

Primary Cutaneous Extranodal NK/T-Cell Lymphoma, Nasal Type, with Extensive Skin Lesions: A Case Report with Immune Cell Shift

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Case Report

Keywords: Extranodal NK/T-cell lymphoma, Cutaneous, EBV, Tumor microenvironment

Posted Date: November 24th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-112930/v1>

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Abstract

Background: Primary cutaneous extranodal natural killer (NK)/T-cell lymphoma, nasal type (PC-ENKTL), is a rare entity of malignancies of NK cells or cytotoxic T cells, characterized by an association with Epstein-Barr virus (EBV) infection. Despite its aggressive behavior, PC-ENKTL is mostly found as a localized disease. Data regarding PC-ENKTL with generalized skin lesions have only rarely been characterized in clinical studies so far.

Case presentation: We present a case of PC-ENKTL, nasal type, in a 38-year-old female with a history of disseminated cutaneous plaques, ulcers and painful nodules that originated in her right leg skin as a small raised papule and expanded quickly over the entire body, ranging in diameter from 1 cm to 6 cm. The patient did not show any involvement of other sites except skin. Histologic, immunophenotypic, genetic and clinical features consistent with the diagnosis of primary cutaneous NK/T-cell lymphoma, nasal type. The status of immune cells was analyzed using a panel of monoclonal antibodies and revealed negative stain for CD163, CD68, programmed cell death (PD-1)/programmed cell death I ligand 1 (PD-L1), and FoxP3. Chemotherapy followed by radiotherapy was planned but the patient was experienced disease progression and died at 3 months as a result of lymphoma.

Conclusions: In contrast to NK/T-cell lymphoma with localized disease, PC-ENKTL with generalized skin lesions tend to be more aggressive, with short survival and extremely poor response to therapy. We propose that the immune cell shift may be related to the severity of the patient.

Background

Extranodal natural killer (NK)/T cell lymphoma (ENKTL), nasal type is a rare distinct entity of non-Hodgkin lymphoma characterized by an association with Epstein-Barr virus (EBV) infection and extranodal involvement [1, 2]. It is designated an NK/T-cell lymphoma because the lymphoma cells appear to originate from either NK cells or cytotoxic T cells [3]. Therefore, in the latest World Health Organization (WHO) classification of lymphoid malignancies, these lymphomas are referred to as ENKTLs, to reflect their putative cellular origins from both NK-cells and T-cells [4]. The nasal NK/T cell lymphoma commonly presents with midline facial destructive disease and occurs prototypically within the nasal cavity or in the paranasal sinuses. In limited cases, NK/T cell lymphoma may predominantly occur in extranasal sites without involvement of nasal cavity or nasopharynx. This disease entity was recognized as an independent form of disease and defined as nasal-type NK/T cell lymphoma, that has been recognized to present with highly aggressive clinical course associated with a very poor prognosis and share the same histopathologic features and immunophenotypic profile with nasal NK/T cell lymphoma [5–7]. ENKTL arises primarily in the initial presentation in the skin only without any other extracutaneous manifestations is known as primary cutaneous ENKTL (PC-ENKTL) [6].

Clinical presentation of PC-ENKTL is nonspecific and may mimic inflammatory or infectious process in many cases. In the majority of cases, clinical manifestations present as single or multiple nodules or

tumours that persist and progress over time. PC-ENKTL with clinical onset as ulcer-necrotic lesions, with bulla formation or purulent secretion was considered as similar to ulcerative lesions of pyoderma gangrenosum, in particular can be hard to differentiate from pyoderma gangrenosum [8–10]. In contrast to other types of ENKTL, PC-ENKTL is characterized by a highly aggressive clinical course with a high occurrence rate and advanced stage [11]. However, the international prognostic index (IPI) does not discriminate among risk groups clearly in ENKTLs. Several studies focused on identification of new individual prognostic and risk stratification biomarkers and new potential therapeutic target. Tumor microenvironment (TME) may play critical roles in malignant behavior and progression of PC-ENKTLs [12]. In this article, we present a case of unusual PC-ENKTL, nasal type, with generalized skin lesions in a 38-year-old female accompanied with unusual clinical course. The tumor microenvironment, immunohistochemistry profile, in situ hybridization for EBV, and TCR gene rearrangement were performed in order to elucidate its clinical characteristics, prognosis and treatment outcomes of this rare malignancy.

Case Presentation

A 38-year-old Chinese female was referred to the Department of Dermatology, the People's Hospital of Zhengzhou University with a 10-month history of progressive generalized skin lesions. The lesions originate in her right leg skin as a small raised papule and expanded quickly to her extremities, trunk, neck, and face. Physical examination revealed diffuse cutaneous plaques, ulcerated painful nodules and bulla formation over the entire body, ranging in diameter from 1 cm to 6 cm. The progressively ulcerated painful nodules with violaceous border and covered with a hemorrhagic crust, which resembled pyoderma gangrenosum (Fig. 1). She had no history of skin disease, any other medical problems and any family history of malignancies. The patient was directed to our clinic with a presumed diagnosis of Pyoderma gangrenosum.

The patient underwent the usual staging examinations with clinical exam. Radiography and computer tomographic (CT) assessment did not reveal infiltrates or enlarged nodes in the chest. Abdominal ultrasound examination showed normal liver and spleen, and no enlarged lymph nodes. A complete body positron emission tomography-computed tomography (PET/CT) was performed to evaluate the lymphoma status (Fig. 2). None of these assessments uncovered another involved site except skin. In particular, the nasal and nasopharyngeal regions were free of disease.

Laboratory tests revealed a mild hemophagocytic syndrome, white cell count of $1.98 \times 10^9/L$ with a normal differential count, a hemoglobin level of 78 g/L, MCV-88 fl, and platelet count of $166 \times 10^9/L$. The serum LDH was 948 U/L and alkaline phosphatase 123 U/L at time of diagnosis. The bone marrow was free of disease. Mycological tests, including microscopic analysis of native specimens, and culture were negative. Hemoculture, human immunodeficiency serology, and hepatitis B and C viruses were negative. Biopsy from skin lesion was performed and histologic specimen slides stained with hematoxylin and eosin were reviewed by three pathologists. The pathological examination revealed a diffuse dermal lymphomatous infiltration of the skin. The lymphomatous infiltrate had an angiocentric and

angiodestructive growth pattern with a mixed cell population accompanied by an admixture of inflammatory cells (Fig. 3a, b). Immunophenotyping was performed using a panel of monoclonal antibodies and revealed positivity for CD2, cytoplasmic CD3 (Fig. 3c), CD4 (Fig. 3d) CD7, and CD56 (Fig. 3e), as well as a negative stain for CD5, CD8, CD30, CD20, CD163, CD68 (Fig. 3f), programmed cell death (PD-1)/programmed cell death I ligand 1(PD-L1) (Fig. 3g), and FoxP3. The neoplastic cells showed strong granular staining for the cytotoxic molecules granzyme B, perforin and TIA1(Fig. 3h). The immunostaining with a monoclonal antibody for the anaplastic lymphoma kinase (ALK) was negative. The molecular analysis of the T cell receptor gene was in a germline configuration. In situ hybridization for EBV-encoded small RNAs (EBERs) was strongly positive for most of the tumor cells (Fig. 3i). Histologic, immunophenotypic, genetic and clinical features consistent with the diagnosis of PC-ENKTL, nasal type. Despite the chemotherapy (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide, SMILE) followed by radiotherapy was planned, she was going rapidly downhill and died of fetal infection 3 months after the onset of treatment.

Discussion

Extranodal natural killer (NK)/T cell lymphoma (ENKTL), nasal type is an increasingly recognized disease entity with aggressive clinical behavior and exhibit a higher prevalence in East Asians and South Americans than in Europeans. This ethnic predisposition may be partly related to the prevalence of Epstein-Barr virus (EBV) infection in East Asian patients. It mainly affects adult males more often than children and females, and the average age at presentation is the fifth decade [11]. At the time of diagnosis, they are usually localized. The skin lesions may present as a generalized erythematous maculopapular rash or as multiple subcutaneous nodules that may be ulcerated [10]. Our patient had generalized cutaneous plaques, painful nodules, and ulcers with hemorrhagic secretions. Further investigation did not reveal any lesions in soft tissues, or in the visceral organs, and the oral and nasal cavities, tonsils, larynx, and pharynx were not involved. Microscopic features include a mixture of variably sized pleomorphic atypical lymphoid cells with angiocentric infiltration, mimicking vasculitis and fibrinoid changes caused cytokines and tumour cell cytotoxic molecules. In the early stages, relatively few small neoplastic cells are present. As a result, biopsy specimens obtained at an early stage of the disease can be misinterpreted as a benign process. These neoplasms have a propensity to invade and destroy blood vessels, but angiocentricity is present only in 60–70% of cases. In our case, biopsy showed large, atypical lymphoid cells, admixed with inflammatory cells, invading the dermis in an angiocentric pattern.

There have been several cases of PC-ENKTL indicating highly aggressive pattern and overall poor prognosis, and relapses are very common. However, limited cutaneous forms have a longer median survival than extracutaneous variants. To investigate this controversial clinical course, several studies have focused on the potential role of the tumor microenvironment in malignant behavior and progression of tumorigenesis [12, 13]. Immune cells including mast cells, macrophages, and T or B lymphocytes are considered as specific pathogenetic mechanisms. According to the different status of immune cells, ENKTL could be classified as four subgroups with different clinical course [13]. PD-1 is a surface inhibitory receptor expressed by macrophages, dendritic cells, and T cells. PD-L1 is frequently expressed

in ENKTL and immune checkpoint blockade targeting the PD-1/PD-L1 axis is effective in some patients [14–17]. Strong PD-L1 expression correlated with excellent responses. PC-ENKTL with PD-L1 + in tumor cells was associated with unfavorable prognostic factors and resistance to standard therapy. In summary, we report a rare case of PC-ENKTL in a Chinese female with a highly aggressive clinical course and a poor prognosis. Immunohistochemistry profile may be the independent inferior prognostic indicator and further studies in this area are required.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication.

Availability of data and materials

Not applicable.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

Not applicable.

Authors' contributions

Xie Hongjian draft the manuscript, performed the histological and immunohistochemical evaluation. Kong Lingfei consulted Xie Hongjian and reached the pathological diagnosis, Shi Yujie collected and analyzed clinical data. Corresponding authors: Xie Hongjian. All authors read and approved the final manuscript.

Acknowledgments

We would like to thank the patient and the patient's family for the permission to share our knowledge with the scientific community.

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Figures



Figure 1

Clinical features of the patient. a Widespread plaques and nodules with ulceration and hemorrhagic aspects on the lower limb. b Examination of right knee showed large ulcerated lesions (5cm) with violaceous border. c Skin lesions in the face including nasal skin

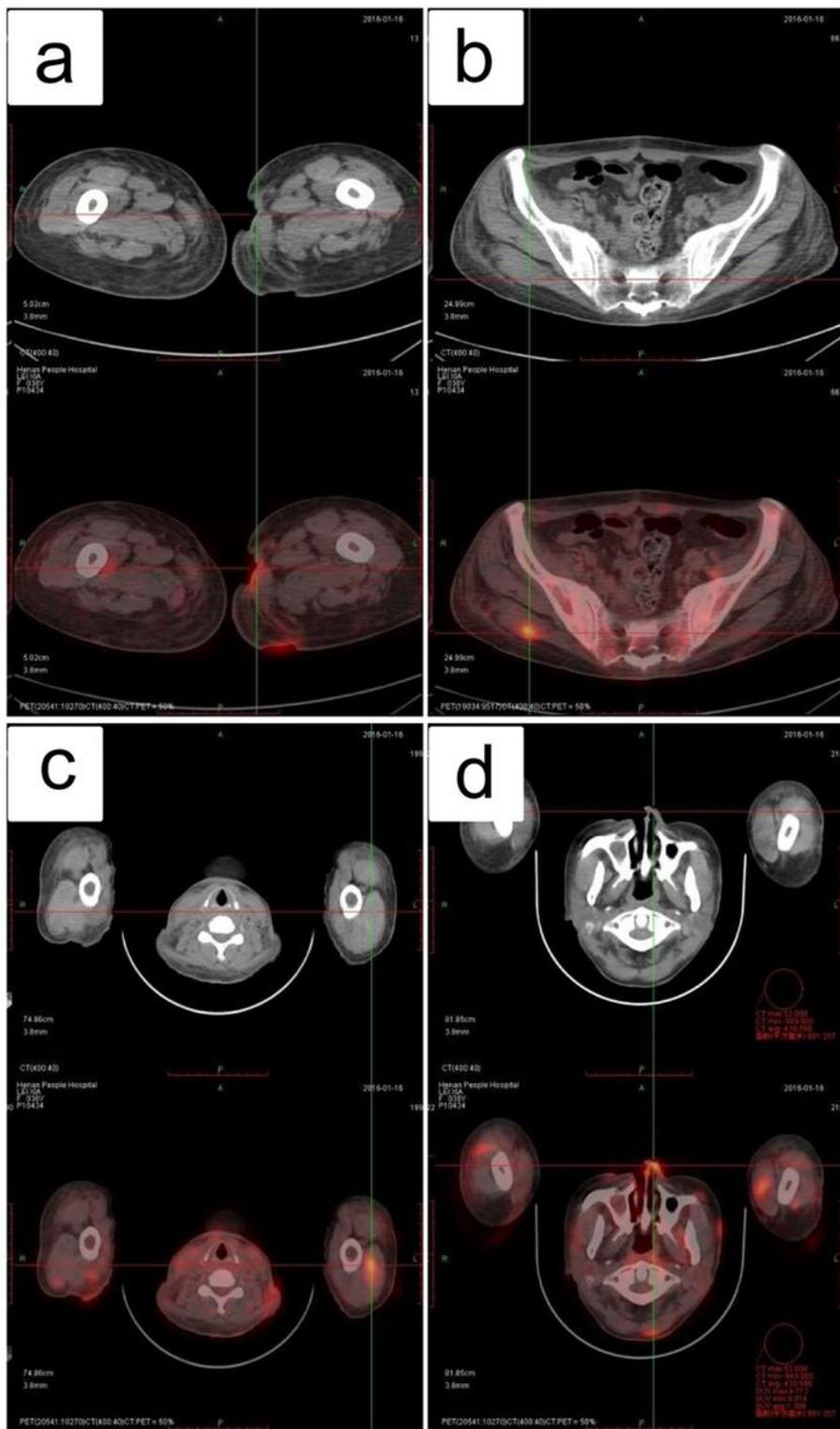


Figure 2

Typical PET/CT image present prominent skin lesions only without involvement other sites. a Skin lesions on the limb. b NK/T-cell lymphoma formed a nodular on the back. c Subcutaneous nodule on the waist. d Lesions encroach on the nasal skin without nasal cavity involvement

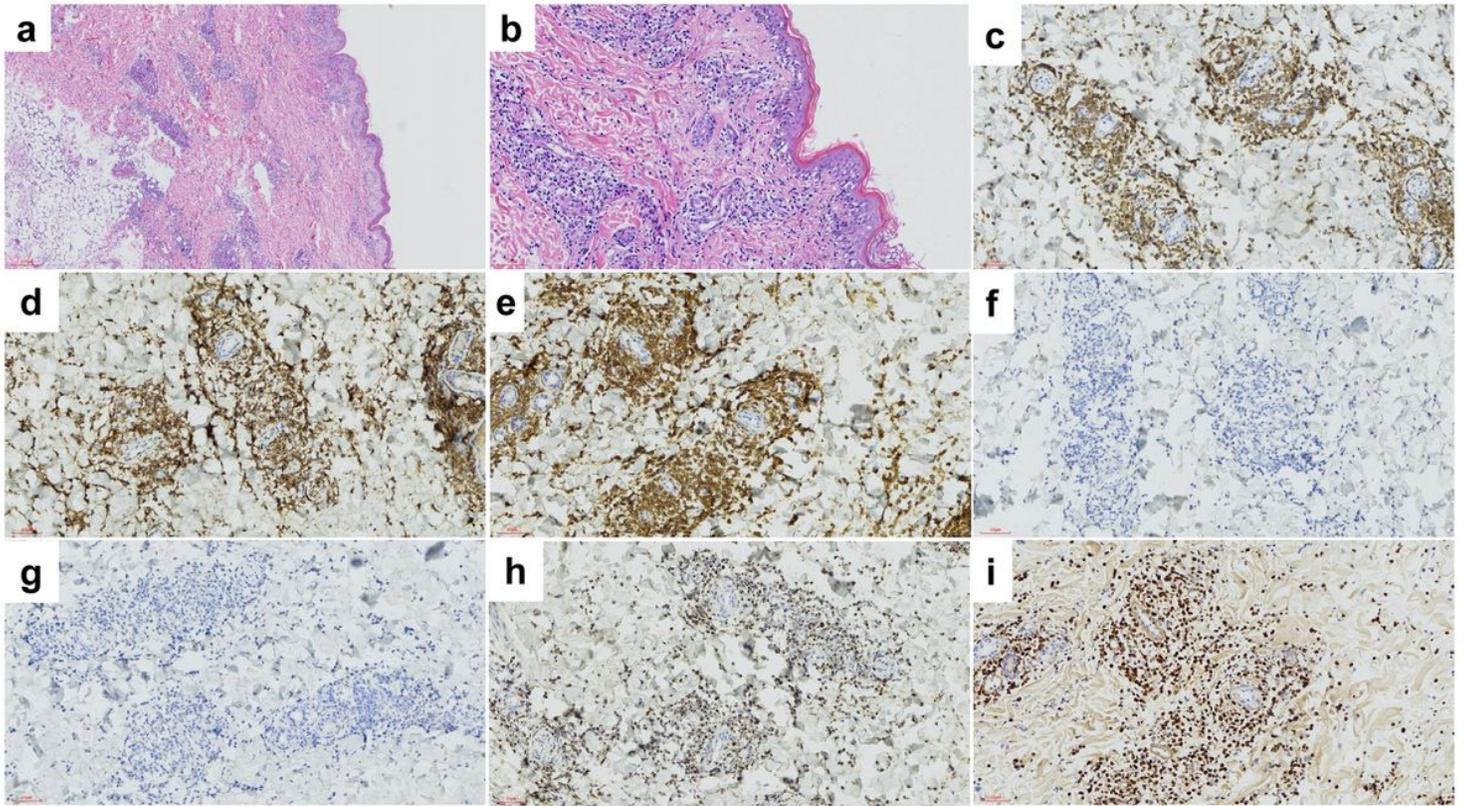


Figure 3

Histologic and immunohistologic features of the skin lesions. a Infiltration of atypical lymphocytes in the subcutaneous area (Hematoxylin-eosin stain, ×40 magnification). b Diffuse lymphocytes infiltrate adnexal structures and blood vessel with angiocentric and angiodestructive pattern (×400 magnification). Tumor cells were positive to CD3(c), CD4(d) and CD56(e). Both of the immune cells and tumor cells were negative to CD68(f) and PD-L1(g). Most of tumor cells showed positive to TIA-1(h) and Epstein-Barr virus (EBV) (f by in situ hybridization)

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