

Extranodal Natural Killer/T-Cell Lymphoma, nasal-type with primary cutaneous involvement. A case report

Linfoma NK/T extra nodal, tipo nasal, con compromiso cutáneo primario. Reporte de un caso

Marcos Silva-Feistner^a, María Jesús Rojas-Lechuga^b, Elena Ortiz^a, Montserrat Molgó^a

^aFaculty of Medicine, Department of Dermatology. Pontificia Universidad Católica de Chile

^bFaculty of Medicine, Pontificia Universidad Católica de Chile

Received: 17-03-2017; Accepted: 28-12-2017

Abstract

Introduction: Extranodal natural killer/T-cell lymphoma (NK/T), nasal type, is an infrequent neoplasm with a high lethality, characterized by bone destruction around the sinus, nasal septum or obstruction of the airway. Also, may be primary skin involvement, airway and other organs. **Objective:** Submit a rare condition in the pediatric population, in order to facilitate the diagnostic suspicion and quick recognition from specialists. **Case report:** a 14-year-old girl, who presented arm and leg lesions, painless, suggestive of subcutaneous panniculitis, which evolve to ulcerated purple maculae. Skin biopsy showed lesion compatible with NK/T lymphoma, nasal type. She was referred to pediatric oncology, where she received chemotherapy treatment. Despite medical efforts, the patient died eight months after due to a serious pulmonary infection secondary to immunosuppression. **Conclusions:** Extranodal NK/T-cell lymphoma, nasal type, is a rare neoplasm that behaves aggressively, with high mortality without treatment, therefore, its recognition has a high importance for early diagnosis and prompt referral to Hematology-Oncology.

Keywords:

Extranodal natural killer/T-cell lymphoma nasal type; pediatric; Epstein-Barr virus

Correspondence:
Dra. María Jesús Rojas Lechuga
mjesusrojasl@gmail.com

Introduction

Peripheral T-cell lymphomas are a heterogeneous group of neoplasms, which are less than 15% of all non-Hodgkin's lymphoma (NHL) in adults^{1,2} and less than 10% in the pediatric and adolescent population¹. These include extranodal NK/T-cell lymphoma, nasal type, also called "angiocentric lymphoma"².

This is an extranodal lymphoma, usually with Natural Killer (NK) cell phenotype and positive for Epstein-Barr virus (EBV), which has a wide range of manifestations and frequently presents with necrosis and angioinvasion. It is called NK/T due to the ambiguity of the origin cells, however, it is mostly due to NK, and only the minority have clonal T-cells³.

The extranodal NK/T-cell lymphoma has a similar clinical presentation in both children and adults; it tends to have a predominance in men, most cases are diagnosed at an early stage and are often accompanied by B symptoms (weight loss, night sweats and/or fever) and high lactate dehydrogenase (LDH) levels. The most common extranodal NK/T-cell lymphoma is the nasal type, in which the tumor can cause bone destruction around the sinuses, the nasal septum, or airway obstruction^{4,5}, manifesting itself with symptoms such as nasal obstruction, epistaxis, and/or mass involving the nose, sinuses, or palate¹. The extranodal NK/T-cell lymphoma, nasal type is characterized by an extra nasal primary location¹, the most common extranasal involvement is the skin, other involvements may be upper airway, Waldeyer's lymphoid ring, gastrointestinal tract, testicles, lung, eyes, and soft tissue. Lymph nodes tend to be involved secondarily. Bone marrow involvement and B symptoms in these cases are observed in only 10-35% of the patients⁶.

The pathogenesis is poorly understood and is explained, in part, by the EBV infection of tumor cells, along with the genes involved in the angiogenesis, in the cell cycle progression, tumor suppressor genes, among others^{1,7}.

The extranodal NK/T-cell lymphoma is most frequent in Asia (China, Japan, Korea, Hong Kong), and in native Central and South American populations, which considered 5-10% of the NHL. The average age of presentation is 45 years¹, however, cases have been reported in childhood⁶.

The objective of this report is to present an illustrative example of a rare and aggressive condition in the pediatric population, in order to facilitate diagnostic suspicion and rapid recognition by specialists.

Clinical case

A 14-year-old female, without known morbid history, went to the Dermatology Service with a 3-month

history of asymptomatic lesions in legs. During the examination, she presented an erythematous plaque with an arciform border slightly raised in relation to the inner side of the right knee (figure 1); at dermoscopy, no pigment network was observed, presented multiple comma-shaped vessels, without other recognizable structures. Soft tissue ultrasound was requested, which showed suggestive signs of subcutaneous panniculitis associated with inflammatory skin process, no suggestive images of fat necrosis were observed (figure 2).

In the control visit five months after the first consultation, purple maculae were observed in places where the lesions were previously found. In this context, it was decided to perform a skin biopsy, which reported skin with hyperkeratosis and mild exocytosis of lymphocytes. Dermis with superficial and deep perivascular lymphocytic infiltrate, and in the hypodermis, it is dense, composed of medium to large lymphocytes with irregular nuclei, granular chromatin, with a moderate amount of clear cytoplasm. Necrosis and numerous atypical mitoses were observed (figure 3). The immunohistochemical study with EnVision FLEX monoclonal antibodies automated technique showed a positive reaction for NK cell markers and positive reaction for EBV using FISH method for EBER-1 and EBER-2 transcripts (figure 4). The findings were compatible with NK/T-cell lymphoma-leukemia, nasal type.

In the context of the diagnosis of extranodal NK/T-cell lymphoma, nasal type, with primary skin involvement, tests were required in which hemogram, liver tests, and biochemical profile were normal, EBV IgM (-) and EBV IgG (+), human T-cell lymphotropic virus Type I (HTLV1) (-). The patient was referred urgently to Hemato-Oncology, where she received two cycles of chemotherapy with cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP), with



Figure 1. Erythematous plaque with a slightly raised arcuate rim in relation to the inner side of the right knee.

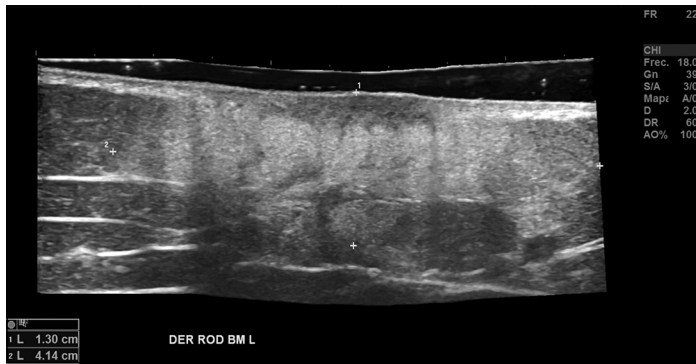


Figure 2. Ultrasonography of soft parts of the internal face of the right knee with signs suggestive of subcutaneous panniculitis with dermal inflammatory process.

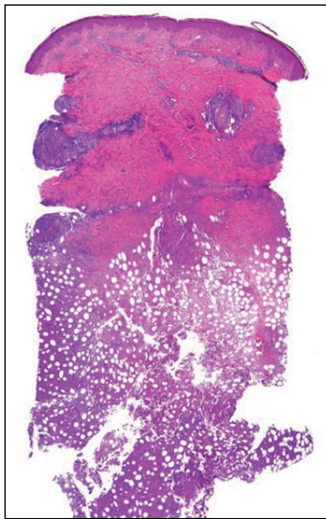


Figure 3. Histological section with hematoxylin-eosin stain. The dermis was observed with superficial, deep and hypodermis lymphocytic infiltrate, dense, composed of medium to large lymphocytes, with irregular nuclei, granular chromatin, with moderate amount of clear cytoplasm, necrosis and numerous atypical mitosis.

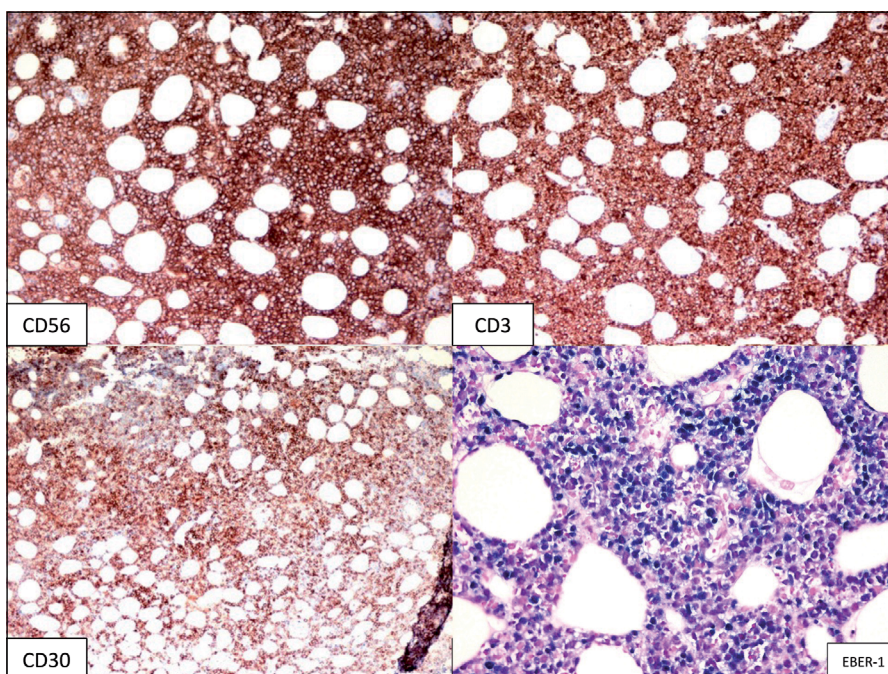


Figure 4. Immunohistochemical study according to automated EnvisionFlex technique with monoclonal antibodies, presents positive reaction for CD3, CD56 and CD30. Positive reaction for EBER1 transcript of the Epstein Barr Virus according to the FISH method.

partial response. Eight months after diagnosis, the patient died due to the disease progression associated with infectious pulmonary complication.

Discussion

Few cases have been reported of extranodal NK/T-cell lymphoma in children and adolescents, in which it has been observed that they are preceded by other EBV-related disorders such as chronic active infection by EBV, hypersensitivity to mosquito bites⁸, hydroa vacciniforme-like eruption, and hemophagocytic lymphocytosis⁹. With regard to the latter, about 3% of these lymphomas can be associated with hemophagocytic syndrome, a complication that can occur with high fever, maculopapular rash, treatment failure, symptoms involving the central nervous system, hepatosplenomegaly, lymphadenopathies, cytopenias, coagulopathies, alteration in liver tests, and/or high levels of ferritin¹⁰. The extranodal NK/T-cell lymphoma not preceded by some of these disorders mentioned before, such as our patient, is extremely rare in the pediatric population, and few cases have been reported⁹.

The diagnosis is made with clinical evaluation and biopsy of the area involved, usually the central facial area. Due to its variable morphology, it is important to consider it as a diagnosis in all cases of aggressive extranodal lymphoma associated with vascular invasion and necrosis¹¹.

With respect to skin involvement, about 2/3 of patients have cellulitis and/or ulcers predominantly

on the face. Therefore, dermatologists and pediatricians should have a high degree of suspicion in the case of lesions with these characteristics that do not heal¹³.

The histology that characterizes this lymphoma is a polymorphic lymphoid infiltration which invades the vascular walls, producing fibrinoid necrosis of the vessel wall and necrosis of surrounding tissue. Tumor cells are variable in morphology, in some cases may have a predominance of small or large cells, but most often are mixed. The diagnostic key is the demonstration of NK/T-cell markers and the presence of EBV. Although CD56 is typically expressed, there are tumors that do not present it and are still classified as extranodal NK/T-cell lymphoma, if both cytotoxic molecules and EBV are positive.

In 90% of cases, where these tumors are of NK-cell origin, CD2, cytoplasmic CD3, CD56, and cytotoxic granule proteins are expressed; they have T-cell receptor genes in their germline configuration and are surface negative for CD3¹¹.

Extranodal NK/T-cell lymphoma, nasal type, is an aggressive lymphoma which without treatment has a survival of months. The prognosis with treatment is widely related to the involvement and stage at the time of diagnosis¹². Regarding survival, primary skin involvement is the most common in the extranasal form, and it is associated with good prognosis. On the other hand, secondary skin involvement of extranodal nasal lymphoma is considered the lymphoma with the worst prognosis, because it corresponds to a spread¹³.

In the case of our patient, we suspect that the unfavorable outcome despite having a primary skin involvement may be due to that the occurrence and clinical-pathological characteristics of the extranodal NK/T-cell lymphoma in children and adolescents not preceded by other EBV-related disorders have not been clearly established⁹.

Recent studies have identified as potential poor prognostic factors the EBV levels, the tumor invasiveness, and the antigen expression¹⁴. Serum antibody values for EBV (EA-IgA EBV \geq 1:10 and VCA IgA \geq 1:160) have recently been related with a worse prognosis: lower survival, lower progression-free survival, lower treatment response rate and higher relapse rate. Therefore, these levels can be useful for risk stratification and prognosis in these patients¹⁵. In the case of our patient, these levels were not measured.

Due to the aggressiveness of this type of lymphoma, an urgent referral to Hemato-Oncology must be made in the face of the diagnosis¹⁶. Regarding management, several schemes have been proposed, in the case of nasal or paranasal NK/T-cell lymphoma, radiotherapy with or without chemotherapy is preferred. In extra-

nodal disease, systemic polychemotherapy is preferred. In the pediatric literature, the role of bone marrow transplantation is uncertain, however, in oncological literature, it is an option for patients with non-localized disease in remission¹.

Conclusion

The extranodal NK/T-cell lymphoma, nasal type, with primary skin involvement in a 14-year-old girl is an extremely rare neoplasm, particularly when it is not preceded by other EBV-related disorders. It is characterized by non-specific skin lesions. Extranodal NK/T-cell lymphoma must be suspected in case of cellulitis lesions and/or ulcers predominantly on the face that do not improve. Its diagnosis is clinical and histological, where it is characterized by NK/T-cell markers, the presence of EBV and CD56.

It is a malignant neoplasm of high aggressiveness, little known, with poor outcomes in survival in children and adolescents, therefore, it is necessary to further deepen on the pathophysiology of the disease and its management.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

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

Financial Disclosure

Authors state that no economic support has been associated with the present study.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

References

1. Termuhlen AM. Natural killer/T-cell lymphomas in pediatric and adolescent patients. *Clin Adv Hematol Oncol*. 2017;15(3):200-9.
2. Stein H, Warnke RA, Chan WC. Diffuse large B-cell lymphoma, not otherwise specified. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues*. 4th ed. Lyon, France: IARC Press; 2008:233-9.
3. Harris NL, Jaffe ES, Stein H, Banks PM, Chan JK, Cleary ML, Gatter KC. A revised European-American classification of lymphoid neoplasms: a proposal from the International Lymphoma Study Group. *Blood*. 1994;84(5):1361.
4. Lee JY, Jang YD, Kim HK. The primary role of the otolaryngologist in managing pediatric sinonasal malignancies: an extranodal NK/T-cell lymphoma originating from the inferior turbinate mucosa of the nasal cavity. *J Pediatr Hematol Oncol*. 2008;30(5):401-4.
5. Lai C, Dunleavy K. NK/T-cell lymphomas in children. *Best Pract Res Clin Haematol*. 2013;26(1):33-41.
6. Au WY, Weisenburger DD, Intratumoral T, et al. Clinical differences between nasal and extranasal natural killer/T-cell lymphoma: a study of 136 cases from the International Peripheral T-Cell Lymphoma Project. *Blood*. 2009;113(17):3931-7.
7. Asano N, Kato S, Nakamura S. Epstein-Barr virus-associated natural killer/T-cell lymphomas. *Best Pract Res Clin Haematol*. 2013;26(1):15-21.
8. Zhang Z, Shi Q, An X, et al. NK/T-cell lymphoma in a child with hypersensitivity to mosquito bites. *J Pediatr Hematol Oncol*. 2009;31(11):855-7.
9. Huang Y, Xie J, Ding Y, Zhou X. Extranodal Natural Killer/T-Cell Lymphoma in Children and Adolescents: A Report of 17 Cases in China. *Am J Clin Pathol*. 2016;145(1):46-54.
10. Brodtkin DE, Hobohm DW, Nigam R. Nasal-type NK/T-cell lymphoma presenting as hemophagocytic syndrome in an 11-year-old Mexican boy. *J Pediatr Hematol Oncol*. 2008;30(12):938-40.
11. Kanavaros P, Lescs MC, Briere J, et al. Nasal T-cell lymphoma: a clinicopathologic entity associated with peculiar phenotype and with Epstein-Barr virus. *Blood*. 1993;81(10):2688-95.
12. Li CC, Tien HF, Tang JL, et al. Treatment outcome and pattern of failure in 77 patients with sinonasal natural killer/T-cell or T-cell lymphoma. *Cancer*. 2004;100(2):366-75.
13. Choi YL, Park JH, Namkung JH, et al. Extranodal NK/T-cell lymphoma with cutaneous involvement: 'nasal' vs. 'nasal-type' subgroups--a retrospective study of 18 patients. *Br J Dermatol*. 2009;160(2):333-7.
14. Park S, Ko YH. Epstein-Barr virus-associated T/natural killer-cell lymphoproliferative disorders. *J Dermatol*. 2014;41(1):29-39.
15. Huang Y, Rao H, Yan S, et al. Serum EBV EA-IgA and VCA-IgA antibodies can be used for risk group stratification and prognostic prediction in extranodal NK/T cell lymphoma: 24-year experience at a single institution. *Ann Hematol*. 2017;96(8):1331-42.
16. Wang ZY, Li YX, Wang WH, et al. Primary radiotherapy showed favorable outcome in treating extranodal nasal-type NK/T-cell lymphoma in children and adolescents. *Blood*. 2009;114(23):4771-6.