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Cutaneous granulomas preceding peripheral cutaneous T-cell lymphoma NOS: A call for ongoing surveillance for late-onset malignancy

İdiyopatik subkütan granülomları takiben ortaya çıkan kutanöz T-hücreli lenfoma NOS olgusu

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To Editor,

Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), a rapidly disseminating form of cutaneous T-cell lymphoma, is diagnosed based on exclusion criteria according to the World Health Organization Classification of Hematolymphoid Tumors: Lymphoid Neoplasms 2022. Patients may present with red-purplish nodules anywhere, usually infected or ulcerated. PTCL-NOS has a poor prognosis[1], with a median overall survival of 20 months and disease-free survival of around 10 months. We present a patient who exhibited cutaneous granulomas for two years prior to the onset of PTCL-NOS.

A 55-year-old woman sought medical attention due to skin lesions on her thigh, characterized by non-itchy subcutaneous nodules with slightly erythematous, otherwise normal-appearing overlying skin. Pathological examination revealed dominant granulomatous inflammation in the lower dermis and subcutaneous fat lobules, displaying well-developed tuberculoid granulomas with large areas of caseous necrosis, palisading epithelioid histiocytes, and multinucleated giant cells (Figure 1c-d). Periodic acid-Schiff-Alcian Blue staining was unremarkable. Mantoux test was positive with a bullous reaction with an induration of 15 mm diameter. *Mycobacterium tuberculosis* and atypical mycobacteria quantitative polymerase chain reaction test from lesion and blood, Ehrlich-Ziehl-Neelsen staining, bacterial and fungal cultures, serology for brucella, syphilis and non-venereal treponematoses were negative, whereas QuantiFERON-TB Gold Test was positive. Angiotensin-converting enzyme, serum calcium levels, and hand and chest X-rays were normal. The patient was diagnosed with erythema induratum of Bazin associated with tuberculosis, and quadruple tuberculosis therapy was initiated.

After six months of tuberculosis treatment, a new lesion appeared on her right forearm (Figure 1a). Antinuclear antibodies and extractable nuclear antigen profiles were negative. Acute phase reactants were normal, and lactate dehydrogenase (LDH) levels were within normal ranges. Computed tomography of the thorax, abdomen, and pelvis showed no signs of malignancy. She had several new similar

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lesions in the following two years at various subcutaneous sites, and multiple biopsies were performed and evaluated by an expert dermatopathologist. All lesions were compatible with granulomatous panniculitis, resolving spontaneously or with antibiotics and non-steroidal anti-inflammatory drugs.

Two years later, three large nodules appeared on the left side of her trunk and axilla (Figure 1b). The patient had no constitutional symptoms. The largest nodule, measuring 30x18 mm appeared heterogeneous, hypoechoic, and edematous. Elevated markers included C-reactive protein [8.8 mg/L (<5 mg/L)] beta-2-microglobulin [2.2 (0.7-1.8 mg/L)], LDH [260 (135-214 U/L)], and alkaline phosphatase [158 U/L, (25-105 U/L)]. A biopsy revealed diffuse infiltrate extending from the dermis to subcutis (Figure 2a), with medium-sized neoplastic cells characterized by round or irregular nuclei, dark chromatin, one or more nucleoli, and eosinophilic cytoplasm (Figure 2b). Immunohistochemistry revealed neoplastic cells expressing CD2, CD3, CD5, and CD4 while lacking CD7 (Figure 2c-f). They were negative for CD20, CD25, CD56, CD8, granzyme B, Epstein-Barr encoding region (EBER-*in situ*), and Terminal deoxynucleotidyl transferase. CD30 was expressed in only a fraction of neoplastic cells (5-8%). Ki-67 was around 60%. After PTCL-NOS diagnosis, the patient underwent six cycles of chemotherapy with cyclophosphamide, doxorubicin, etoposide, vincristine, and prednisone (CHOEP) regimen and stem cell transplantation, achieving complete remission. However, six months post-treatment, a lymphoma relapse involving cranial nerves III and V occurred.

Granulomatous reactions can hinder the timely diagnosis of lymphoma, leading to initial misdiagnosis. Some cases involve a granulomatous component in lymphomas, making the lymphoma diagnosis challenging, especially when granulomatous infiltration is intense. In our case, PTCL-NOS onset was two years after the onset of granulomatous panniculitis. The possibility of the paraneoplastic origin of granulomatous reactions is debated in the literature[2]. For instance, granuloma annulare is occasionally reported to occur before the systemic lymphomas[3]. In a longitudinal study over twenty years, 14% of patients with granuloma annulare had neoplasia. Granulomatous vitritis and granulomatous angiitis are paraneoplastic disorders associated with systemic malignancy[4,5].

Notably, the presentation of PTCL-NOS is not well-documented; however, similar cases have been reported in the literature. One remarkable case involved a 54-year-old woman with focal segmental glomerulosclerosis and granulomas, diagnosed with PTCL-NOS 46 months after the onset of kidney disease and 15 months following the appearance of granulomas[5].

This case underscores that granulomas can be a paraneoplastic reaction preceding lymphoma by several months rather than masking an existing lymphocytic infiltrate. Long-term cautious follow-up is recommended for patients with granulomatous panniculitis of unknown etiology.

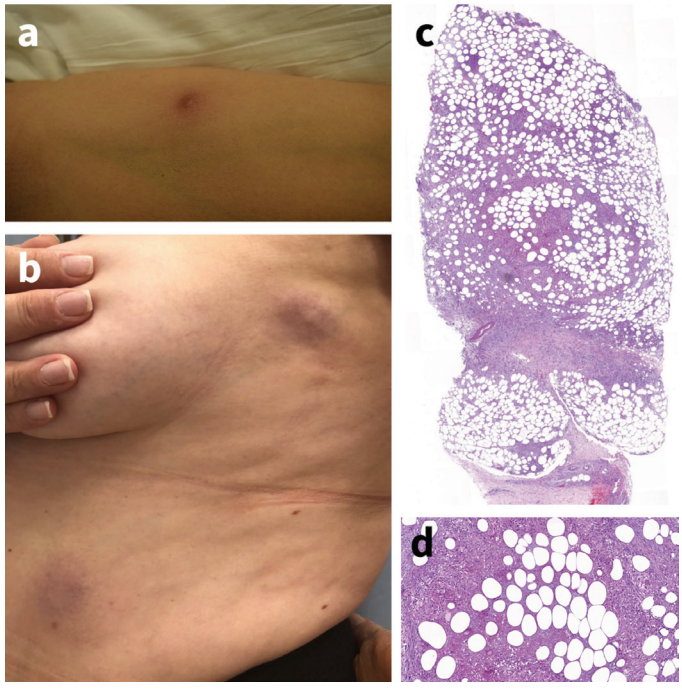

Figure 1. (a) Erythematous nodular lesion on right forearm, lateral to the right cephalic vein, December 2019. **(b)** The palpable nodules on the left axilla and the left lateral side of the abdomen, November 2021. **(c)** Granulomatous lobular panniculitis (stained with H&E: Magnification with 2.37x). **(d)** Granulomas with large areas of caseous necrosis in the middle (stained with H&E: Magnification with 10.56x)

H&E: Hematoxylin and eosin

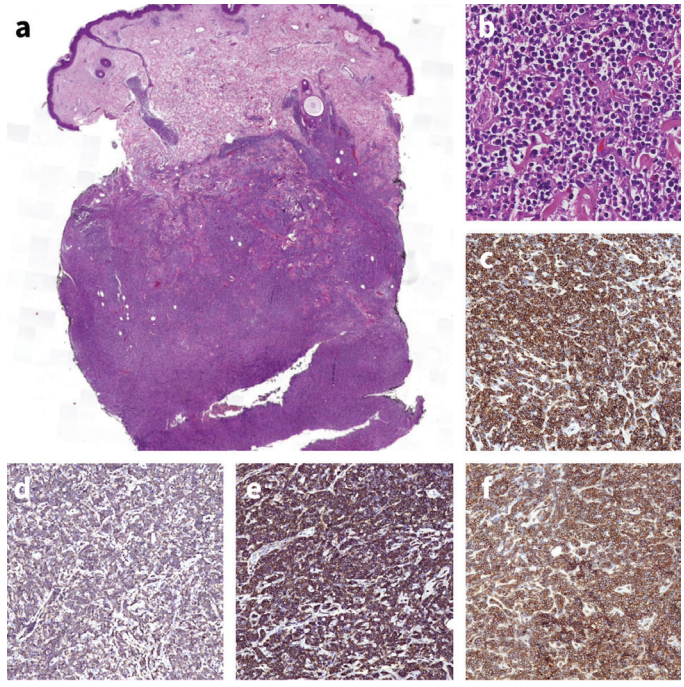

Figure 2. (a) Dense bottom heavy infiltrate of lymphoid cells extending throughout the dermis to the subcutaneous fat tissue (stained with H&E: Magnification with 2.81x), **(b)** The infiltrate was predominantly composed of medium-sized lymphoid cells with dark chromatin (stained with H&E: Magnification with 34.07x), **(c)** Cutaneous peripheral T-cell lymphoma NOS neoplastic cells express CD2, **(d)** CD3, **(e)** CD5, **(f)** CD4

H&E: Hematoxylin and eosin, NOS: Not otherwise specified

Ethics

Informed Consent: It was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.R., M.O.A., S.V., Concept: S.V., Design: S.V., Data Collection or Processing: S.K., C.D., M.O.A., S.V., Analysis or Interpretation: C.D., S.V., Literature Search: S.K., G.R., M.O.A., Writing: S.K., S.V.

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References

1. Kempf W, Mitteldorf C, Battistella M, et al.: Primary cutaneous peripheral T-cell lymphoma, not otherwise specified: results of a multicentre European Organization for Research and Treatment of Cancer (EORTC) cutaneous lymphoma taskforce study on the clinico-pathological and prognostic features. J Eur Acad Dermatol Venereol. 2021;35:658-68.
2. Müller CSL, Vogt T: Granuloma annulare - is it a paraneoplastic condition for malignant lymphoma? J Dtsch Dermatol Ges. 2021;19:803-12.
3. Kawakami T, Kawanabe T, Soma Y: Granuloma annulare-like skin lesions as an initial manifestation in a Japanese patient with adult T-cell leukemia/lymphoma. J Am Acad Dermatol. 2009;60:848-52.
4. Graus F, Ariño H, Dalmau J: Paraneoplastic neurological syndromes in Hodgkin and non-Hodgkin lymphomas. Blood. 2014;123:3230-8.
5. McGrath LA, Mudhar HS, Sheard R, et al.: Paraneoplastic granulomatous vitritis: elaboration of 8 cases. Ophthalmol Retina. 2019;3:589-96.