

# Extranodal natural killer T-cell lymphoma, nasal type, presenting as periorbital cellulitis: A case report

Katherine Miller, Amir Kamran, Anna Koget

## ABSTRACT

**Extranodal NK T-cell Lymphoma (ENKTL), nasal type is a rare and aggressive malignancy most commonly seen in South East Asia. It comprises less than 1.5% of all Non-Hodgkins lymphomas worldwide and is seen in only 5–8% of extranodal lymphomas of the head and neck. Typically, it presents with nasal obstruction, sinusitis, ulcer, and epistaxis. There are very few cases in the literature where the presentation is orbital in nature. We present a case of ENKTL, nasal type in a previously healthy 52-year-old Caucasian male presenting with persistent orbital cellulitis and swelling, and treated with chemotherapy and radiation**

**Keywords: Epstein Barr Virus, Nasal lymphoma, Orbital lymphoma, Smile**

### How to cite this article

Miller K, Kamran A, Koget A. Extranodal natural killer T-cell lymphoma, nasal type, presenting as periorbital cellulitis: A case report. J Case Rep Images Med 2018;4:100048Z09KM2018.

Article ID: 100048Z09KM2018

Katherine Miller<sup>1</sup>, Amir Kamran<sup>2</sup>, Anna Koget<sup>2</sup>

**Affiliations:** <sup>1</sup>Department of Internal Medicine, Allegheny General Hospital, Pittsburgh, Pennsylvania, United States of America, North Ave Pittsburgh, Pennsylvania; <sup>2</sup>Department of Hematology and Oncology, Allegheny General Hospital, Pittsburgh, Pennsylvania.

**Corresponding Author:** Katherine Miller, DO, Department of Internal Medicine, Allegheny General Hospital, 320 E. North Ave Pittsburgh-15212, Pennsylvania; Email: katherine.miller@ahn.org

Received: 14 July 2018

Accepted: 30 October 2018

Published: 29 November 2018

\*\*\*\*\*

doi: 10.5348/100048Z09KM2018CR

## INTRODUCTION

Extranodal Natural Killer T-cell Lymphoma (ENKTL), nasal type is a rare and aggressive malignancy. It is seen in only 5–8% of extranodal lymphomas of the head and neck and constitutes about 1.4% of all lymphomas. ENKTL is most commonly seen in South East Asia and South America and has a male preponderance with a 2:1 to 3:1 male to female ratio. It is rarely seen in the United States or amongst the Caucasian population. Typically, it is diagnosed in the fifth decade of life, and generally presents with non-specific symptoms in the early stages of the disease. Overall prognosis is dismal, with a five-year survival rate of 30%, with some sources citing a survival rate of 13% beyond 13 months for patients with orbital involvement [1–4].

Those occurring outside of the nasal cavity are highly aggressive and carry a poorer prognosis. It presents with very nonspecific symptoms, such as nasal obstruction and epistaxis in tumors that originate within the nasal cavity. Those involving the mid facial structures can sometimes present with proptosis and occasionally with involvement of the hard palate. Symptoms such as weight loss, fever, night sweats, and anemia tend to occur only in the later stages of the disease. For ENKTLs presenting outside of the nasal cavity, uveitis is the most common presenting symptom. Orbital cellulitis as a presenting symptom is very rare, with few cases described in the literature. A literature review compiled by Ely et al reported nine cases that presented as isolated orbital involvement, and a review by Termote et al reported three. Hughes et al and Shawabkeh et al reported one case each [1–4].

Here we describe a case of ENKTL, nasal type, presenting as orbital cellulitis in a fifty-two-year-old Caucasian male from the United States.

## CASE REPORT

A 52-year-old Caucasian male with no past medical history presented to his primary care doctor with right periorbital edema and erythema, along with intermittent fevers. He was treated for sinusitis without improvement of symptoms. He was seen by ENT and ophthalmology and received additional antibiotics and steroids without improvement. He underwent four endoscopic washouts with drainage, and an orbitotomy with orbital biopsy and dacryocystorhinostomy for blockage of the right lacrimal sac and duct. The biopsy taken at that time demonstrated a submucosal infiltrate of a neoplastic population with irregular nuclear membranes, prominent nucleoli, and a moderate amount of granular cytoplasm (Figure 1A and Figure 1B). Immunophenotyping of the biopsy specimen revealed CD3 positive (Figure 2A), CD4 negative (Figure 2B), CD8 negative (Figure 2C), CD56 positive (Figure 2D), TIA-1 positive (Figure 2E) and EBV RNA in situ hybridization positive (Figure 2F) consistent with ENKTL, nasal type. Computed tomography (CT) was done and showed involvement of the right maxillary and ethmoid sinuses, a left deviation of the nasal septum, and no intracranial extension. CT neck showed bilateral level 1 and 2 reactive lymphadenopathy, and CT of the chest, abdomen, and pelvis was unremarkable. Lab work at the time of diagnosis was significant for pancytopenia with a white blood cell count of 3.78k per microliter, red blood cell count of 3.53k per microliter, hemoglobin of 10.4 grams per deciliter, hematocrit of 31.0%, and platelet count of 98k per microliter. Quantitative EBV DNA by PCR at the time of diagnosis revealed a viral load of 3100 copies per milliliter with a normal reference range of negative copies per milliliter. Both the bone marrow biopsy and cerebral spinal fluid (CSF) flow cytometry were negative for involvement with ENKTL. He was initiated on emergent chemotherapy with the SMILE (Dexamethasone, Methotrexate with Leucovorin, Ifosfamide, L-asparaginase, and Etoposide) regimen. He underwent three cycles of SMILE, followed by twenty treatments of radiation therapy. EBV DNA titers at that time were undetectable. After radiation therapy, he received a fourth cycle of SMILE with omission of L asparaginase due to symptomatic rhinovirus and atrial fibrillation. A restaging magnetic resonance imaging (MRI) was performed, which showed findings concerning for disease progression. New involvement of the masticator space, parapharyngeal and pterygoid muscle regions was seen, along with new right exophthalmos and possible residual disease. A fluorine-18 fluorodeoxyglucose positron emission tomography computerized tomography (18-FDG PET CT) was then done, which showed FDG avid left cervical lymph nodes. Biopsy of the cervical lymph node was positive for involvement with ENKTL. EBV DNA titers measured at the time of progression showed an increase from <200 to 604. SMILE regimen was discontinued

due to disease progression, and Pembrolizumab 2mg/kg every three weeks was initiated for salvage therapy.

## DISCUSSION

ENKTL, nasal type is a rare malignancy most commonly seen in South East Asia with a male preponderance, and typically presents in the fifth decade of life. Orbital involvement as the presenting symptoms occurs in 0-3% of cases. Symptoms are nonspecific in the early stages of the disease, and often mimic more benign conditions such as sinusitis and orbital cellulitis. Literature review reveals limited cases of ENKTL with isolated orbital involvement as the presenting symptom [1-4].

It is derived from cytotoxic T-lymphocytes, generally occurs within the nasal cavity or nasopharynx, and is locally destructive along the midline [2, 3]. Additionally, EBV plays a role in its development with greater than 95% of cases reported in the literature associated with the virus. Per WHO guidelines, diagnosis of ENKTL requires

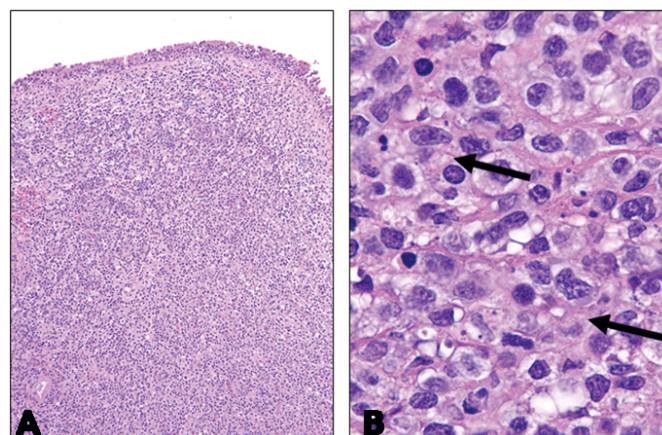


Figure 1: Submucosal infiltrate of small to medium sized cells (A) which upon higher examination (100x) demonstrates a slightly larger neoplastic population with irregular nuclear membranes, prominent nucleoli (one or more), and a moderate amount of granular cytoplasm (arrow) (B).

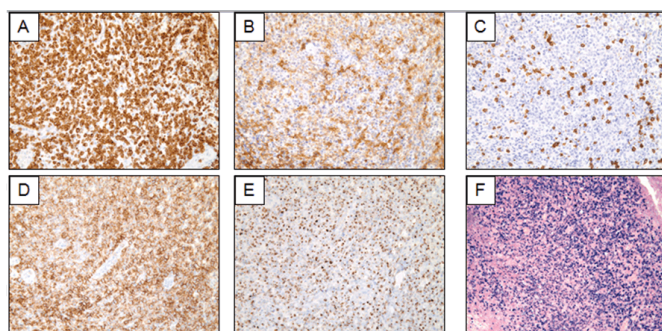


Figure 2(A-F): Immunohistochemical stains demonstrate a neoplastic population that is CD3 positive (A), CD4 negative (B), CD8 negative (C), CD56 positive (D), TIA-1 positive (E) and EBV RNA in situ hybridization positive (F). These findings are consistent with an extranodal NK/T-cell lymphoma, nasal type.

both EBV positivity and expression of cytotoxic granules. Higher quantities of plasma EBV DNA by PCR correlates with more extensive disease, poorer response to therapy, and poorer outcome. EBV DNA by PCR can be utilized as a tumor marker to gauge response to therapy [2].

Histologically, initial biopsies may show inflammatory cells which obscure the few neoplastic cells that are present early in the disease. In advanced stages, this neoplasm is characterized by angiocentric and angioinvasive growth with areas of necrosis and lymphocytic infiltration causing extensive coagulative necrosis and apoptosis [2, 5]. ENKTL tumors demonstrate NK T-cell markers with CD2+, CD56+, and CD3ε+, along with cytotoxic molecule positivity (Granzyme B+, TIA-1+, and perforin +). Negativity of the T cell markers CD4, CD5, and CD3 along with the negative B cell marker CD20 are also noted [5].

Imaging modalities in the work up of ENKTL include CT and MRI which aid in evaluating the extent of the disease. The most sensitive image test though, is the 18-FDG PET CT. Treatment of ENKTL utilizes a combination of radiation therapy and chemotherapy. It is a known radiosensitive tumor with radiation therapy alone achieving high response rates of 77-100% for early stage localized disease, but has a relapse rate of 25-40%. CHOP (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone) had been the previous regimen of choice for treatment of ENKTL tumors. Responses to the combination therapy of CHOP followed by radiotherapy were still poor, with relapse rates of 58% and a 59% 3-year survival rate [2, 5-7].

Further studies have showed that ENKTL tumors manifest resistance to anthracycline based regimens such as CHOP, through overexpression of the gene encoding P-glycoprotein [2, 5-7]. P-glycoprotein is a transmembrane glycoprotein that is part of the ATP-binding cassette (ABC) transporter family, and the multi-drug resistance (MDR) pathway [8]. It functions as a biological barrier, and actively effluxes toxins and xenobiotics out of the cell [8]. Anthracycline agents are amongst the substances which P-glycoprotein actively exports from the cell. Newer regimens such as MEDA (Methotrexate, Etoposide, Dexamethasone, Pegasparagase) and SMILE utilize non-P-glycoprotein efflux agents, thus increasing their effectiveness. Methotrexate also acts independently of the multi drug resistant (MDR) pathway, and Etoposide has been observed to be effective in treating T/NK lymphomas within the pediatric population [5]. Additionally, L-asparaginase has been effective in reducing relapse rates, and improving overall long-term survival, but carries significant risk of adverse events, particularly life threatening allergic reactions. SMILE therapy used alone has response rates of 86% and with the addition of concurrent radiotherapy response rates increase to 89% [2, 5-7].

Despite advances in chemotherapy regimens and overall response rates, long term survival remains poor. The five-year survival rate remains at 30%, with

some sources citing a survival rate of only 13% beyond 13 months for patients with orbital involvement [1-4]. Delay in diagnosis further decreases the chances of survival. The presence of nonspecific symptoms that mimic more benign conditions compounds the difficulty of early diagnosis. Patients outside of the population in which this disease typically presents are at an even higher risk for delayed diagnosis.

## CONCLUSION

Our case demonstrates uniqueness in several aspects, with presentation in a Caucasian male outside of South East Asia, as well as an initial presenting symptom of orbital cellulitis. He underwent multiple rounds of antibiotics, steroids, and wash outs prior to performance of a biopsy. This case illustrates the importance of keeping a broad differential in patients with benign appearing diseases that do not respond to conventional therapy. Rare and aggressive diseases can have rare presentations, and delay in diagnosis only further reduces a patient's chance of long term survival. Further work up is thus warranted in benign conditions that do not respond to appropriate medical therapy.

## REFERENCES

1. Hughes E, Fogarty H, Fortune A, Keegan D. Ocular presentation of natural killer/T-cell lymphoma in a Caucasian man. *BMJ Case Rep* 2016 Apr 26;2016.
2. Al Shawabkeh MA, Al Sulaiti M, Al Sa'ey H, Ganesan S. Nasal type extranodal natural killer/T (NK/T) cell lymphoma presenting as periorbital cellulitis: A case report. *Am J Case Rep* 2016 Dec 9;17:934-8.
3. Termote K, Dierickx D, Verhoef G, Jorissen M, Tousseyn T, Mombaerts I. Series of extranodal natural killer/T-cell lymphoma, nasal type, with periorbital involvement. *Orbit* 2014 Aug;33(4):245-51.
4. Ely A, Evans J, Sundstrom JM, Malysz J, Specht CS, Wilkinson M. Orbital involvement in extranodal natural killer T cell lymphoma: An atypical case presentation and review of the literature. *Orbit* 2012 Aug;31(4):267-9.
5. Obama K, Tara M, Niina K. L-asparaginase-Based induction therapy for advanced extranodal NK/T-cell lymphoma. *Int J Hematol* 2003 Oct;78(3):248-50.
6. Ding H, Chang J, Liu LG, et al. High-dose methotrexate, etoposide, dexamethasone and pegaspargase (MEDA) combination chemotherapy is effective for advanced and relapsed/refractory extranodal natural killer/T-cell lymphoma: A retrospective study. *Int J Hematol* 2015 Aug;102(2):181-7.
7. Hattori Y, Murai T, Iwata H, et al. Chemoradiotherapy for localized extranodal natural killer/T-cell lymphoma, nasal type, using a shrinking-field radiation strategy: Multi-institutional experience. *Jpn J Radiol* 2016 Apr;34(4):292-9.
8. Lin JH, Yamazaki M. Role of P-glycoprotein in pharmacokinetics: Clinical implications. *Clin Pharmacokinet* 2003;42(1):59-98.

\*\*\*\*\*

**Author Contributions**

Katherine Miller – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Amir Kamran – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Anna Koget – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

**Guarantor of Submission**

The corresponding author is the guarantor of submission.

**Source of Support**

None.

**Consent Statement**

Written informed consent was obtained from the patient for publication of this case report.

**Conflict of Interest**

Authors declare no conflict of interest.

**Data Availability**

All relevant data are within the paper and its Supporting Information files.

**Copyright**

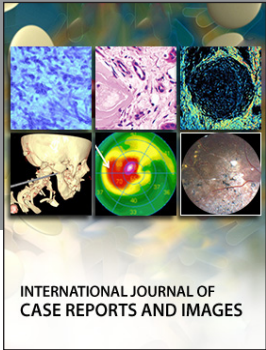
© 2018 Katherine Miller et al. This article is distributed under the terms of Creative Commons Attribution License which permits unrestricted use, distribution and reproduction in any medium provided the original author(s) and original publisher are properly credited. Please see the copyright policy on the journal website for more information.

Access full text article on  
other devices



Access PDF of article on  
other devices





INTERNATIONAL JOURNAL OF CASE REPORTS AND IMAGES



VIDEO JOURNAL OF CLINICAL RESEARCH



VIDEO JOURNAL OF BIOMEDICAL SCIENCE



INTERNATIONAL JOURNAL OF HEPATOBILIARY AND PANCREATIC DISEASES



INTERNATIONAL JOURNAL OF BLOOD TRANSFUSION AND IMMUNOHEMATOLOGY



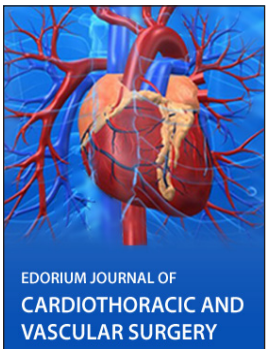
EDORIUM JOURNAL OF OPHTHALMOLOGY



**Submit your manuscripts at**  
[www.edoriumjournals.com](http://www.edoriumjournals.com)



EDORIUM JOURNAL OF MEDICINE



EDORIUM JOURNAL OF CARDIOTHORACIC AND VASCULAR SURGERY



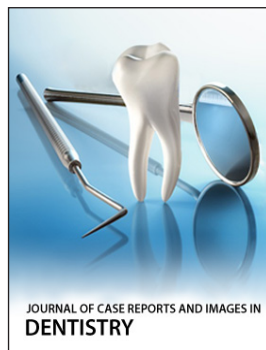
JOURNAL OF CASE REPORTS AND IMAGES IN ORTHOPEDICS AND RHEUMATOLOGY



EDORIUM JOURNAL OF PSYCHOLOGY



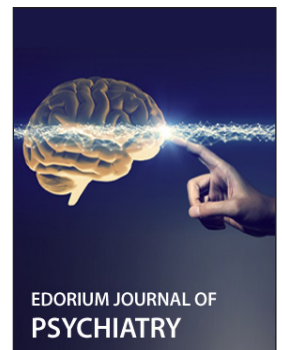
EDORIUM JOURNAL OF CELL BIOLOGY



JOURNAL OF CASE REPORTS AND IMAGES IN DENTISTRY



EDORIUM JOURNAL OF CANCER



EDORIUM JOURNAL OF PSYCHIATRY



JOURNAL OF CASE REPORTS AND IMAGES IN INFECTIOUS DISEASES



EDORIUM JOURNAL OF ANATOMY AND EMBRYOLOGY



EDORIUM JOURNAL OF SURGERY



JOURNAL OF CASE REPORTS AND IMAGES IN PATHOLOGY



EDORIUM JOURNAL OF ANESTHESIA