an uneventful recovery post discharge.

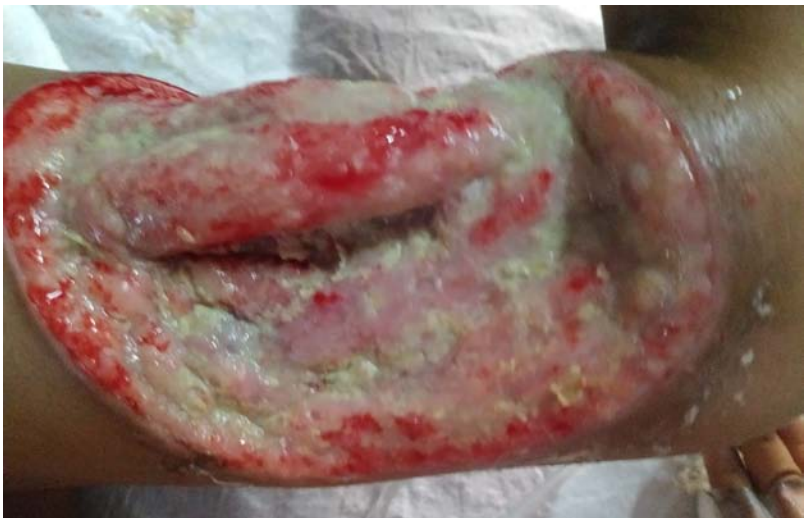


Figure 10: Post first debridement nonhealing ulcer over the posterior aspect of the right thigh

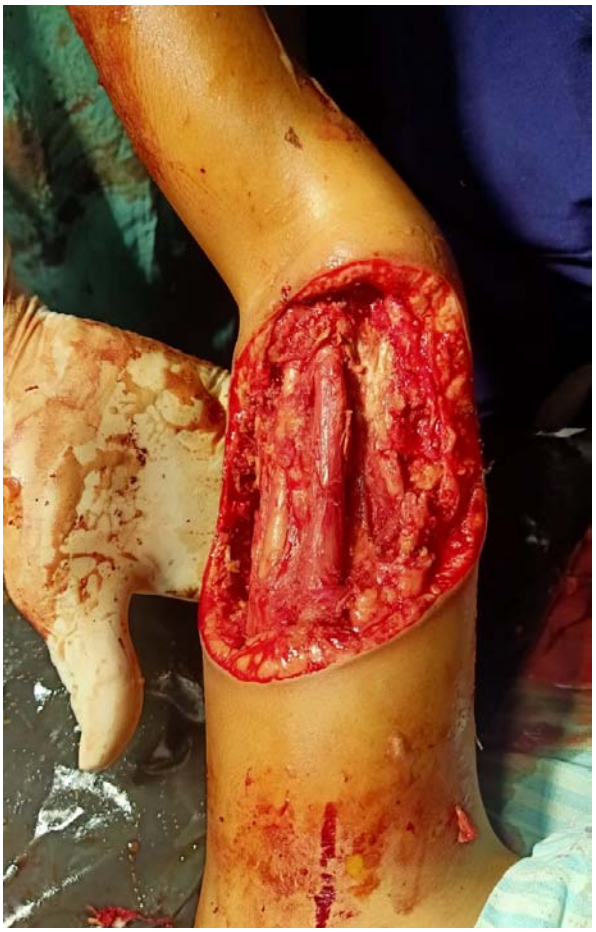


Figure 11: Post second debridement intraoperative photograph of the right posterior aspect of thigh ulcer

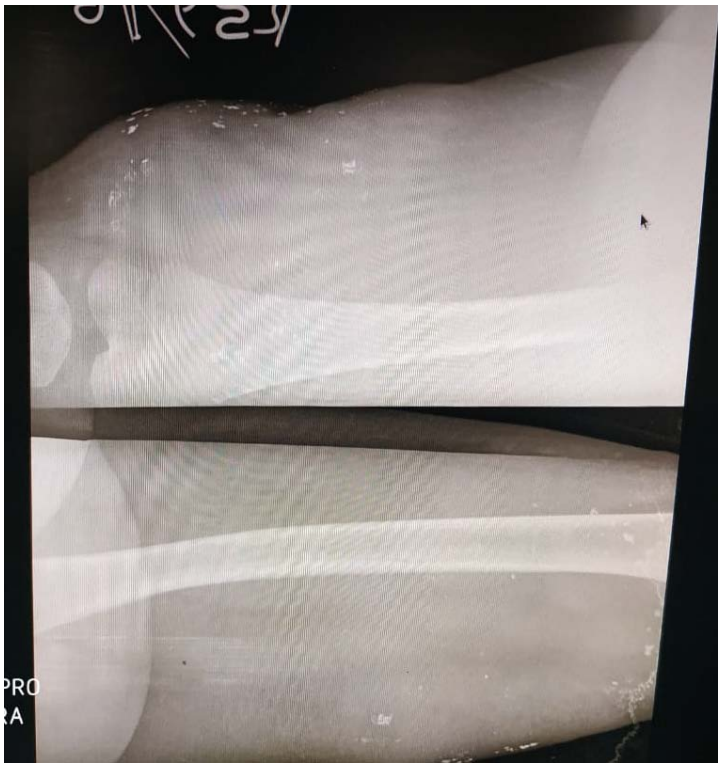


Figure 12: X-ray photograph of the right thigh to look for bony involvement

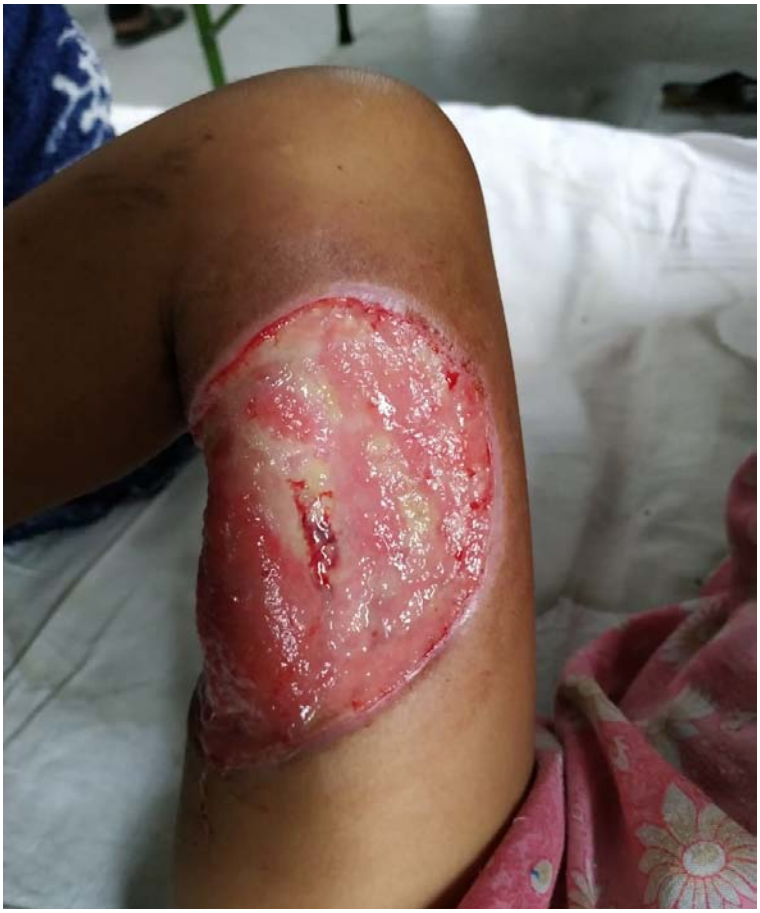


Figure 13: Healing Ulcer over the right thigh posterior aspect at the start of Doxycycline

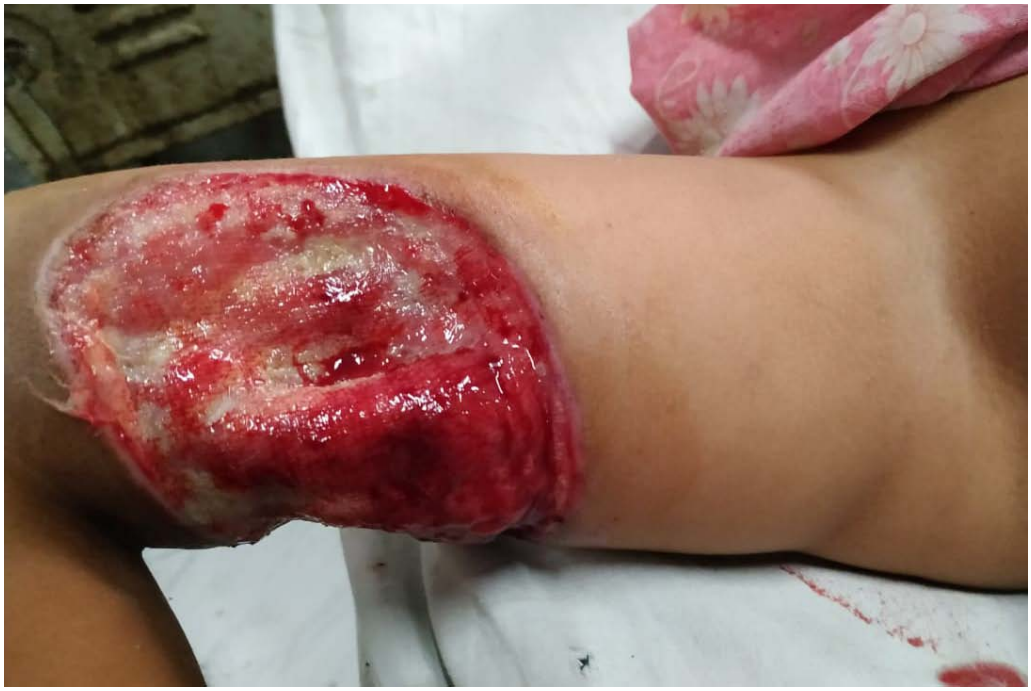


Figure 14: Healing Ulcer over right thigh posterior aspect after completion of course of Doxycycline

II. Discussion

Rickettsial pathogens are gram-negative bacteria causing fever and rash, usually transmitted to humans by contamination of bite sites or skin abrasions with *Rickettsia*-containing flea feces or directly by the bite of ticks (9). Rickettsial infection should be suspected in the presence of above clinical features in a patient with a likelihood of tick exposure. They should undergo relevant hematological and biochemical testing, and those with a high probability of rickettsial infection should be treated with appropriate antimicrobials.

The Weil Felix test still serves as a useful and cheapest available tool for the laboratory diagnosis of rickettsial diseases. A four-fold rise in agglutinin titres in paired sera is diagnostic for infection with these febrile agents. However, with a single serum sample available, the test is suggestive of infection only at a high cut-off titre (>1:320) at which the positive predictive value and the specificity is reliable (10).

Rickettsial diseases can be easily confused with a variety of viral (measles, enteroviralexanthems, dengue, infectious mononucleosis), protozoal (malaria), bacterial (meningococcemia, typhoid, leptospirosis, toxic shock syndrome, scarlet fever) and collagen vascular (Kawasaki disease, other vasculitis) diseases, and adverse drug reactions. Doxycycline is the drug of choice.

III. Conclusion

Rickettsial infections are difficult to diagnose and require consideration of clinical presentation, various environmental factors, and even the response to antibiotics. The common clinical presentation includes fever with chills and rigor, headache, vomiting, cough, conjunctival congestion and eschar. Rashes are a rare symptom(1).Persistence of fever even after 48 h, the presence of rash and tick exposure with altered biochemical parameters should alert the clinician toward rickettsial diseases (11). Rickettsial diseases, due to diagnosis of exclusion, lead to extensive investigations in children with fever of undetermined origin contributing to financial burden on families.

The fulminant course of rickettsial infections can lead to life-threatening manifestations such as disseminated intravascular coagulation, mening-oencephalitis syndrome, acute renal failure, hepatic failure, non-cardiogenic pulmonary edema, interstitial pneumonitis, and myocarditis (8).

In view of low index of suspicion, nonspecific signs and symptoms, and absence of widely available sensitive and specific diagnostic tests, these infections are notoriously difficult to diagnose. Failure of timely diagnosis leads to significant morbidity and mortality. With timely diagnosis, treatment is easy, affordable and often successful with dramatic response to antimicrobials. It is necessary to increase awareness among doctors as these infections are often the last to be suspected.

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