Short Report

Inflammatory leg nodules: A clinical and investigational study

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ABSTRACT

Background. Inflammatory leg nodules are a diagnostically challenging group of dermatoses with limited tools for diagnosis. Considerable overlapping patterns exist despite their distinct clinical and histological features. We attempted to understand if undertaking investigations and studying the clinical course and treatment response can help in differentiating these dermatoses.

Methods. Forty-three patients presenting with inflammatory leg nodules underwent a series of investigations apart from histopathology. The patients were treated as per the final histological diagnosis and observed for response to treatment and followed up to evaluate the clinical course.

Results. There was considerable overlap in the investigations done among various dermatoses. These included elevated erythrocyte sedimentation rate (ESR), Mantoux test and anti-streptolysin-O (ASLO) titres in the majority of patients while a few had abnormal findings on chest X-ray, CT scan of the chest and doppler ultrasonography of the legs. About 86% of patients with erythema nodosum, 50% with erythema induratum, 57% with cutaneous medium vessel vasculitis and 93% with unclassified panniculitis responded to non-steroidal non-inflammatory drugs (NSAIDs) alone or had spontaneously resolved with only post-inflammatory hyperpigmentation. Other patients required specific treatment with immuno-suppressive or immunomodulatory agents.

Conclusions. There is considerable overlap in dermatoses manifesting as inflammatory leg nodules on investigations, treatment received and response to treatment. To categorize them better into distinct entities, this group of dermatoses may require long-term follow-up of the clinical course and response to treatment, repeated investigations especially histopathology during different phases of evolution and progression of disease.

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INTRODUCTION

Inflammatory nodules involving the extremities are a complex group of disorders with considerable clinico-histopathological overlap. These dermatoses are often investigated for an associated infection, connective tissue disease, drug aetiology or an underlying malignancy.[1,2] Treatment involves administration of anti-inflammatory and immunosuppressive agents besides specific treatment for the underlying aetiology.[1,2] There is no consensus on the investigations to be done in these patients and the value of a positive test. Also there is no clarity on the treatment to be initiated. We evaluated the investigations done, and the treatment response in this group of dermatoses.

METHODS

Over 21 months, we prospectively studied consecutive patients presenting to us with tender erythematous nodules predominantly involving the extremities. We excluded those with pyogenic infections and erythema nodosum leprosum. All the patients had a detailed history taken followed by a thorough clinical examination, a deep punch biopsy for histopathological analysis and other investigations. Clinico-histopathological correlation was done in all patients. The final diagnosis was made based on the histopathology.[3]

The laboratory investigations done in all patients included a complete haemogram including erythrocyte sedimentation rate (ESR), renal and liver function tests, fasting blood sugar, urine and stool analysis, anti-nuclear antibody (ANA), rheumatoid factor (RF), chest X-ray, Mantoux test, serum anti-streptolysin-O (ASLO) titre (raised >200 U/ml; considerably raised >400 U/ml or rising trend in serial titres) and throat swab for culture and sensitivity. Other tests such as culture of the skin biopsy specimen; blood, urine and stool culture and sensitivity; serum angiotensin-converting enzyme (ACE) levels, complement and cryoglobulin levels, viral markers for hepatitis B, C and HIV screening, serum anti-neutrophil cytoplasmic (ANCA) and anti-double stranded DNA (dsDNA) levels, serum lipase or alpha-1 antitrypsin and radiological investigations such as ultrasound or CT scan of the chest and abdomen or doppler of the extremities, were done on the basis of clinical suspicion in specific patients. The deranged parameters were correlated with the final diagnosis made. Appropriate treatment was initiated as per the final histological diagnosis and patients were observed for response to treatment. They were also followed up to evaluate the course of disease. The study was approved by the institutional ethics committee and written informed consent was obtained from all the patients.

RESULTS

Forty-three patients (21 men), with a mean (SD) age of 37.4 (12.7) years (range 11–65 years) were included in the study. The mean (SD) duration of disease at the time of presentation was 2.4 (4.7) years (range 8 days to 23 years, median 5 months). After histological examination, the final diagnoses made were erythema nodosum (EN; showing septal panniculitis/predominantly septal panniculitis without vasculitis on histopathology) in 14 (32.6%), erythema induratum (EI; histopathology showing lobular panniculitis with vasculitis) in 4 (9.3%), cutaneous medium vessel vasculitis (CMVV; evidence of inflammation and vessel wall damage within and around the medium-sized vessel without involvement of distant subcutaneous septa or lobules) in 7 (16.3%) and lupus panniculitis (LEP; lobular panniculitis with or without septal panniculitis with chronic inflammation and plasma cells with or without lymphoid follicle formation or hyaline changes in lobules.

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Associated epidermal/dermal changes of lupus erythematosus (may or may not be present) in 3 (7%) patients while 15 (35%) were in the undecided category (unclassified panniculitis—a heterogeneous group of panniculitis showing variable histological features suggestive of a panniculitis, but not conforming to any well-recognized entity; Figs 1–4). The derangements observed on investigations were varied (summarized in Table I). The treatment given and response to treatment were also varied (Table II).

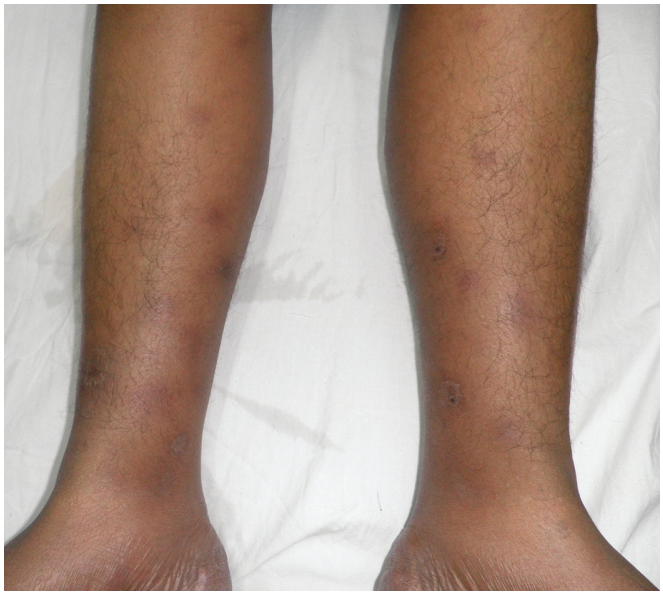

FIG 1. Erythema nodosum: Multiple erythematous nodules on the medial aspect of both legs

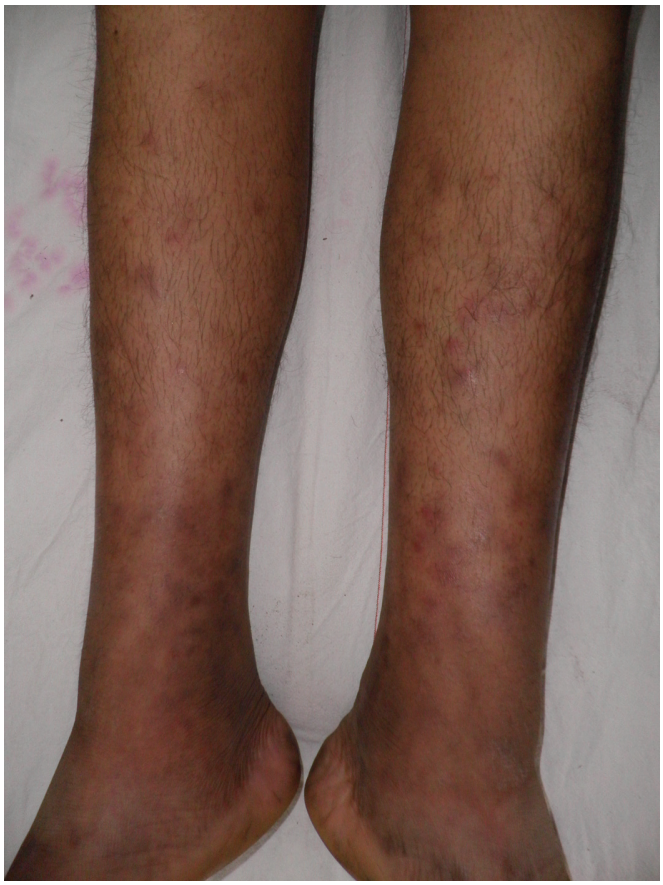

FIG 3. Medium-vessel vasculitis: Multiple grouped erythematous nodules on both lower legs

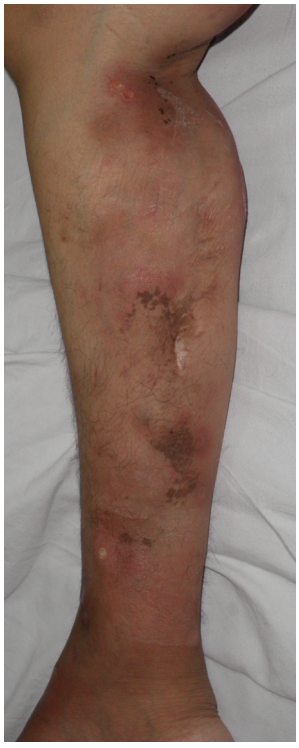

FIG 2. Erythema induratum: Multiple ulcerated nodules over the leg, healing with scarring

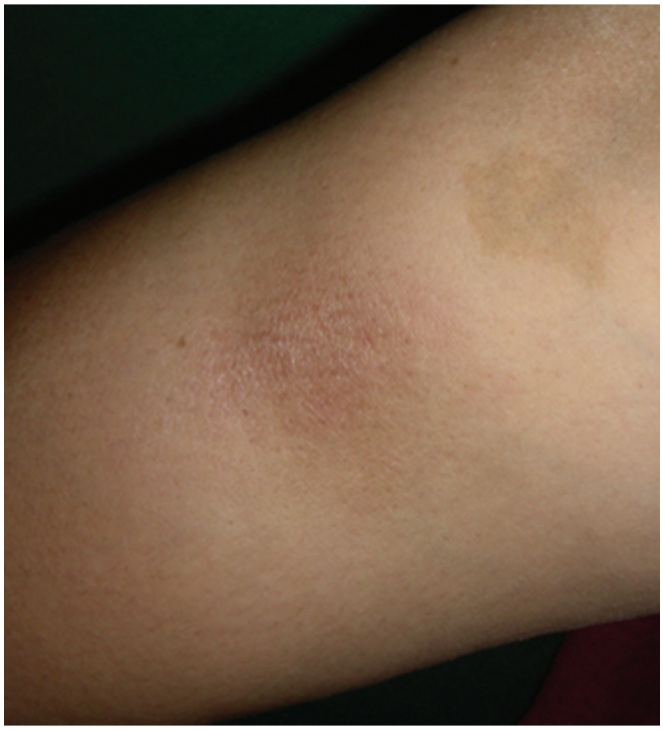

FIG 4. Lupus panniculitis: Erythematous nodules on the lateral aspect of the arm, healing with subcutaneous atrophy

TABLE I. Derangement in investigations in patients of inflammatory nodules over extremities

Histological or final diagnosis	Raised ESR (mm at 1 hour)	Raised Mantoux (mm at 48 hours)	Raised ASLO titre†/ Throat swab	Abnormal investigations*	Microcytic hypochromic anaemia	Radiological abnormalities
Erythema nodosum (*n*=14)	14 Mean: 28 Median: 26.5	12 Mean: 17.5 Median: 15.5	1 1 (*beta haemolytic streptococci* grown)	↑ AST/ALT: 1 (7%)	1	*X-ray chest*: Diffuse reticular opacity in both lungs suggestive of interstitial lung disease *CT chest*: Mediastinal and bilateral hilar lymphadenopathy with ground glass opacity in lower lobes suspicious of sarcoidosis in 1 *Ultrasound Doppler lower limbs*: Varicose veins with multiple incompetent perforators in right leg in 1 *Ultrasound abdomen*: Fatty liver in 1
Erythema induratum (*n*=4)	4 Mean: 46 Median: 52.5	3 Mean: 13.5 Median: 14.5	2	↑ Blood sugar: 1	2	*Ultrasound abdomen*: Fatty liver in 1
Medium vessel vasculitis (*n*=7)	5 Mean: 33.6 Median: 22	4 Mean: 16 Median: 18	3	Nil	0	*X-ray chest:* Small patchy opacity in the left lower lobe suggestive of old healed infection in 1 *CT chest with normal X-ray chest*: 2 1. Calcified granuloma in the left lower lobe, sequelae of tuberculosis 2. Few necrotic lymph nodes in the mediastinum, active tuberculosis *Ultrasound Doppler*: 2 1: Superficial venous thrombosis in the left calf 2: Incompetent left ankle perforator
Lupus panniculitis (LEP) (*n*=3)	2 Mean: 21 Median: 25	0	1	Rheumatoid factor positive: 1 (not associated with rheumatoid arthritis)	1	*Ultrasound abdomen*: Fatty liver in 1
Unclassified (*n*=15)	14 Mean: 40 Median: 36	14 Mean: 17.4 Median: 15	4 1 (*S. aureus* grown)	Nil	1	*X-ray chest*: Bulky left hilum, ?lymph node *CT chest*: Homogeneous lymphadenopathy in pretracheal, para-aortic, subcarinal regions due to tuberculosis in 1 *USG Doppler lower limb*: Varicose veins with bilateral incompetent calf perforators in 1

* antinuclear antibody (ANA) was negative in all (equivocal titre of 1:40) † ASLO titre not significantly raised AST aspartate transaminase ALT alanine transaminase

DISCUSSION

The commonest cause of inflammatory nodules was EN and nearly an equal number were unclassified. We found elevated ESR in all patients with EN, and Mantoux test was positive in 37 (86%) with a mean Mantoux of 17.5 mm despite no evidence of active tuberculosis. X-ray and CT chest with transbronchial tissue biopsy findings suspicious of sarcoidosis were present in 1 patient. Various studies have found elevated ESR in 60%–83% of patients with EN.[4–8] Mantoux test positivity has been reported in 14%–90% of EN.[4,5,7–9] Mert *et al.* detected underlying pulmonary tuberculosis in 10% of patients with EN based on chest X-ray, CT scan and culture; 90% of patients with tuberculosis had Mantoux positivity ranging from 13.5 to 35 mm while the remaining were Mantoux negative.[8] Garcia-Porrua *et al.* found that 4.8% of patients with EN had tuberculosis while 14% patients were Mantoux positive.[4] Cribier *et al.* showed Mantoux positivity in 66 of 129 patients with EN but only 1 had underlying tuberculosis based on sputum culture positivity and an abnormal chest X-ray.[7] In India, where there is a high prevalence of tuberculosis, Mantoux positivity does not indicate underlying tuberculosis. It merely suggests hypersensitivity to *Mycobacterium tuberculosis*.[10,11] Ramam *et al.* from India observed Mantoux readings ranging from 0 to 40 mm in patients with cutaneous tuberculosis and from 0 to 30 mm in those who did not have tuberculosis.[11] Pai *et al.* recorded Mantoux readings of 0–25 mm without active tuberculosis in healthcare workers in rural India.[12] For tuberculosis to be the underlying cause in EN, other evidence should be present.[8] Evidence of pulmonary sarcoidosis has been observed in 10%–21% of patients with EN.[4,7–9] A history of sore throat was obtained in 3 of our patients (21%), with an elevated ASLO titre (not significantly raised as the level was <400 U/ml) and beta-haemolytic streptococci growth on culture in 1 patient each (7%). However, EN responded to non-steroidal anti-inflammatory drugs (NSAIDs) and no antibiotics were given to these patients. Mert *et al.* observed sore throat in 11% of patients with EN, all with a raised ASLO titre but only 1 grew beta-haemolytic streptococci in culture.[8] Cribier *et al.* found 35%, 22.5% and 7% of patients with EN had sore throat, raised ASLO titre and beta-haemolytic streptococci in culture, respectively.[7] Hence, except for 2 patients, the rest (86%) of our patients were of the idiopathic type, this feature being observed in 37%–55% of patients in other studies.[4,7,8]

Of the 14 EN patients, the majority (9, 64%) achieved resolution of lesions with NSAIDs, 3 (21%) had spontaneous resolution while in 1 patient the lesions subsided in 5 days with prednisolone and remission was maintained with NSAIDs. The patient with underlying sarcoidosis had partial response of the EN lesions to indomethacin and was referred for further management for systemic sarcoidosis. Mert *et al.* treated a majority of their patients with EN with naproxen for 2–3 weeks. They responded within 7 days, while 5 who did respond achieved remission with potassium

TABLE II. Treatment response and follow-up

Histological or final diagnosis	Duration of disease, range (median)	Response to treatment and follow-up
Erythema nodosum (*n*=14)	8 days–20 years (4.5 months)	9 (64%) patients: Treated with indomethacin (*n*=8), paracetamol (*n*=1); resolution of lesions with hyperpigmentation in 4–14 days in 6 patients and in 4–12 weeks in 3 patients. During the mean follow-up of 9.5 weeks, 7 were in remission; 2 had recurrence. In the patient with streptococcal sore throat, the nodules resolved with NSAIDs. Antibiotic given after lesion resolution. No recurrence. 3 (21%) patients: spontaneous resolution of lesions with hyperpigmentation in 4–7 days. No relapse in next 2 weeks. 1 patient: lesions resolved with hyperpigmentation in 5 days with tapering doses of prednisolone (given for chorioretinitis) and then started on indomethacin. No new lesions in next 4 weeks. 1 patient: lost to follow-up.
Erythema induratum (*n*=4)	35 days–5 years (8 months)	1 patient: resolution with indomethacin and no new lesions in next 2 months. 1 patient: received systemic steroids and azathioprine with subsidence of lesions and no new lesions in next 6 months. 1 patient: spontaneous resolution with hyperpigmentation in 7 days and no new lesions in next 6 weeks. 1 patient: lost to follow-up.
Medium vessel vasculitis (*n*=7)	20 days–23 years (1 year)	3 (43%) patients: With indomethacin had resolution in 2–8 weeks. During the follow-up period of 27 weeks, 2 patients had one episode of recurrence that resolved with continued indomethacin. 1 patient: with antitubercular therapy (CT chest suggestive of active mediastinal tubercular lymphadenopathy), had resolution in 7–10 days; completed 6 months of antitubercular therapy with no recurrence. 1 patient: with tapering prednisolone and indomethacin, ulcerated lesions resolved with hyperpigmentation in 3 weeks; dapsone added and steroid stopped with no recurrence in next 4 months. 1 patient: with prednisolone and indomethacin had only partial control in 6 weeks and was still getting new lesions. Later developed deep vein thrombosis of left leg, got admitted for evaluation and received injectable low molecular weight heparin and oral acecoumarin. Then lost to follow-up. 1 patient: spontaneous resolution of lesions during 2 weeks of follow-up.
Lupus panniculitis (*n*=3)	1 year–9 years (2 years)	1 patient: lesions resolved with subcutaneous atrophy with hydroxychloroquine over 5 months with no new lesions. 1 patient: with prednisolone and azathioprine, all nodules resolved with atrophy/normal skin over 5 months. No new skin lesions developed. 1 patient: lost to follow-up.
Undecided (*n*=15)	10 days–5 years (3 months)	8 (53%) patients: Treated with indomethacin (*n*=7), naproxen (*n*=1); complete resolution of lesions in 1–3 weeks in 6 patients and partial resolution at week 5 and 8 in 2. In next 7 weeks, 7 patients in remission, 1 had recurrence. The patient with finding of mediastinal lymph nodal tuberculosis on CT chest was considered normal by pulmonary medicine and not given antitubercular therapy. Skin nodules resolved with indomethacin. 6 (40%) patients: spontaneous resolution of lesions with hyperpigmentation. No recurrence during the mean follow-up of 6 weeks. 1 patient: with dapsone lesions resolved in 3 weeks, recurred at 4 months, indomethacin added with resolution in 4 weeks. In remission in next 6 weeks.

iodide within 7 days. Specific treatment was initiated only when an underlying cause was found.[8] Handa *et al.* treated 16 idiopathic EN cases with NSAIDs with good response. However, 2 patients required a short course of corticosteroids.[6]

In the patients with EI, the ESR was raised in all and Mantoux test was positive in 3 of 4 (75%) patients. We did not observe any evidence of active tuberculosis (pulmonary or extrapulmonary) or any other cause on clinical and laboratory evaluation in any of the patients. Cho *et al.* observed a high ESR in 88% of patients with EI.[13] Various studies have shown Mantoux positivity in 90%–100% of patients with EI.[9,13,14] Cho *et al.* recorded the personal history and chest X-ray evidence of tuberculosis in 28.2% and 15.7% of patients with EI, respectively, while Mantoux positivity ranged from 13 to 100 mm and bulla at 48 hours in all patients.[13] Niemi *et al.* observed history of tuberculosis and retroperitoneal lymphography suggestive of tuberculosis in 18.2% of patients each, normal chest X-rays in all but with Mantoux positivity in all patients. Hence, all patients with EI in the Niemi study were Mantoux positive but few had a focus of tuberculosis.[9] Other studies reported past or present history of extracutaneous tuberculosis in 50% patients, of which pulmonary tuberculosis was the most common followed by tubercular cervical lymphadenitis.[3,15] Rarely HIV, hepatitis C and vaccination have been associated with EI.[16] EI is therefore a reaction pattern secondary to various underlying diseases of which tuberculosis (EI of Bazin) is one of them.[2]

Of the 4 patients with EI, none was prescribed antitubercular therapy (ATT), since no definitive evidence of active tuberculosis was found and all showed resolution with anti-inflammatory or immunosuppressive agents. Simple measures such as bed rest or use of NSAIDs can lead to complete remission in most patients with EI while those with severe manifestations require potassium iodide, dapsone, colchicine, antimalarials, tetracyclines, gold salts and prednisolone, although these do not prevent late recurrences.[3,15] A good response with lower relapse rates with ATT has been shown in patients in whom underlying tuberculosis was identified.[15] Schneider *et al.* successfully treated 20 patients with EI with ATT within 1 to 6 months; all had Mantoux positivity with no evidence of active tuberculosis in any, except lesional polymerase chain reaction being positive in 5 patients.[17]

Of our 7 CMVV patients, raised ESR was seen in 5 (71%), Mantoux positivity in 4 (57%) with 3 patients having past (*n*=2) or current evidence (*n*=1) of pulmonary tuberculosis and raised ASLO titre (not significantly) in 3 (43%). A raised ESR in 31%–60% of cutaneous polyarteritis nodosa (PAN), patients has been reported.[18,19] Daoud *et al.* observed ANA positivity and raised RF

in 20% and 4% of patients, respectively.[18] However, all our patients were non-reactive for these tests.

Our patients with CMVV responded to NSAIDs alone or in combination with anti-inflammatory agents (dapsone), with 2 patients requiring oral steroids (due to ulceration and severe disease activity) and the other with active underlying tuberculosis showing resolution in a week without recurrence after ATT. Ishiguro and Kawashima treated 11 of 16 patients with cutaneous PAN with NSAIDs, with 1 also receiving dapsone and 5 being treated and maintained on prednisolone.[19] Daoud *et al.* treated 79 patients with cutaneous PAN using NSAIDs, prednisolone and a combination of the following drugs: dapsone, sulphapyridine, colchicine, pentoxifylline, hydroxychloroquine, azathioprine, cyclophosphamide and methotrexate, with good control. Ulcerated lesions required an initial high dose of prednisolone, which was tapered over 6–8 weeks followed by substitution with steroid-sparing agents.[18]

In the 3 patients with LEP, ESR was raised in 2 and ASLO titre and RF in 1 patient each. ANA and Mantoux test were negative in all patients. Ng *et al.*[20] and Winkelmann[21] observed ANA positivity in 3 of 11 (27.3%) and 18 of 27 (66.6%) patients with LEP, respectively. In a retrospective review of 44 patients with LEP, Arai and Katsuoka found that in LEP alone without SLE, many ANA positive patients had low antibody titres of 1:40 or 1:80.[22] In our patients, lesions resolved with hydroxychloroquine, or prednisolone and azathioprine. Treatment of LEP with antimalarials such as chloroquine, quinacrine and hydroxychloroquine or corticosteroids and other immunosuppressive drugs has been found to be effective in various studies.[2,21,23]

Of the 15 patients kept in the histologically undecided category (unclassified panniculitis), 14 (93%) had elevated ESR and Mantoux positivity while 4 (27%) had elevated ASLO titres, with evidence of staphylococcal throat infection in 1 patient. Nine cases (60%) treated with NSAIDs achieved complete-to-partial resolution and the remaining 6 (40%) had spontaneous resolution.

To summarize, 86% of patients with EN, 50% with EI, 57% with cutaneous medium vessel vasculitis and 93% unclassified patients responded to NSAIDs alone or had spontaneous resolution with post-inflammatory hyperpigmentation only. Other patients required specific treatments including ATT or immunosuppressive agents.

The limitations of our study include a small sample size and a short follow-up period.

In conclusion, dermatoses manifesting as inflammatory leg nodules are a challenging group of disorders. We observed similar patterns of derangements on investigations as also on response to treatment, since more than half the patients responded to anti-inflammatory agents alone and only few required specific treatment. The unclassified category formed a major proportion of such patients. However, they showed similar derangements on investigations and response to treatment. This suggests that there is considerable overlap in this group of dermatoses both with regard to investigational alterations and response to treatment. Distinguishing between them and finding an underlying aetiology may therefore be possible only on long-term observation of the clinical course and response to treatment, repeated investigations during different phases of evolution and progression of disease.

Conflicts of interest: None declared.

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