Nonhealing Ulcers with Rimming of the Adipose Tissues

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\textbf{Keywords}
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\textbf{Abstract}
Extranodal NK/T-cell lymphoma, nasal type (ENKTCL-NT) is a rare condition which has a very aggressive clinical outcome. The most common and typical presentation is the destructive tumor involving the nasal cavity or nasopharynx, referred to as lethal midline granuloma, while cutaneous involvement is found to be the second most involved site. In this report, we describe a case of an otherwise healthy 40-year-old female solely presenting with ulcerative plaques and subcutaneous nodules on her lower extremities. Although the rimming of adipocytes by atypical lymphocytes, which resembles subcutaneous panniculitis-like T-cell lymphoma, was found on histopathology, immunohistochemistry revealed the diagnosis of cutaneous ENKTCL-NT which portends a much worse prognosis. A positron emission tomography scan also detected a hypermetabolic mass on her nasal cavity despite negative findings on history and initial examination. After thorough investigation, her final diagnosis was ENKTCL-NT with extranasal involvement (cutaneous) stage IV.

\textbf{Introduction}
Extranodal NK/T-cell lymphoma, nasal type (ENKTCL-NT) is a rare and aggressive EBV-associated non-Hodgkin lymphoma. This entity carries poor response to current treatment, associated with a high relapse rate and mortality [1, 2]. Various cutaneous manifestations
have been reported, and histopathologic examination can mimic both inflammatory condition and other hematologic malignancies. To avoid misdiagnosis and treatment delay, awareness and proper investigations are mandatory.

**Case Report/Case Presentation**

A 40-year-old female, with no known underlying conditions, presented with two erythematous to violaceous plaques, which subsequently enlarged and became ulcerated on her left thigh, together with a few painless nodules on her right leg for 2 months (shown in Fig. 1). She had no fever, night sweat, or weight loss. Prior treatments with topical and systemic antimicrobial agents did not result in any improvement.
The histopathology from both ulcerative and intact lesions revealed dense perivascular lymphohistiocytic infiltrates in the entire dermis. Lymphocytic lobular panniculitis with rimming of large atypical lymphocytes was present (shown in Fig. 2).

Immunohistochemistry for T-cell phenotypes was positive for CD3 and CD7 and weakly positive for CD8. There was a positive reaction to CD56 and granzyme B, a cytotoxic granule-associated protein. Ki-67 was positive in >70% of the infiltrates. In situ hybridization for Epstein-Barr virus-encoded RNA was also positive in tumor cells. Polymerase chain reaction for T-cell receptor gene rearrangement was unremarkable. The provisional diagnosis of cutaneous ENKTCL-NT was made.

Physical examination was unremarkable for lymph nodes, liver, and spleen. Laboratory investigations revealed normal complete blood cells count, serum LDH, and undetected Epstein-Barr viral load. Bone marrow examination revealed no immunohistochemical evidence of lymphoma involvement. Fluorodeoxyglucose positron emission tomography (PET)-magnetic resonance imaging/computerized tomography scan demonstrated a 3.0 × 1.5 cm hypermetabolic mass in the left nasal cavity and hypermetabolic skin lesions at the posterolateral aspect of the left thigh and anterior right proximal leg (shown in Fig. 3).

She was finally diagnosed with ENKTCL-NT with extranasal involvement (cutaneous) stage IV. Sequential treatment with L-asparaginase-based systemic chemotherapy and radiotherapy was undertaken.

**Discussion/Conclusion**

ENKTCL-NT is a rare and aggressive EBV-associated non-Hodgkin lymphoma. The most common site of primary ENKTCL-NT is the nasopharynx and upper aerodigestive tract, while the skin is the most frequent initial extranasal presentation [3]. In addition, the skin is also the most common site of secondary spread [1].

Various clinical presentations of cutaneous ENKTCL-NT have been reported, from erythematous papules to subcutaneous nodules or ulcerative plaques. Extremities are the most commonly involved [4]. Cutaneous ENKTCL-NT could be further classified into three categories, i.e., primary cutaneous ENKTCL-NT, which has no evidence of systemic or extracutaneous disease at the time of diagnosis, ENKTCL-NT with secondary cutaneous involvement, and ENKTCL-NT with extranasal manifestation and secondary cutaneous involvement, with the former type being the most common and the latter type having the worst prognosis [1, 4].

Both primary and secondary cutaneous ENKTCL-NT have a poor prognosis with 5-year overall survival of 12–61% [2, 5] and median survival time from 2 to 15 months [4], and
limited skin involvement portends a better outcome than those with extracutaneous involvement [4, 5]. According to the proposed prognostic index of natural killer cell lymphoma (PINK) and PINK with EBV DNA (PINK-E), our patient was stratified as an intermediate-risk group using PINK (1 risk factor) and a low-risk group using PINK-E (1 risk factor), with 3-year overall survival rates of 62% and 55%, respectively [6].

Diagnosis of ENKTCL-NT is made by histology and immunohistochemistry findings, comprising large atypical lymphoid cells, expressing CD3, CD8, CD56, and positive Epstein-Barr virus-encoded RNA. T-cell receptor gene rearrangement can be negative in nearly half of patients; however, a negative result does exclude peripheral T-cell lymphoma, not otherwise specified, and subcutaneous panniculitis-like T-cell lymphoma that can mimic ENKTCL-NT, histologically [1, 7, 8].

Although rimming of adipocytes by neoplastic lymphocytes on histopathology is considered a characteristic morphologic feature of subcutaneous panniculitis-like T-cell lymphoma, it is not specific to this condition. This finding can also be found in various hematologic malignancies, including B-cell lymphoma, T-cell lymphoma, and leukemia, and inflammatory conditions such as lupus panniculitis [9]. To make a definite diagnosis, immunohistochemistry and detection of clonality from immunoglobulin gene rearrangement or T cell receptor gene rearrangement might be crucial.

Further investigations with bone marrow study and PET scan are mandatory for complete staging and evaluation of the tumor extent [3, 10]. Furthermore, a PET scan is considered superior to conventional computerized tomography or magnetic resonance imaging to rule out occult primary lesions or detect subclinical metastases in the nasal area [10].

Current standard treatment for both skin-limited and extracutaneous ENKTCL-NT is sequential chemoradiotherapy with platinum- or asparaginase-containing chemotherapy, which significantly improves the survival outcomes, especially in the early stages [4, 7, 10]. Furthermore, hematopoietic stem cell transplantation, targeted therapy such as monoclonal
antibodies (anti-CD30, anti-CD38), and checkpoint inhibitors, i.e., programmed death 1 inhibitor, pembrolizumab, are viable options in relapsed/refractory condition [2, 5, 10–12].

**Statement of Ethics**

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval was not required for this study in accordance with local/national guidelines.

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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**Author Contributions**

Kittipong Wantavornprasert: investigation and writing – original draft; Thiti Asawanumas: writing – review and editing; Pravit Asawanonda: review, editing, and supervision.

**Data Availability Statement**

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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