Atypical Clinical Manifestation of Bilateral Erythema Nodosum Migrans: A Case Report and Literature Review

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ABSTRACT:
Erythema nodosum migrans is a rare form of panniculitis referring to migratory subcutaneous nodules or plaques, predominantly involving the lower extremities. We report a case of a 26-year-old female with erythema nodosum migrans presented with bilateral, expanding annular erythematous to brownish nodules and plaques with central clearing on both anterior and posterior lower legs. The biopsy revealed marked septal thickening with mixed inflammatory cell infiltration, multinucleated giant cells and prominent granuloma formation, which was corresponding with erythema nodosum migrans. The patient demonstrated clinical improvement with colchicine and indomethacin therapy.
Key words: Erythema nodosum migrans, Septal panniculitis, Subacute nodular migratory panniculitis, Vilanova disease

Introduction

Erythema nodosum migrans was first reported in 1954 by Bafverstedt as the clinical characteristics were different from classic erythema nodosum[1]. Erythema nodosum, the most common form of panniculitis, is characterized by fat septal inflammation. The disease can be associated with diverse etiologies, including infection, pregnancy, medications, and various systemic conditions[2]. Clinical variants of erythema nodosum have been identified and documented by several terminologies, such as erythema nodosum migrans, subacute nodular migratory panniculitis, and chronic erythema nodosum[3]. However, these clinical subtypes could be broader spectrum of erythema nodosum[4]. Erythema nodosum migrans is an uncommon disorder identified by tender, erythematous subcutaneous nodules or plaques. These lesions typically present on lower extremities and exhibit a migratory pattern[1].

Case report

A 26-year-old Thai female presented to the outpatient clinic at the Institute of Dermatology with a four-month history of bilateral, non-tender, non-indurated, erythematous plaques with hyperpigmentation on both anterior and posterior aspects of the lower legs. One month after the initial presentation, the patient developed expanding additional annular, hyperpigmented nodules and plaques on the same areas, still non-indurated and non-tender. There were no associated systemic symptoms such as fever, malaise, or weight loss. The patient denied any history of trauma and underlying medical conditions. No family members exhibited similar dermatological

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presentations. The dermatological examination revealed bilateral, well-defined, non-indurated, non-scaly, annular erythematous to brownish nodules and plaques with central clearing on both anterior and posterior surfaces of the lower legs (Figure 1). The differential diagnoses are erythema nodosum, erythema nodosum migrans, lipodermatosclerosis, erythema induratum, lupus panniculitis, necrobiosis lipoidica, granuloma annulare, and pretibial myxedema. An incisional biopsy was performed on the right leg. Histopathological examination revealed inflammation of subcutaneous fat mainly septal pattern. Lobular inflammation was also evident with focal small necrosis. Neither vasculitis nor atypicality of cell was seen. The inflammatory cells were comprised of lymphocytes, plasma cells, neutrophils, eosinophils, and histiocytes. Several granulomas were noted in deep dermis and subcutaneous septa. Multinucleated giant cells were noted. No central necrosis was seen (Figure 2). The laboratory investigations showed fasting blood glucose 302 mg/dl, cholesterol 245 mg/dl, low-density lipoprotein 120 mg/dl, triglyceride 546 mg/dl, HbA1c 7.4 mg%. The anti-streptolysin O (ASO) titer was negative. Thyroid function test was normal. Tissue culture for fungus was negative. PCR for mycobacterium tuberculosis complex and nontuberculous mycobacteria were negative. Direct Immunofluorescence of C3, Fibrinogen, IgA, IgG, and IgM were negative. The clinical and pathological findings were consistent with the diagnosis of erythema nodosum migrans. The patient was also first diagnosed with diabetes mellitus and dyslipidemia. The management included colchicine 1.2 mg daily for 1 month and indomethacin 75 mg daily for 3 months. After that indomethacin was decreased to 50 mg daily for 2 months and then 25 mg daily due to clinical improvement.

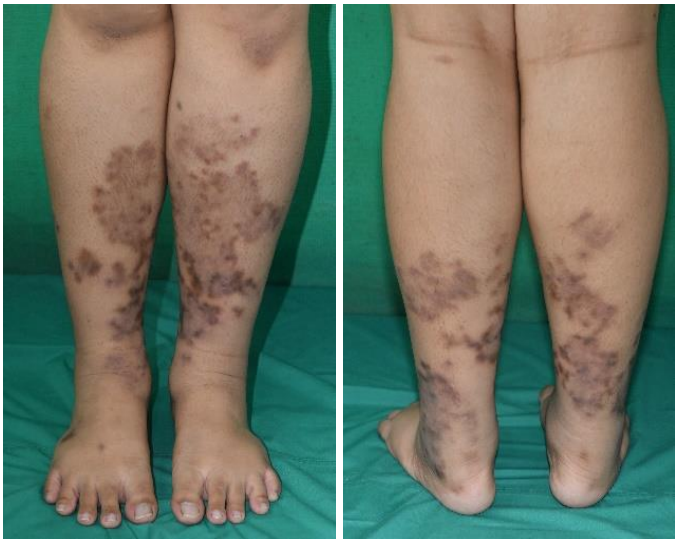

Figure 1 Bilateral, well-defined, non-indurated, non-scaly, annular erythematous to brownish nodules and plaques with central clearing on both anterior and posterior surfaces of the lower legs

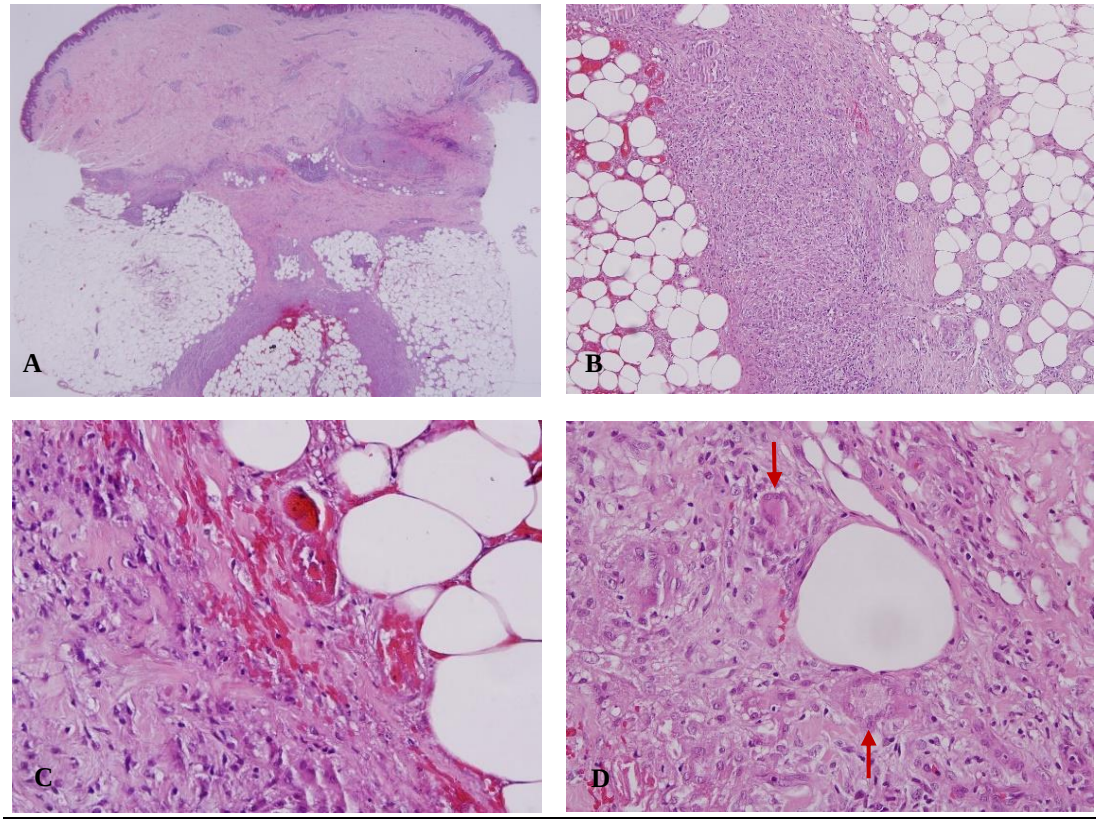

Figure 2 Incisional biopsy from right leg. (A, B) Histopathology showed subcutaneous fat septal thickening (H&E, ×20, ×100). (C) Mixed inflammatory cell infiltration and prominent granuloma formation were seen (H&E, ×400). (D) Multinucleated giant cells were present (H&E, ×400, red arrows)

Discussion

Erythema nodosum migrans mostly occurs in females aged between 30 and 60 years and often unilaterally migrates or expands peripherally with central clearing[5]. It might present with erythematous edge and yellowish appearance in the center of older lesions[6]. Comparing to erythema nodosum, the individual lesions of erythema nodosum migrans are less tender, fewer in number and last longer for months rather than weeks. There are few associated systemic symptoms reported such as arthralgias and elevation of erythrocyte sedimentation rate level[3]. The causes are still undetermined and most cases are idiopathic. However, there are reports that the disease relates to thyroid disease, streptococcal infection, inflammatory diseases, drugs, and malignancy[7,8]. The disease was reported followed by streptococcal infections confirmed by increased anti-streptolysin O and anti-DNase B titers[9]. Case reports of erythema nodosum migrans were reviewed and summarized in Table 1.

Table 1 Case reports of erythema nodosum migrans

Authors	Year of publication	Nation	No. of cases	Age (year), Gender	Morphology	Distribution	Histopathology	Treatment
Vilanova[3]	1959	Spain	19	18-66, 1M and 18F	Plaques and/or nodules	-Thigh (2 cases) -Lower leg (17 cases)	-Capillary endothelial proliferation in earliest stage -Giant cells, infiltration of mix cells in late stage	N/A
Hannuksela[9]	1973	Finland	56	16-25=18 26-35=21 36-45=9 46-55=6 ≥56=2, 3M and 53F	1-8 Nodules	-Unilateral (40 cases) -Frontal or lateral leg	-Perivascular infiltration with lymphocytes -Lymphocytes, histiocytes and giant cells in fat septum -Small and medium vessel vasculitis (some cases)	N/A
Rostas et al.[14]	1980	Canada	1	16, F	Erythematous nodules, centrifugal pattern with central clearing	Left lower leg	-Dermal perivascular infiltration with lymphocytes and histiocytes -Septal panniculitis	SSKI (1 g/mL) 0.25mL 3 times daily for 3 weeks
Almeida Prestes and Winkelmann[7]	1990	USA	14	29-79 (mean= 50), 2M and 12F	Nodules and plaques	-Unilateral (13 cases) -Lower leg	-Thickened and fibrotic fat septum -Granulomatous inflammation with epithelioid cells and multinucleated giant cells - capillary proliferation	-SSKI (9 cases) -NSAIDs (2 cases) -Thyroxine (1 case)
Ross et al.[6]	1992	USA	1	37, F	Erythematous plaque	Left lower shin	-Septal panniculitis -Infiltration of lymphocytes, histiocytes and multinucleated giant cells	SSKI 300 mg 3 times daily
Campalani and Higgins[15]	2003	UK	1	21, F	Erythematous plaque with central clearing	Left lower leg	-Septal panniculitis -Infiltration of mix cells -Small vessel vasculitis	N/A
Yun et al.[16]	2004	Korea	1	32, F	Erythematous to yellowish patches with hypertrichosis	Both shins	-Lymphocytes, histiocytes and multinucleated giant cells in fat septum	Prednisolone and intralesional triamcinolone acetonide

Table 1 Case reports of erythema nodosum migrans

Authors	Year of publication	Nation	No. of cases	Age (year), Gender	Morphology	Distribution	Histopathology	Treatment
Lee et al.[17]	2005	Korea	1	37, F	Erythematous to brownish plaques with central clearing and serpiginous borders	Both shins	-Septal panniculitis with granulomatous inflammation - Capillary proliferation	N/A
Lazaridou et al.[18]	2009	Greece	1	33, M	Erythematous nodule with central clearing	Left lower leg, followed by right lower leg after 4 weeks	-Septal panniculitis -Capillary proliferation -Granulomatous inflammation	SSKI 200 mg daily, then 600 mg daily and then 100 mg daily
Mokhtari et al.[8]	2014	Iran	1	75, F	Erythematous plaque	Left lower leg	-Lymphocytes, histiocytes, neutrophils and multinucleated giant cells in fat septum -Septal panniculitis -Mild perivascular inflammatory infiltration	Oral indomethacin for 3 weeks and topical clobetasol propionate lotion twice daily
Mufti et al.[9]	2016	Canada	1	77, F	Annular plaque with erythematous border	Left thigh	-Lymphocytes and histiocytes in fat septum -Septal panniculitis -Dermal vascular proliferation	Topical clobetasol propionate cream for 2 weeks
Sehrawat et al.[12]	2018	India	1	30, M	Erythematous plaque	Left lower leg	-Septal panniculitis -Infiltration of lymphocytes, histiocytes and multinucleated giant cells	SSKI (1 g/ml) 300 mg 3 times daily and topical heparin (Thrombophob™-Heparin 50 IU) twice daily for 6 weeks
Liu et al.[20]	2022	China	1	72, F	Erythematous plaques with hyperpigmentation	Left leg	-Septal panniculitis and fibrosis -Infiltration of lymphocytes, neutrophils, histiocytes and multinucleated giant cells	-Discontinue Valsartan -Prednisolone 20 mg for 1 week, then 10 mg for another 1 week

Abbreviations: N/A=Not applicable, SSKI=Saturated solution of potassium iodide, M=Male, F=Female, NSAIDs=Non-steroidal anti-inflammatory drugs

The pathological features of erythema nodosum comprise inflammation of the subcutaneous fat septum, with or without dermis involvement and Miescher's radial granulomas[10]. Panniculitis with granuloma formation can be seen mostly in late-type erythema nodosum and nodular vasculitis[11]. Histopathological examination of erythema nodosum migrans may appear resembling to erythema nodosum, nevertheless thickened fat

septum and granulomatous inflammation are more prominent in erythema nodosum migrans. Multinucleated giant cells, granulation tissue, and vascular proliferations are present along the margin of widened fat septa without phlebitis or hemorrhage[7,10]. There are slightly differences in chronic erythema nodosum which displays less pronounced septal thickening and inflammation, despite the presence of abundant phlebitis and erythrocyte extravasation[7]. However, there is a hypothesis that these two conditions are the same entity with different stages of disease evolution[4,10]. Necrobiosis lipoidica can cause septal panniculitis without vasculitis; however, it is commonly characterized by palisading granulomas with collagen degeneration in the dermis extending into the subcutaneous fat[10], which were not observed in this case. In our case, the clinical presentation of migratory and expanding annular erythematous plaques with central clearing was consistent with erythema nodosum migrans, with the exception of bilateral involvement, as erythema nodosum migrans typically presents unilaterally. The incisional biopsy in this patient revealed marked septal thickening with mixed inflammatory cell infiltration and prominent granuloma formation, which was corresponding with the previous reported cases of erythema nodosum migrans.

Erythema nodosum migrans may persist for several months or even years if patients do not receive treatments[12]. Potassium iodide 360 to 900 mg daily for 3 to 4 weeks is usually the effective treatment, leading to remission of the disease within several weeks[6]. Naproxen, other NSAIDs, and hydroxychloroquine could be beneficial[8]. Moreover, there were other cases report of 32-year-old and 75-year-old women with erythema nodosum migrans successfully treated with indomethacin 75 mg daily for 4 weeks and 3 weeks, respectively[8,13]. A combination of saturated potassium iodide solution and topical heparin also showed effectiveness[12].

In summary, our patient presented with bilateral well-defined, non-indurated, non-scaly, expanding annular, erythematous to brownish nodules and plaques with central clearing on both anterior and posterior of lower legs. The biopsy demonstrated inflammation of subcutaneous fat mainly septal pattern with marked septal thickening. Several granulomas were noted in deep dermis and subcutaneous septa. The patient was diagnosed as erythema nodosum migrans. Clinical improvement was observed after 1 month of treatment.

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