An erythematous plaque on the leg of a female

A 43-year-old lady presented for evaluation of a gradually enlarging, mildly painful, non-pruritic, reddish raised scaly lesion of 5-months duration on her right leg. She was a known case of hypothyroidism on treatment and had accompanying high-grade fever and night sweats. She had no history of ulceration, local trauma, joint pains, weight loss, cough with expectoration, sore throat, oral/genital ulcers or photosensitivity. She was previously treated with oral and intravenous antibiotics and oral steroids for presumed cellulitis and erythema nodosum, respectively. Though she experienced transient improvement with corticosteroids, there was no improvement with antibiotics.

Inspection revealed an ill-defined, slightly depressed, annular erythematous plaque, approximately 18 × 16 cm in size, with minimal central hyperpigmentation and peripheral scaling on the medial aspect of the upper right leg [Figure 1a and b]. The plaque was warm, slightly tender and firm on palpation. Lymph nodes, liver and spleen were not enlarged. Clinical diagnoses of chronic erythema nodosum and cutaneous lymphoma were considered.

Total leucocyte count was 3300/cm^3. Titers of antistreptolysin O antibodies, antinuclear antibodies (performed by indirect immunofluorescence) and anti-double-stranded DNA antibodies were not elevated. Mantoux test was negative. Blood and urine cultures were sterile. Chest X-ray was normal. Serum ferritin was 460 ng/ml. Histopathological examination and immunohistochemistry were performed on a deep incisional skin biopsy and findings are demonstrated [Figures 2-4].

What is Your Diagnosis?

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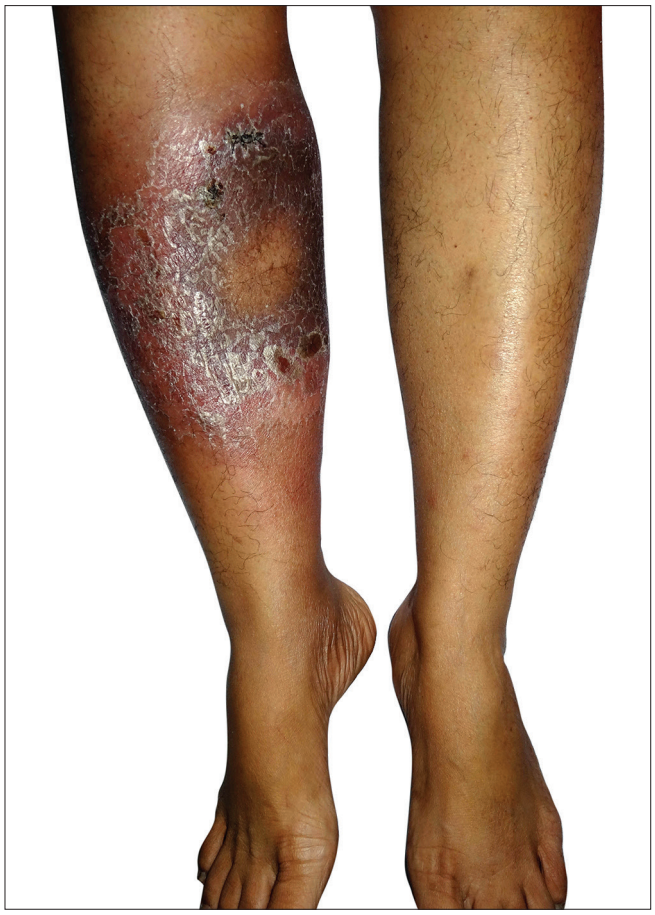

Figure 1a: There is an ill-defined, slightly depressed, annular erythematous plaque, about 18 cm × 16 cm, with mild central hyperpigmentation and peripheral scaling on supero medial aspect of the right leg

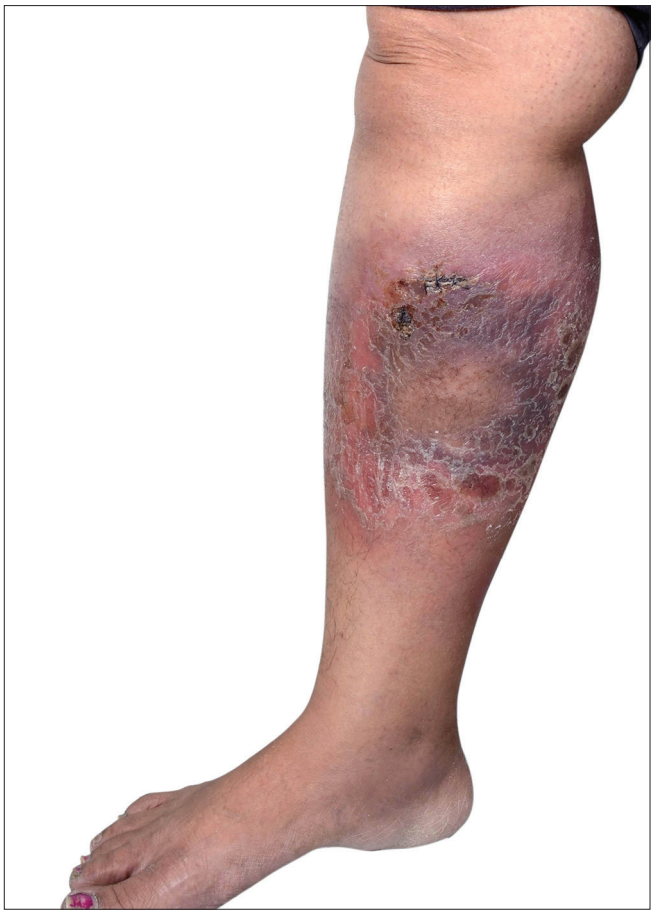

Figure 1b: An ill-defined, annular erythematous plaque with central hyperpigmentation and peripheral scaling on supero medial aspect of right leg (another view of the same lesion)

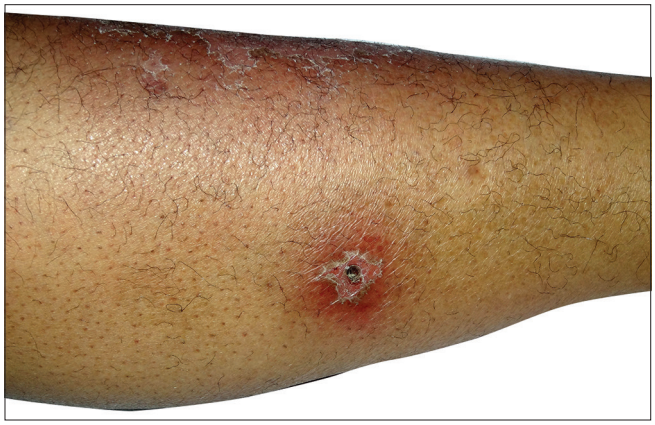

Figure 1c: New erythematous plaque developed in vicinity of the primary lesion after 3 weeks of admission

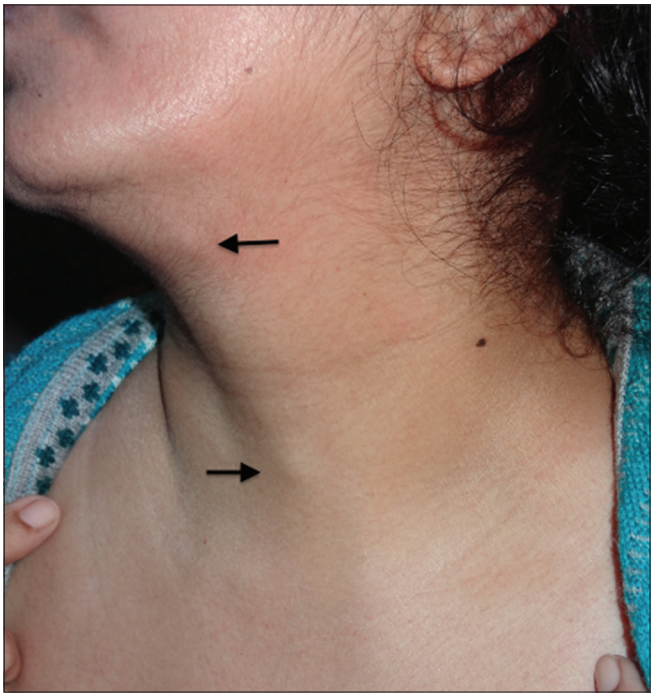

Figure 1d: New skin coloured nodules developed on chin and neck. The nodules were barely visible, but palpable

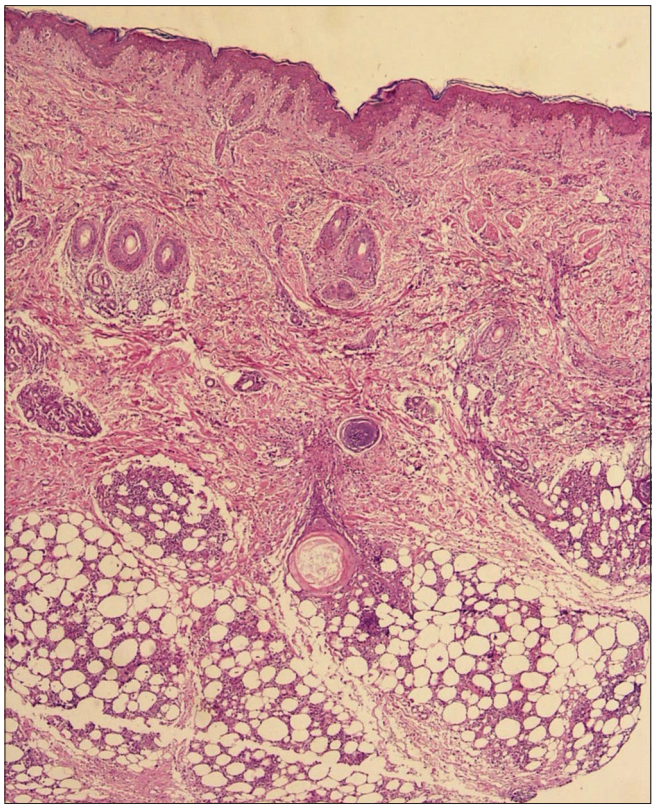

Figure 2a: Deep inflammatory infiltrate, predominantly in lobules of subcutaneous fat (H and E, ×20)

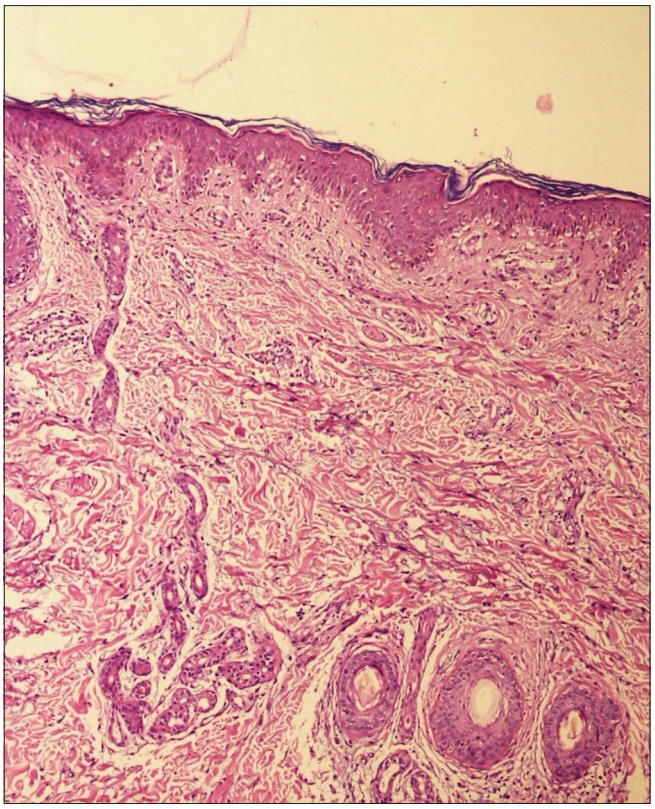

Figure 2b: Dermoepidermal junction and upper dermis is visualized and features minimal lymphomononuclear infiltrate. There is no hyperkeratosis, follicular plugging and atrophying interface dermatitis (H and E, ×100)

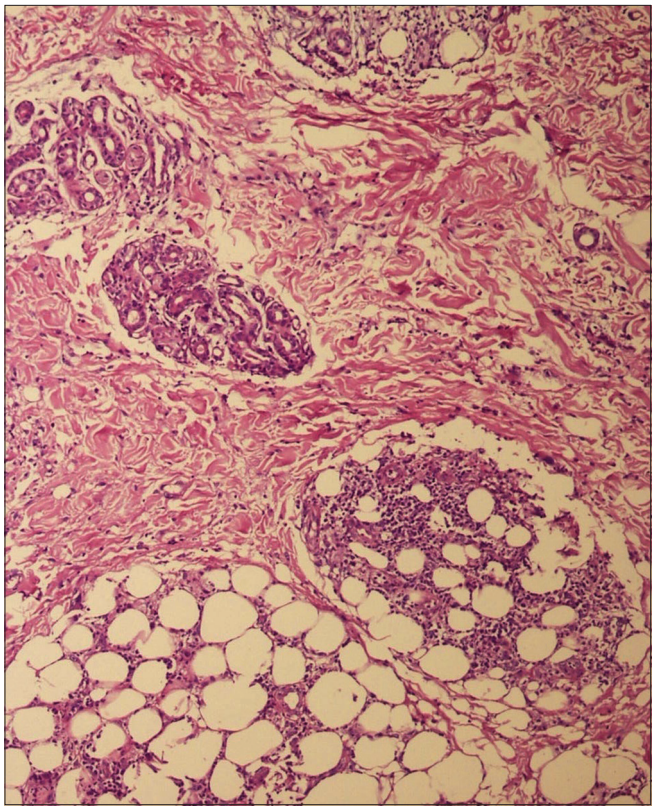

Figure 2c: Lymphomononuclear infiltrate is seen surrounding the eccrine ducts and infiltrating fat lobules, largely sparing the septa, suggestive of lymphocytic lobular panniculitis (H and E, ×200)

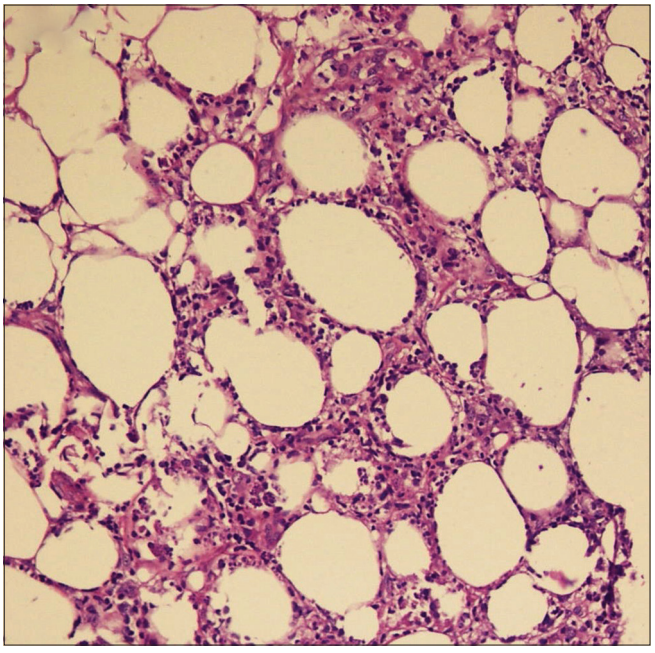

Figure 2d: Atypical lymphoid cells, 1–1.5 times larger than a mature lymphocyte with high nuclear: cytoplasmic ratio, indented nuclear margins and coarse chromatin are rimming individual lipocytes. Foci of angiodestruction are seen (H and E, ×400)

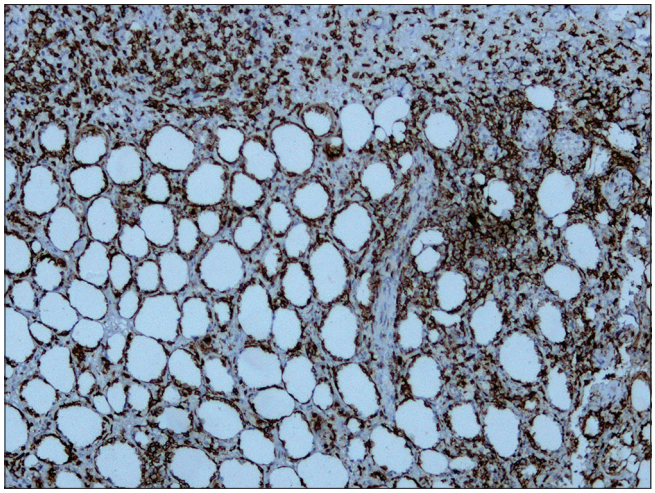

Figure 3a: Immunohistochemistry highlighting the rimming of individual lipocytes by CD8+ atypical lymphocytes (immunohistochemistry, CD8, ×200)

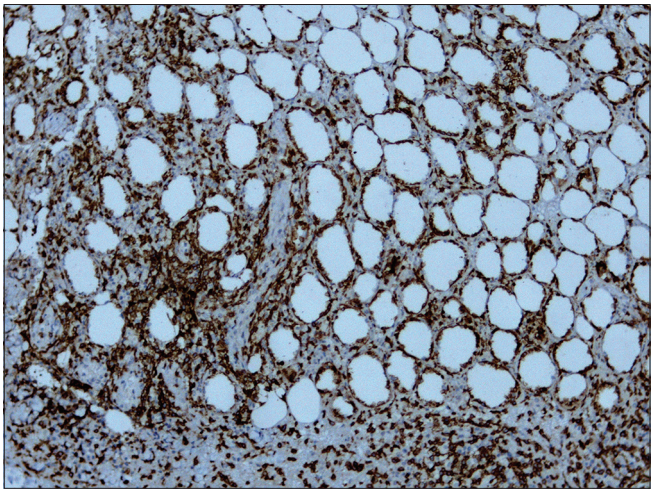

Figure 3b: Immunohistochemistry showing positive staining for CD3 (immunohistochemistry, CD3, ×200)

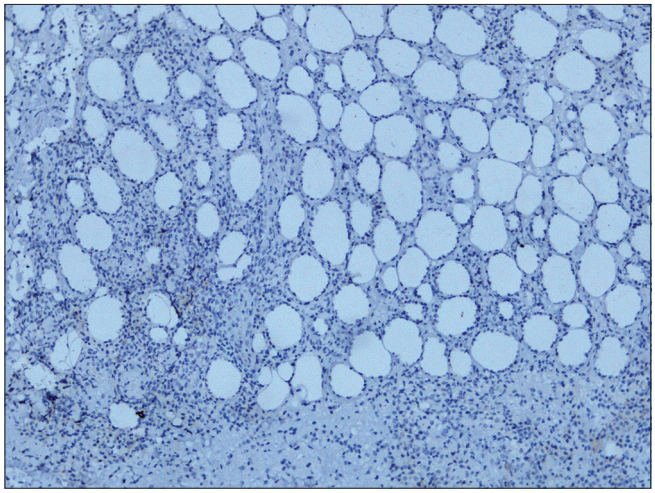

Figure 4a: Immunohistochemistry demonstrating negative staining for CD20 (immunohistochemistry, CD20, ×200)

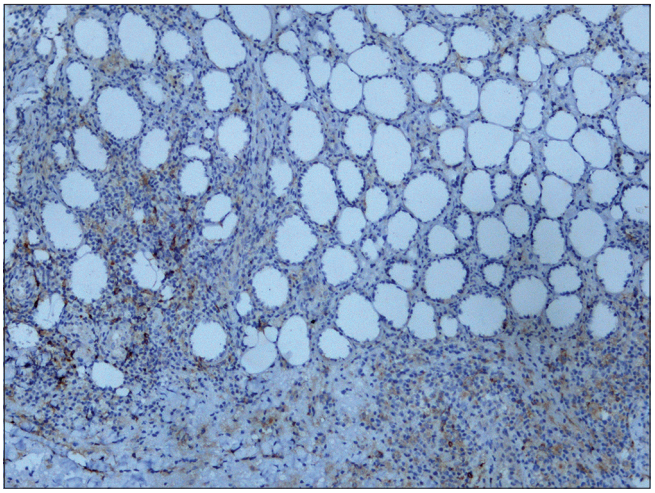

Figure 4b: Immunohistochemistry demonstrating negative staining for CD4 (immunohistochemistry, CD4, ×200)

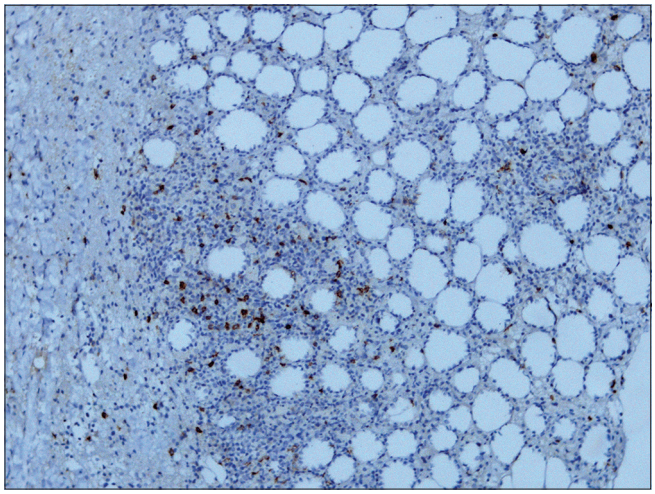

Figure 4c: Immunohistochemistry demonstrating negative staining for CD56 (immunohistochemistry, CD56, ×200)

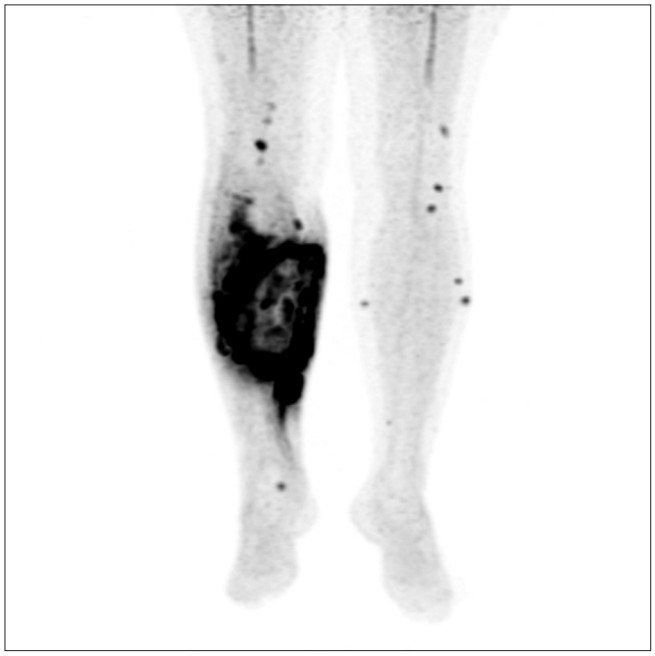

Figure 5a: Positron emission tomography scan showing increased uptake in the lesion and subcutaneous soft tissue of left lower limb

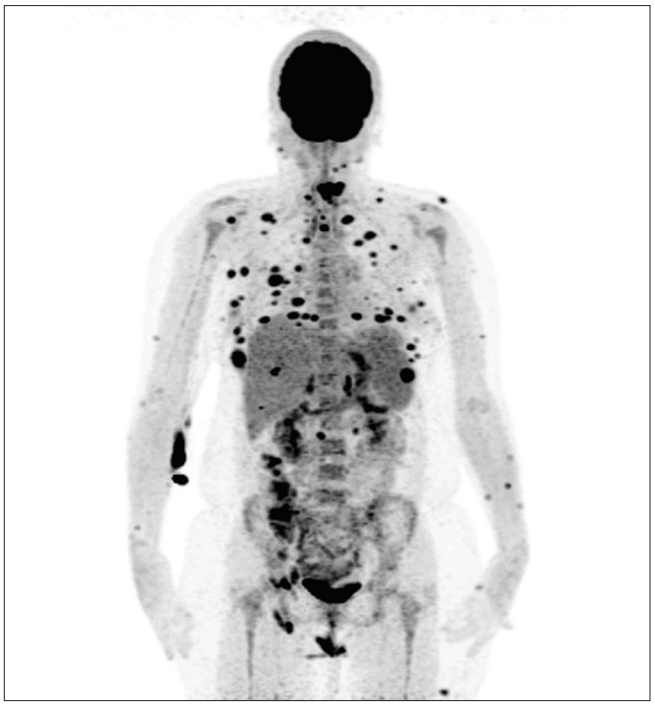

Figure 5b: Positron emission tomography scan showing increased uptake in subcutaneous soft tissue of chest, lymph nodes in abdomen and adrenals

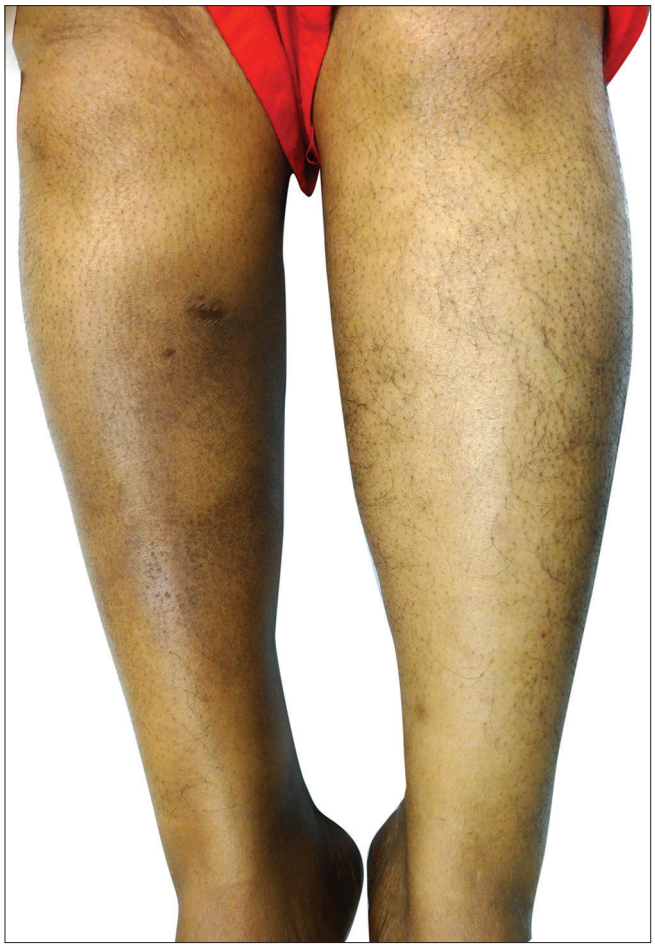

Figure 6: Plaque has regressed leaving behind lipoatrophy

Diagnosis

Subcutaneous panniculitis-like T-cell lymphoma.

Microscopic Findings

Histopathology demonstrated deep inflammatory infiltrate, predominantly in the subcutaneous fat [Figure 2a and b]. On higher power, the infiltrate was chiefly composed of atypical lymphoid cells, which were 1–1.5 times larger than a mature lymphocyte with high nuclear: cytoplasmic ratio, indented nuclear margins and coarse chromatin [Figure 2c and d]. There were scattered histiocytes and rare plasma cells. On immunohistochemistry, atypical lymphocytes were positive for CD3 and CD8 [Figure 3a and b] and negative for CD20, CD4 and CD56 [Figure 4a-c]. Immunohistochemistry highlighted the rimming of individual lipocytes by CD8+ atypical lymphocytes. Features were consistent with subcutaneous panniculitis like T-cell lymphoma (alpha beta type). She was started on prednisolone 60 mg/day. Meanwhile, positron emission tomography scan revealed multiple avid uptakes in the subcutaneous soft tissue (lesion, left leg, neck and chest), abdominal and pelvic lymph nodes and adrenals [Figure 5a and b]. By the time of completion of staging investigations, the patient had developed multiple new erythematous plaques and skin-colored nodules on her neck and upper chest [Figure 1c and d]. She was subsequently administered cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone chemotherapy regimen. She attained partial remission after 8 cycles of chemotherapy. Subsequently, she was given local-site radiotherapy, after which she attained complete remission. The plaque resolved leaving behind lipoatrophy [Figure 6]. She is following regularly with us.

Discussion

Subcutaneous panniculitis like T-cell lymphoma accounts for less than 1% of all non-Hodgkin's lymphomas.[1] Patients often present with subcutaneous nodules and plaques on extremities and trunk, which usually resolve with lipoatrophy. Systemic symptoms and cytopenias are common. Hemophagolymphohistiocytosis develops in approximately 15–20% of the patients.[2] Bone marrow biopsy was performed and our patient did not have evidence of hemophagolymphohistiocytosis or malignant infiltration of bone marrow.

Histologically, atypical lymphocytes with irregular hyperchromatic nuclei infiltrate fat lobules causing lobular panniculitis with relative sparing of dermis and epidermis. Rimming of individual lipocytes by these atypical cells is characteristic, though not specific, for subcutaneous panniculitis-like T-cell lymphoma.[3] Repeated skin biopsies are often required before a definitive diagnosis is made, and a sincere effort should be made to include ample subcutaneous fat while procuring skin biopsy. The index patient had to be biopsied twice before a diagnosis of subcutaneous panniculitis-like T-cell lymphoma was made. Reactive histiocytes are frequently seen but are usually present singly and do not form granulomas.[4] Erythrophagocytosis by histiocytes has been ascribed as a defining feature of subcutaneous panniculitis-like T-cell lymphoma.[4]

T-cell lymphomas causing panniculitis can have alpha-beta or gamma-delta T-cell-receptor phenotype. Subcutaneous panniculitis-like T-cell lymphoma shows alpha-beta phenotype with simultaneous expression of CD3, CD8 and betaF1. Expression of CD56 is usually absent. Presence of CD56 and gamma-delta T-cell phenotype and absence of CD8 is seen in primary cutaneous gamma-delta T-cell lymphoma involving subcutis, which has a poor 5-year survival of just 20% compared to the classic subcutaneous panniculitis-like T-cell lymphoma, where it exceeds 80% in the absence of hemophagolymphohistiocytosis and is approximately 50% in the presence of hemophagolymphohistiocytosis.[1] Another entity that can manifest as panniculitis is extranodal natural killer-T cell lymphoma, which stains positively for Epstein–Barr virus.[5] Our patient showed positive beta F1, and negative Epstein–Barr virus and gamma T-cell receptor staining, confirming the diagnosis of subcutaneous panniculitis-like T-cell lymphoma.

Diffuse large B-cell lymphoma leg-type presents with erythematous-bluish nodules on the legs of elderly females. Immunohistochemistry helps to differentiate subcutaneous panniculitis-like T-cell lymphoma from diffuse large B-cell lymphoma leg-type, where infiltrate is dense dermal and composed of malignant centroblasts that stain positively with CD20 and Bcl2.

CD8+ lymphoproliferative disorders primarily involving the skin include subcutaneous panniculitis-like T-cell lymphoma, primary cutaneous aggressive epidermotropic cytotoxic T-cell lymphoma and type D lymphomatoid papulosis. Subcutaneous panniculitis-like T-cell lymphoma primarily involves panniculus, whereas the other two potentially cause epidermal invasion by CD8+ and CD30+ atypical lymphocytes respectively.[6]

Lupus erythematosus panniculitis/lupus panniculitis is a potential histopathological mimicker of subcutaneous panniculitis like T-cell lymphoma. It usually involves face, breast and proximal extremities, though lesions have also been described on legs. Histopathology is characterized by presence of numerous plasma cells, eosinophilic hyaline fat necrosis and infiltration by small, bland lymphocytes forming lymphoid follicles with germinal centers consisting of CD20+ B lymphocytes.[7] Lymphocytic vasculitis and karyorrhexis can be seen in both subcutaneous panniculitis like T-cell lymphoma and lupus panniculitis. Perieccrine infiltrates could be seen in both, though more characteristically and commonly observed in subcutaneous panniculitis-like T-cell lymphoma.[4] Rarely, lupus panniculitis

Table 1: Salient histopathological differences between subcutaneous panniculitis like T-cell lymphoma and lupus panniculitis

Histopathological features observed	Subcutaneous panniculitis like T-cell lymphoma	Lupus panniculitis
Lymphocytic lobular panniculitis	Present	Present
Atypia (variable size of cells)	Atypia present with large sized cells	Atypia absent, Small bland lymphocytes splay the adipocyte lobules apart
True adipocyte rimming	Present, adipocytes rimmed by CD8+ atypical lymphocytes	Absent, sometimes there is an impression of rimming due to artifactual distortion of adipocytes by infiltrating lymphocytes, but on IHC, the rimming cells have been found to be a mixed cell-population, with CD4+ lymphocytes typically more than CD8+ lymphocytes
Interface dermatitis, follicular plugging, atrophic epidermis	Rare	Common
Periadnexal inflammation	Rare	Common
Perieccrine inflammation	More	Present, but lesser than subcutaneous panniculitis like T-cell lymphoma
Mucin deposition	Rare	Common
Foci of vasculitis/necrosis	Present	Present
Plasmacytoid dendritic cells	Single cells	Clusters (clustering of >10 cells is typically seen)
Plasma cells	May be there, usually lesser in number	Abundant to numerous (clustering of >10 cells is a relatively specific finding)
Histiocytes	Present in a single cell distribution, granuloma formation is usually not there	Abundant histiocytes can be seen
Erythrophagocytosis	Specific feature, may herald hemophagocytotic syndrome	Not seen
Hyaline fat necrosis	Absent	Present with lipomembranes
Reactive germinal centers	Absent	Present
Paraseptal follicles	Absent	Present
Immunohistochemistry	CD8+ lymphocytes predominate	CD4+ lymphocytes more numerous than CD8+ lymphocytes

IHC: Immunohistochemistry

can focally simulate adipocyte rimming due to splaying of adipocyte lobules and resultant artifactual distortion, but immunohistochemistry demonstrates rimming cells to be of mixed population with CD4+ lymphocytes outnumbering CD8+ lymphocytes, which are the predominant cells in subcutaneous panniculitis-like T-cell lymphoma.[8] Magro *et al*. have described minimal epitheliotropism with mild basal vacuolopathy, a classical Grenz zone and subjacent heavy infiltrate in deeper dermis and panniculus in subcutaneous panniculitis-like T-cell lymphoma.[4] LeBlanc *et al*. proposed that the presence of plasma cells, interface dermatitis and mucin neither negates nor exemplifies either diagnosis, though absence of plasma cells supports a diagnosis of subcutaneous panniculitis-like T-cell lymphoma.[9] Bosisio *et al*. recently proposed that clusters of plasmacytoid dendritic cells, if identified, are specific for lupus panniculitis.[8]

Magro *et al*. highlighted few lupus panniculitis cases having similar immunohistological features as subcutaneous panniculitis like T-cell lymphoma and rightfully proposed the term "subcuticular T-cell lymphoid dyscrasia/ indeterminate lymphocytic lobular panniculitis" to define the cases that have clinicopathological features suggestive of a phenomenon intermediate between a reactive polyclonal process classical of lupus panniculitis and a malignant process defining subcutaneous panniculitis-like T-cell lymphoma. Such patients should be closely followed up to see whether they develop overt lymphoma over time.[4] Subcutaneous panniculitis-like T-cell lymphoma has been associated with concomitant systemic lupus erythematosus in 20% of the cases.[10] Our patient did not have any evidence of systemic lupus erythematosus after thorough investigations. Dermal inflammation was minimal, and panniculus showed infiltration by malignant pleomorphic lymphocytes showing significant atypia and a conspicuous rimming of adipocytes, which on further characterization by immunohistochemistry, revealed these cells to be CD8+, CD3+ and CD4- as well as CD20- that strongly supports the diagnosis of subcutaneous panniculitis-like T-cell lymphoma. Magro *et al*. suggest that absence of hyperkeratosis, follicular plugging, atrophying interface dermatitis and presence of significant constitutional symptoms with lesion progression and nonresponse to hydroxychloroquine/corticosteroids, as seen in the index patient, favors the diagnosis of subcutaneous panniculitis-like T-cell lymphoma.[4] Table 1 further highlights the salient histopathological differences between subcutaneous panniculitis-like T-cell lymphoma and lupus panniculitis.

Treatment of subcutaneous panniculitis-like T-cell lymphoma consists of cyclophosphamide, hydroxydaunorubicin, vincristine and prednisolone chemotherapy regimen. Radiotherapy has been used in localized lesions. Cyclosporine has been used in refractory cases as well as the primary treatment option with good outcomes and exerts significant inhibitory effect on the cytokine storm and systemic symptoms associated with subcutaneous panniculitis-like T-cell lymphoma.[11] Extracutaneous dissemination is quite rare in subcutaneous panniculitis-like T-cell lymphoma. To conclude, we emphasize

on performing deep incisional skin biopsy for any suspicious deep-seated leg plaques associated with systemic symptoms so that subcutaneous panniculitis-like T-cell lymphoma is not missed.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understand that name and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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References

1. Willemze R, Jansen PM, Cerroni L, Berti E, Santucci M, Assaf C, *et al.* Subcutaneous panniculitis-like T-cell lymphoma: Definition, classification, and prognostic factors: An EORTC Cutaneous Lymphoma Group Study of 83 cases. Blood 2008;111:838-45.
2. Gonzalez CL, Medeiros LJ, Braziel RM, Jaffe ES. T-cell lymphoma involving subcutaneous tissue. A clinicopathologic entity commonly associated with hemophagocytic syndrome. Am J Surg Pathol 1991;15:17-27.
3. Salhany KE, Macon WR, Choi JK, Elenitsas R, Lessin SR, Felgar RE, *et al.* Subcutaneous panniculitis-like T-cell lymphoma: Clinicopathologic, immunophenotypic, and genotypic analysis of alpha/beta and gamma/delta subtypes. Am J Surg Pathol 1998;22:881-93.
4. Magro CM, Crowson AN, Kovatich AJ, Burns F. Lupus profundus, indeterminate lymphocytic lobular panniculitis and subcutaneous T-cell lymphoma: A spectrum of subcuticular T-cell lymphoid dyscrasia. J Cutan Pathol 2001;28:235-47.
5. Gallardo F, Pujol RM. Subcutaneous panniculitic-like T-cell lymphoma and other primary cutaneous lymphomas with prominent subcutaneous tissue involvement. Dermatol Clin 2008;26:529-40, viii.
6. Davick JJ, Mutgi KAJ, Wanat KA, Link BK, Liu V. Disseminated CD8-positive, CD30-positive cutaneous lymphoproliferative eruption with overlapping features of mycosis fungoides and primary cutaneous anaplastic large cell lymphoma following remote solitary lesional presentation. J Cutan Pathol 2017;44:703-12.
7. Fraga J, García-Díez A. Lupus erythematosus panniculitis. Dermatol Clin 2008;26:453-63, vi.
8. Bosisio F, Boi S, Caputo V, Chiarelli C, Oliver F, Ricci R, *et al.* Lobular panniculitic infiltrates with overlapping histopathologic features of lupus panniculitis (lupus profundus) and subcutaneous T-cell lymphoma: A conceptual and practical dilemma. Am J Surg Pathol 2015;39:206-11.
9. LeBlanc RE, Tavallaee M, Kim YH, Kim J. Useful parameters for distinguishing subcutaneous panniculitis-like T-cell lymphoma from lupus erythematosus panniculitis. Am J Surg Pathol 2016;40:745-54.
10. Shiau CJ, Abi Daoud MS, Wong SM, Crawford RI. Lymphocytic panniculitis: An algorithmic approach to lymphocytes in subcutaneous tissue. J Clin Pathol 2015;68:954-62.
11. Iqbal N, Raina V. Successful treatment of disseminated subcutaneous panniculitis-like T-cell lymphoma with single agent oral cyclosporine as a first line therapy. Case Rep Dermatol Med 2014;2014:201836.