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CLINICAL CASE

Primary cutaneous extranodal NK/T cell lymphoma, nasal: presentation with ulcerative lesions in lower limbs. A case report

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Abstract

Nasal-type extranodal natural killer (NK)/T cell lymphoma is a rare type of highly aggressive lymphoma, accounting for approximately 10% of non-Hodgkin lymphomas and 30% of extranodal lymphomas. This article discusses the case of a patient who presented multiple ulcerative lesions in the lower extremities, whose biopsy revealed an extranodal NK/T cell lymphoma, which presented a good response after six cycles of chemotherapy with the dexamethasone 4 mg, asparaginase 10,000 IU, cisplatin 50 mg, and gemcitabine 1 g (DGGP) regimen. The rarity of this case lies in the potential of this entity to mimic other dermatological pathologies.

Keywords: *Extranodal natural killer/T-cell lymphoma. Nasal type. Pathology. Chemotherapy. Case report.*

Linfoma cutáneo primario extraganglionar de células NK/T, nasal: presentación con lesiones ulcerosas en miembros inferiores. Reporte de caso

Resumen

El linfoma de células NK/T extranodal tipo nasal es un tipo raro de linfoma altamente agresivo, que representa aproximadamente el 10% de los linfomas no Hodgkin y el 30% de los linfomas extraganglionares. Este artículo aborda el caso de un paciente que presentó múltiples lesiones ulcerosas en extremidades inferiores, cuya biopsia reveló un linfoma extraganglionar de células NK/T, el cual presentó buena respuesta luego de seis ciclos de quimioterapia con dexametasona 4 mg, asparaginasa 10.000 UI, cisplatino 50 mg y pauta de gemcitabina 1 g (régimen DGGP). La rareza de este caso radica en el potencial de esta entidad para mimetizar otras patologías dermatológicas.

Palabras clave: *Linfoma extraganglionar de células T/asesinas naturales. Tipo nasal. Patología. Quimioterapia. Reporte de caso.*

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Introduction

Extranodal natural killer (NK)//T-cell lymphoma nasal-type (ENKTCL-NT) is a highly aggressive non-Hodgkin's lymphoma that is associated with Epstein-Barr virus (EBV) infection. It was initially described by McBride in 1897 in patients with destructive ulcerative and necrotizing lesions located in the midline of the face, mainly in the nasal region and upper airway, which were refractory to various types of treatment[1]. Although this lymphoma was initially described in the upper aerodigestive tract, its appearance has been reported in extranodal locations such as skin, soft-tissues, testicles, and gastrointestinal tract; from which the skin is the site with the greatest primary involvement[1,2]. ENKTCL-NT is the most frequent neoplasm of NK/T-cell origin and represents approximately 10% of non-Hodgkin's lymphomas and 30% of extranodal lymphomas[1]. This type of lymphoma has a preference for certain geographic regions in Asia and Latin America. In Asia, cases have been reported in China, Japan, Taiwan, Thailand, and Korea, while in Latin America, ENKTCL-NT developed in indigenous descendants in countries such as Peru, Mexico, Brazil, and Guatemala, possibly because these populations are genetically related to Asian populations[1,3].

Primary cutaneous ENKTL lymphoma (PCENKTL) is one of the most aggressive skin neoplasms and has diverse clinical and histopathological characteristics that make diagnosis difficult. The clinical presentation can vary from the presence of subcutaneous nodules with ulceration to the development of purpuric and erythematous plaques[3]. This article discusses a case of PCENKTL that presented with multiple ulcerative lesions in the lower limbs. A biopsy revealed an atypical lymphoid infiltrate with the presence of angionecrosis. The patient attained a good response after six cycles of chemotherapy with the DGGP (dexamethasone 4 mg, asparaginase 10,000 IU, cisplatin 50 mg, and gemcitabine 1 g) regimen.

Case presentation

A 34-year-old female patient from Peru was evaluated because, approximately 6 months before evaluation, she noticed the development of multiple nodular lesions in the lower limbs. The patient denied the presence of B symptoms. The patient's medical history did not show any comorbidity except for a history of pulmonary tuberculosis treated 10 years prior with complete treatment.



Figure 1. A-C: ulcerative lesions in the lower extremities with evidence of exudation and central necrosis surrounded by scaling plaques and perilesional edema.

The patient did not presented family history of cancer or psychosocial background of importance.

Due to the persistence of the lesions and the presence of increased volume and redness of the skin of the lower extremities, the patient was referred to the dermatology department, where the decision was made to hospitalize the patient for further studies. The patient was admitted to the internal medicine service where immunological studies were performed.

On admission, vital signs were as follows: blood pressure: 90/60 mmHg, heart rate (HR): 90×,' respiratory rate: 18×,' O_2 saturation: 99% on room air. Physical examination revealed multiple indurated nodular lesions of approximately 1-2 cm in diameter with an erythematous base and perilesional edema, some lesions were ulcerated with a necrotic center and moist scabs. On the medial border of the dorsum of the right foot, an ulcerated lesion of approximately 2 × 3 cm in diameter with indurated erythematous edges was evident (Fig. 1). Venous engorgement was observed in both lower limbs. In addition, inguinal lymph nodes of approximately 0.5 cm in diameter were palpable on both

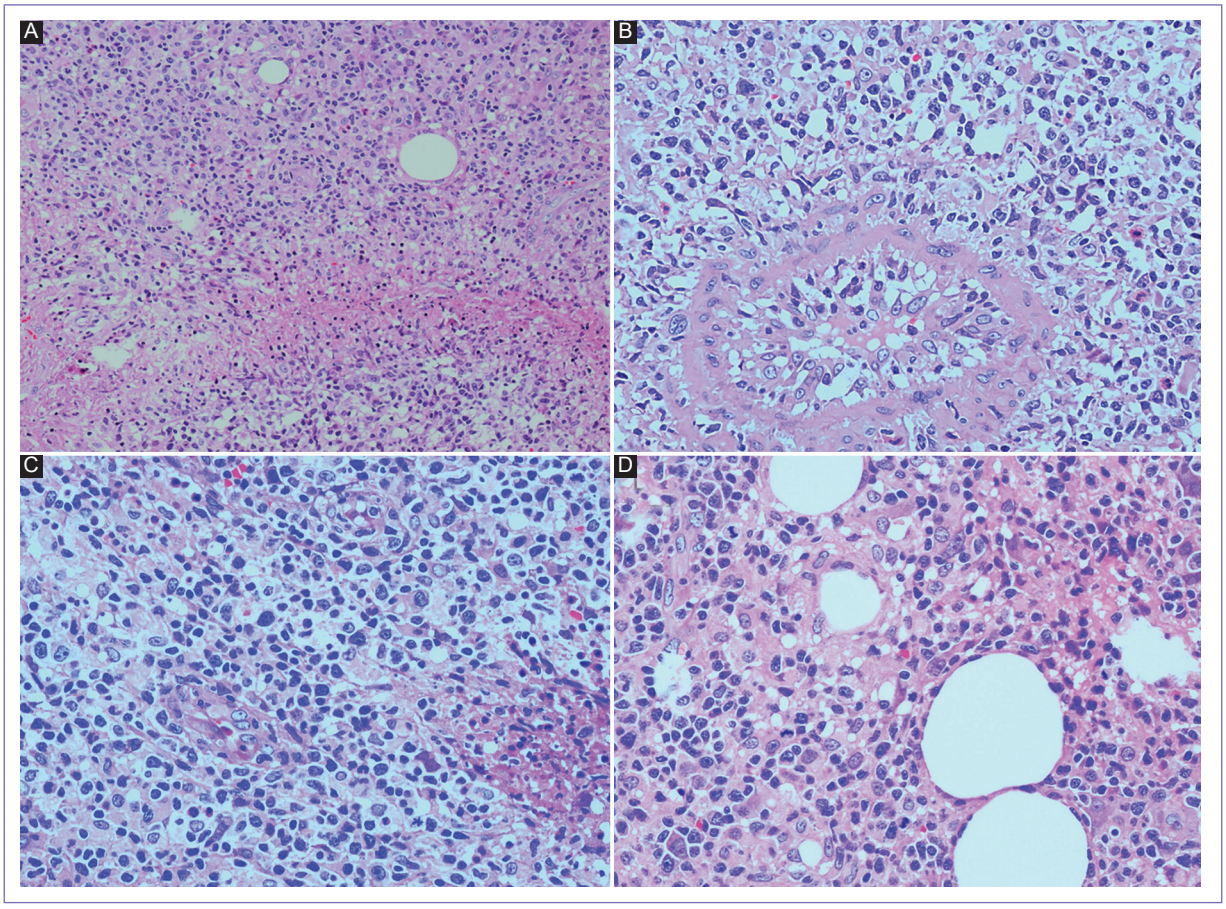


Figure 2. Skin biopsy, H-E sections. **A:** the lymphomatous infiltrate is diffuse in the dermis and shows foci of necrosis (100×). **B:** the infiltration describes a characteristic angiocentric/angiodestructive pattern (400×). **C:** the neoplastic cells are small to medium atypical lymphocytes with irregular nuclei, pale cytoplasm, and moderate proliferation rate (400×). **D:** some large cells are seen with scatter eosinophils and histiocytes in the subcutis (400×).

sides. No significant alterations were found in the other systems.

Laboratory tests on admission showed a hemoglobin level of 11.3 g/dL (12.3-16.3 g/dL), platelet count of 315 K/μL (150-450 × 10^3 cells/μL), white blood cell count of 5.65 K/μL l (4-11 × 103 cells/mm^3), serum albumin of 3.89 g/dL (3.4-5.4 g/dL), fibrinogen of 380 mg/dL (200-400 mg/dL), C-reactive protein of 4.14 mg/dL (< 0.9 mg/dL), uric acid of 2.12 mg/dL (3.5-7.2 mg/dL), serum lactate dehydrogenase of 295 U/L (135-225 U/L). Renal and liver function tests were within normal limits. Panniculitis was initially suspected because the nodular lesions were suggestive of erythema nodosum. However, the patient's immunological panel was negative for antinuclear antibodies, extractable nuclear antigen antibodies, cytoplasmic antinuclear cytoplasmic antibodies, perinuclear antinuclear cytoplasmic antibodies, anti-double-stranded DNA antibodies, anti-Smith (Sm) antibodies, rheumatoid factor and anti-cyclic citrullinated peptide antibodies.

The skin biopsy of the posterior aspect of the right thigh showed: an atypical, polymorphous lymphoid infiltrate that compromised the dermis and extended to soft tissues with areas of necrosis (Fig. 2). Immunohistochemistry showed: CD3+, CD56+, CD20: in some residual lymphocytes, and a Ki67 proliferation index of 60-80%, EBV-EBV-encoded small RNA (EBER): Positive (Fig. 3). These findings were consistent with primary cutaneous nasal-type extranodal NK/T-cell lymphoma.

Serology studies for HIV and HTLV-1 and 2 were negative. Likewise, a bone marrow biopsy did not show neoplastic infiltration (Fig. 4). The patient's computed tomography scan showed no distant metastases. The patient was classified as clinical stage IIIC (T4N1Mx), prognostic index for NK (PINK) SCORE: 2.

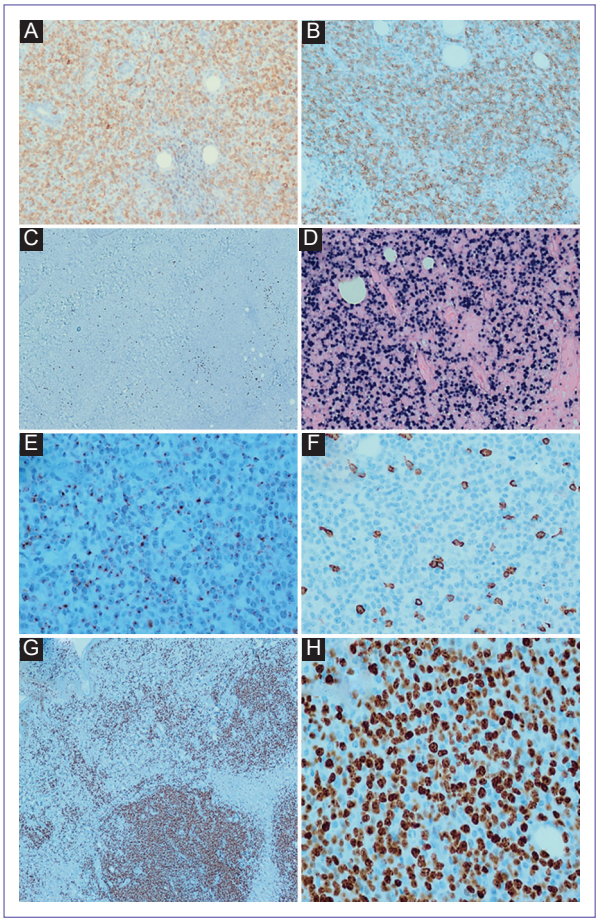


Figure 3. Immunohistochemistry of the lesion. **A:** CD3+. **B:** CD56+. **C:** CD20 +/- (variable expression in some lymphocytes). **D:** Epstein-Barr virus-encoded small RNA (EBER-EBV) +. **E:** Granzyme B +. **F:** CD8+. **G:** Ki-67 proliferation index shows 60-80% (20x). **H:** Ki-67 proliferation index shows 60-80% (40x).

Once the diagnosis was confirmed, six cycles of chemotherapy were started with the dexamethasone, cisplatin, gemcitabine, and peg-asparaginase (DDGP) regimen (dexamethasone 4 mg, asparaginase 10,000 IU, cisplatin 50 mg, and gemcitabine 1 g) achieving a complete response. To date, the patient has tolerated chemotherapy and no serious adverse events have been reported. The patient is waiting to undergo an allogeneic transplant.

Discussion

Nasal-type extranodal NK/T lymphoma is a neoplasm of NK cells and mature T cells characterized by the presence of vascular destruction (angionecrosis and angiodestruction), which produces the necrotizing lesions so characteristic of this entity[1,2]. Although this neoplasm was initially described in the nasal region and in the upper aerodigestive tract, its presence has been reported in other tissues such as the skin, testicles, and gastrointestinal tract, of which the skin represents the most common place of origin with the denomination of PCENKTL[4]. This neoplasm is more prevalent in populations of Asia, Latin America, and Central America, and because it is extremely rare, its worldwide incidence is unknown to date[2-4]. Extranodal NK/T lymphomas can be classified according to their location into primary localized disease and disseminated or extended disease. Within the former, the most frequent location is the skin, followed by soft tissues and the gastrointestinal tract[5].

This entity usually affects adults between the ages of 46 and 60 and its prevalence is higher in males[2]. The clinical presentation of this entity is usually variable with skin lesions similar to cellulitis or abscesses, subcutaneous nodules, ulcerative lesions, purpuric lesions, or even generalized erythema[6,7]. A systematic review by Jung et al. in a Korean population reported that the most frequent location of the lesions was in the lower limbs, followed by the upper limbs, head, and neck. Furthermore, the majority of study patients had multiple skin lesions (75%), while 48% of patients had skin lesions spread over multiple body areas. The clinical morphology most frequently reported in this study was that of subcutaneous nodules (63%), followed by ulcerative lesions (44%) and tumors that simulated cellulitis or abscess (26%)[2].

Due to its highly variable clinical morphology, it should be highly suspected in patients with skin lesions of undetermined etiology. This entity is among the mimicking diseases since many systemic diseases tend to have similar skin manifestations, so the presence of this entity must be excluded[2,6,7]. Cases of PCENKTL have been reported in the medical literature that they simulated rheumatological pathologies such as systemic lupus erythematosus, panniculitis, cellulitis, soft-tissue infections, inflammatory dermatitis, vasculitis, erythema multiforme, erythema nodosum, calciphylaxis, and among others[6,8-13]. The patient in our case presented multiple nodular and ulcerated lesions in the lower limbs. It is necessary to mention that the presence of atypical ulcerative lesions involves a wide spectrum of pathologies, including inflammatory, neoplastic, vasculopathic, infectious, hematological, and drug-induced etiologies[14].

Histopathologically, cutaneous ENKTL lymphoma is characterized by the presence of an infiltrate of atypical lymphocytes located in the dermis and subcutaneous fatty tissue with evidence of vascular destruction (angiodestruction) and patterns similar to panniculitis[2,15].

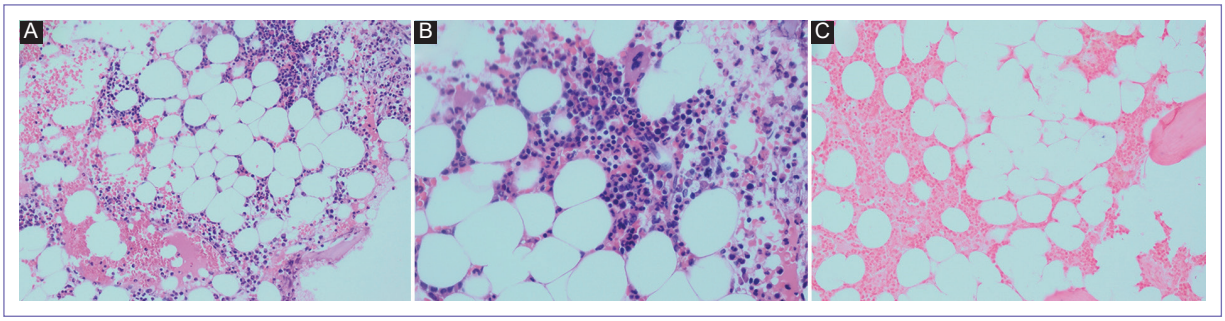


Figure 4. Bone marrow biopsy. **A:** bone marrow biopsy is negative for lymphoma in H-E sections (100×). **B:** three series with normal maturation is seen (400×). **C:** Epstein-Barr virus-encoded small RNA CISH is negative (400×).

To date, studies comparing the clinicopathological characteristics according to the clinical morphology of ENKTL cutaneous lymphoma are scarce[16,17]. ENKT lymphoma cells present an immunophenotype of CD2+, CD3+, and CD56+, as well as the presence of cytotoxic molecules such as perforin, granzyme B, and T lymphocyte intracellular antigen. A hallmark of ENKTL is evidence of EBV infection detected by *in situ* hybridization for EBV early mRNA (EBER). The absence of EBV infection excludes the diagnosis of ENKTL[15-17].

For the evaluation of the prognosis of ENKTL, the PINK cell lymphomas has been proposed, which is made up of four independent prognostic factors: age > 60 years, clinical stage III/IV, distant lymph node involvement and non-nasal type, where according to the score obtained it is classified as low risk (no risk factors), intermediate risk (1 risk factor) and high risk (2 or more risk factors). On the other hand, the presence of EBV DNA titers has been added to the model, and the PINK-E model has been proposed[1,18].

A systematic review conducted by Vásquez et al. demonstrated through multivariate analysis that advanced TNM stages (HR: 4.72; 95% confidence interval [CI]: 2.42-9.22; $p < 0.001$) and lower extremity location (HR: 3.45; 95% CI: 1.84-6.47; $p < 0.001$) were associated with a worse prognosis[19]. On the other hand, ENKTL of non-nasal location has been shown to have a worse prognosis with a 5-year progression-free survival of 4.2% compared to 50.9% for the nasal type. Likewise, the total survival at 5 years for the non-nasal was 16% compared to 55.8% for the nasal[19].

Studies have shown that anthracycline-based systemic chemotherapy regimens are not effective in patients with ENKTL. Recently, several clinical trials and prospective studies have demonstrated the efficacy of combination chemotherapy regimens with L-asparaginase, including dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide (SMILE), L-asparaginase, methotrexate, and dexamethasone, and DDGP[1,18]. The patient in our case presented an adequate response to treatment with DDGP. These results reaffirm what was reported in the clinical trial conducted by Li et al. where the superiority of DDGP over SMILE was demonstrated in patients with recently diagnosed advanced-stage ENKTL[20].

The purpose of this case is to illustrate the wide clinical presentation of extranodal nasal type primary cutaneous NK/T lymphoma and the ability that has to mimic other systemic pathologies in the skin, as well as the response to management with a combination chemotherapy regimen based on L-asparaginase. Further studies are needed to evaluate the different types of clinical presentation that this entity can manifest.

Conclusion

Primary cutaneous nasal type extranodal NK/T cell lymphoma is a highly aggressive neoplasm that usually has a variable clinical presentation, and can mimic other skin pathologies, so the clinician must have a high index of suspicion about this entity, for his aggressive nature. At present, treatment regimens based on combined chemotherapy regimens with L-asparaginase have shown good results.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of people and animals. The authors declare that no experiments have been carried out on humans or animals for this research.

Data confidentiality. The authors declare that they have followed their workplace's protocols regarding the publication of patient data.

Right to privacy and informed consent. The authors have obtained informed consent from the patients and/or subjects referred to in the article. This document is in the possession of the corresponding author.

Use of artificial intelligence to generate texts. The authors declare that they have not used any type of generative artificial intelligence in the writing of this manuscript or for the creation of figures, graphs, tables, or their corresponding captions or legends.

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