Coexistence of primary erythema migrans and erythema multiforme in early Lyme disease

Sir,

The discovery of natural habitats of *Ixodes* tick in the Himalayan region, a transmitting vector that harbours the spirochete *Borrelia burgdorferi sensu lato,* has led to increase in the incidence of Lyme borreliosis in the Indian subcontinent recently.[1] Herein, we report a case of early Lyme disease with interesting clinical features.

A 34-year-old man presented to the dermatology outpatient department at King George's Medical University, Lucknow, with a gradually expanding red painful lesion on the right sole for a month. Before its development, he had a history of walking barefoot in the fields, wherein five days later, he developed low-grade fever for a day that subsided spontaneously. There was no history of any prior drug intake, oral ulceration, cough, rhinitis, joint pain, weakness of limbs, palpitation, travel, unprotected sexual intercourse or blood transfusion.

On physical examination, a single, annular, erythematous and tender plaque measuring 3.8 × 3.8 cm was seen on the central aspect of the right sole with morphology of a typical target lesion [Figure 1a]. He was treated considering a provisional diagnosis of erythema multiforme with clobetasol propionate 0.05% ointment. After 15 days further expansion of plaque to 5.5 × 9.5 cm [Figure 1b] with multiple smaller, typical target plaques measuring 0.5 × 0.5–1.5 × 2 cm on elbows, palms, knees and left sole were observed [Figure 1c]. General and systemic examinations were within normal limits.

Routine laboratory investigations were unremarkable except for mild leucocytosis and neutrophilia. The patient was further evaluated; serology and polymerase chain reaction for herpes simplex virus, serology for *Mycoplasma pneumoniae*, anti-nuclear antibodies and venereal disease research laboratory test were negative. Serology for Lyme borreliosis involved a two-step approach.[1] Enzyme-linked immunosorbent assay for Lyme disease showed positive immunoglobulin M with titre 17.58 NovaTech unit (normal reference range: 9–11 NovaTech unit) and negative immunoglobulin G. Western blot for *Borrelia* showed immunoglobulin M positive (against VIsE Bg antigen and borderline against two antigens P41 Ba and OspC Bs) and immunoglobulin G positive (against four antigens P41, OspB, Ospa Ba and OspA Bg). Histopathology from the expanding lesion on the right sole revealed mild interface pathology, dermal perivascular lymphocytes and occasional plasma cells. In contrast, the smaller target lesions on the palm and left knee showed extensive epidermal necrosis, lymphocytes and apoptotic keratinocytes obscuring

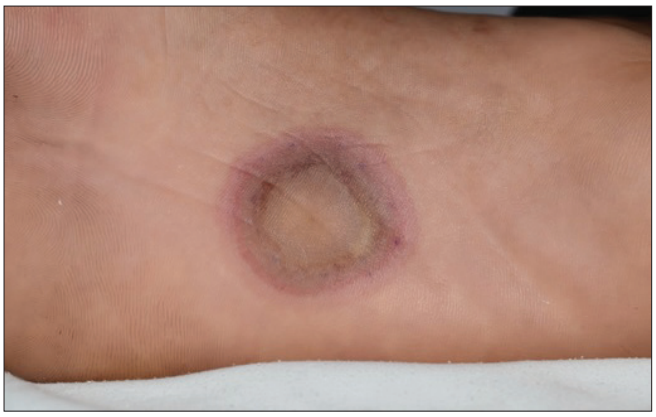

Figure 1a: Primary erythema migrans on the right sole presenting as typical target plaque with two peripheral erythematous rings and a pale centre

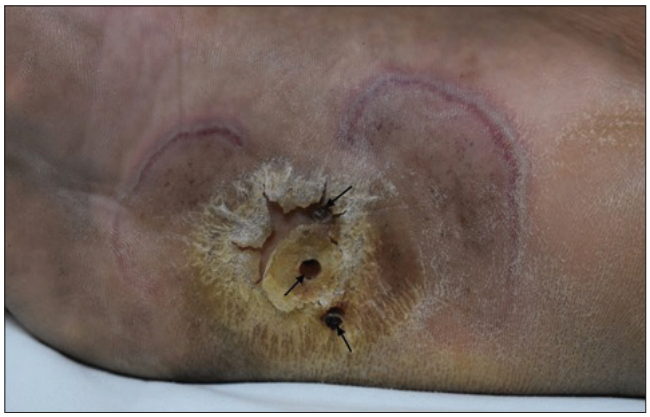

Figure 1b: Expansion in size of primary erythema migrans on the right sole with thick exfoliating keratinous scales at the centre and erythematous ring surrounded by a pale halo. Biopsy sites in healing phase are visible at the centre (arrows)

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the dermoepidermal junction [Figure 2a and 2b]. Polymerase chain reaction from biopsy of the right sole lesion was negative for *Borrelia* species. A diagnosis of early Lyme disease was made due to clinical features and positive serology. The patient was given oral doxycycline 100 mg twice daily for three weeks. Complete resolution of all the cutaneous lesions was noticed at the end of four weeks [Figure 3a and 3b] and no features of late disseminated disease appeared during post-treatment follow-up of six months.

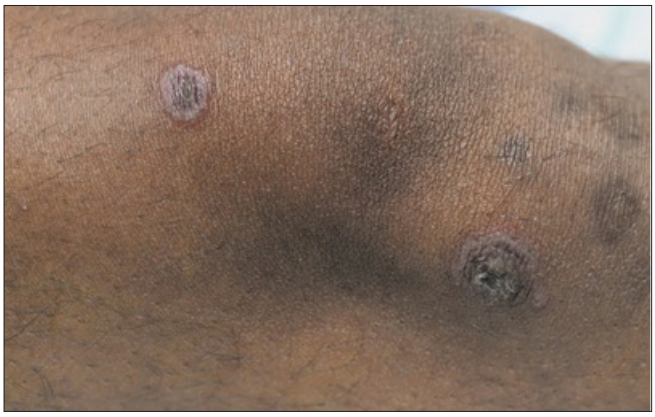

Figure 1c: Smaller typical target plaques on the left knee—erythema multiforme

Primary erythema migrans usually appear in an unperturbed site (skin folds) where the tick can remain attached for 48 h, but primary erythema migrans on the sole is atypical.[1] Moreover, the 'classic target pattern' of primary erythema migrans observed here is known to occur in only 20% of the cases.[2,3] Histopathological findings of the expanding plaque on the right sole were consistent with primary erythema migrans.[1] Mild interface changes, observed here, have been described by Tekin *et al*. (2020) as a more frequent finding of primary erythema migrans in contrast to the earlier belief.[4] Although typical target morphology, presentation on sole and interface changes in histopathology are features of erythema multiforme, we preferred diagnosis of primary erythema migrans over erythema multiforme on account of its expanding nature

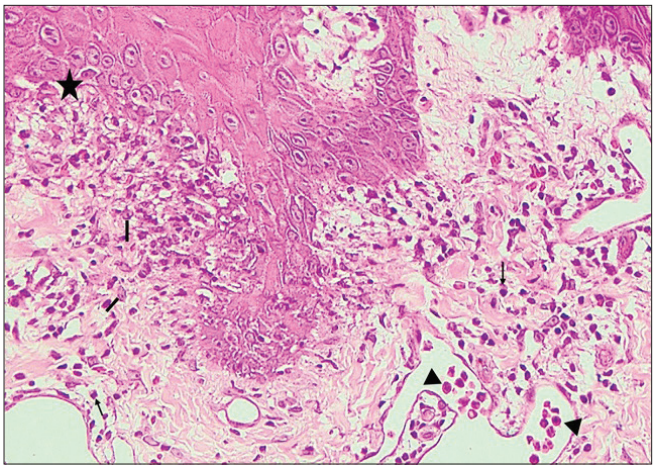

Figure 2a: Right sole: section shows skin with focal interface dermatitis (star) and perivascular and intravascular eosinophils (arrowheads), lymphocytes, histiocytes (lines) and plasma cells (arrows) in the dermis (haematoxylin and eosin, ×200)

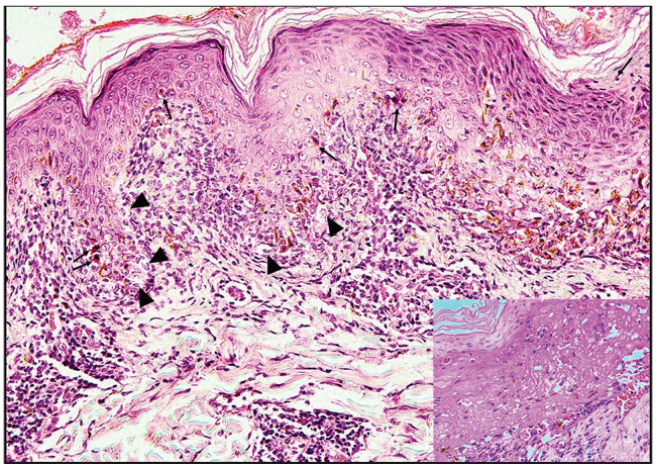

Figure 2b: Left knee: section shows skin with numerous apoptotic keratinocytes (arrows), papillary dermal oedema, basal cell degeneration (arrowheads) and lymphocytic infiltrate obscuring the dermoepidermal junction. Dermis shows perivascular infiltration of lymphocytes and histiocytes. Inset shows epidermal necrosis (haematoxylin and eosin, ×200)

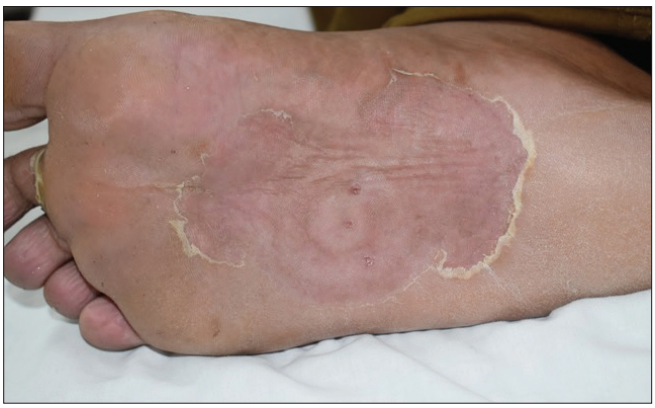

Figure 3a: Primary erythema migrans on the right sole nearing resolution with mild peripheral scaling at the end of four weeks

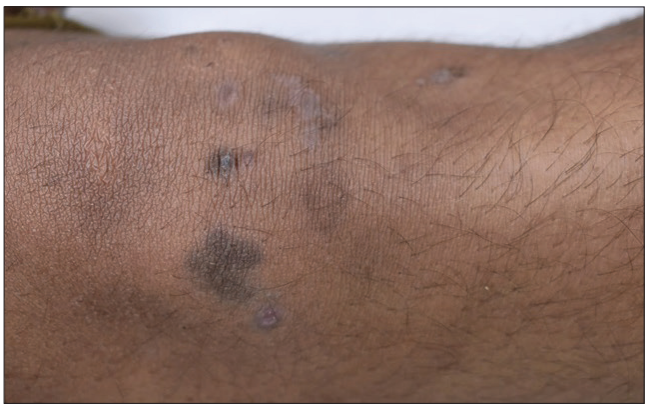

Figure 3b: Erythema multiforme on the left knee healing with residual hyperpigmentation

and size >5 cm which was in concordance with Centers for Disease Control and Prevention criteria for erythema migrans and hence not compatible with diagnosis of erythema multiforme.[1,4,5] Furthermore, enzyme-linked immunosorbent assay and Western blot test for Lyme borreliosis demonstrated seroconversion pattern similar to the previous description in the literature where immunoglobulin G peaks over several months.[6] Besides, seroconversion in Lyme disease is unpredictable from being completely absent to taking few weeks or months.[6,7] The sensitivity of polymerase chain reaction for *Borrelia* from cutaneous biopsy of primary erythema migrans is only 71% which could explain the negative polymerase chain reaction in this patient.[1]

An additional diagnosis of erythema multiforme due to Lyme disease was considered for subsequent smaller typical target lesions. Other causes for erythema multiforme such as herpes simplex virus, *Mycoplasma pneumoniae* and drugs were ruled out based on corroborative clinical and serological findings. Although erythema multiforme in early Lyme disease has been reported previously, neither the typical target morphology nor the specific histopathological findings of erythema multiforme have been described.[8] Erythema multiforme, in this case, needs to be primarily differentiated from secondary erythema migrans, because secondary erythema migrans can also occur in a patient with Lyme disease within few weeks after appearance of primary erythema migrans. Association of systemic symptoms such as low-grade fever, lymphadenopathy along with sparing of palms, soles and dermal perivascular plasma cell infiltrate in histopathology is characteristics of secondary erythema migrans These were totally absent in our case favouring a diagnosis of erythema multiforme over secondary erythema migrans.[1,8,9]

To conclude, a large (>5 cm) expanding plaque on the right sole gave us the clue to the diagnosis of primary erythema migrans which was further corroborated by positive serology, consistent histopathology as well as therapeutic response to oral doxycycline. The atypical site of primary erythema migrans on the right sole, subsequent eruption of erythema multiforme at other sites and typical target morphology of both these lesions, all these collectively are uncommon features of early Lyme disease. Such unusual manifestations in a non-endemic region create a diagnostic dilemma and assert the need for strong clinical suspicion to reach the diagnosis in a timely manner and avert the advanced stage of Lyme disease.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest
There are no conflicts of interest.

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References

1. Vasudevan B, Chatterjee M. Lyme borreliosis and skin. Indian J Dermatol 2013;58:167–74.
2. Edlow JA. Erythema migrans. Med Clin North Am 2002;86:239–60.
3. Aucott JN, Crowder LA, Yedlin V, Kortte KB. Bull's-eye and nontarget skin lesions of Lyme disease: An internet survey of identification of erythema migrans. Dermatol Res Pract 2012;2012:451727.
4. Tekin B, Song Y, DiCostanzo D, Lee BA. Erythema migrans and interface changes: More than a fortuitous association. Am J Dermatopathol 2020;42:745–50.
5. Shrihari T G, Shetty SR. Erythema multiforme: A mysterious lesion!Indian J Med Paediatr Oncol 2018;39:363–7.
6. Borchers AT, Keen CL, Huntley AC, Gershwin ME. Lyme disease: A rigorous review of diagnostic criteria and treatment. J Autoimmun 2015;57:82–115.
7. Aberer E, Schwantzer G. Course of antibody response in Lyme borreliosis patients before and after therapy. ISRN Immunol 2012;2012:719821.
8. Lesire V, Machet L, Toledano C, de Muret A, Maillard H, Lorette G, et al. Atypical erythema multiforme occurring at the early phase of Lyme disease? Acta Derm Venereol 2000;80:222.
9. Yager JA. Erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis: A comparative review. Vet Dermatol 2014;25: 406–e64.