

# An Unexpected Presentation of a Maxillary Non-Hodgkin Lymphoma in an Elderly Hispanic Patient

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**Extranodal NK/T-cell lymphoma (ENKTL), nasal type and aggressive NK-cell leukemia are rare in Western World been less than 1% in USA to 8% in Asia among Non-Hodgkin's lymphomas. It is aggressive, with poor outcome and optimal treatment is unclear. A combination therapy that includes Peg-Asparaginase (SMILE) has been employed in young patients. An 85-year-old Puerto Rican male presented with anorexia, epistaxis, vertigo and involuntary facial movements. He was treated with injectable Onabotulinum toxin A due to suspicion of a hemifacial spasm. However, a CT scan demonstrated a left maxillary sinus lesion extending into the left middle turbinate with biopsy consistent with ENKTL. We adjusted therapy to patient's age and performance receiving Gemcitabine-Oxaliplatin (Gemox) with radiation obtaining a complete response with persistent negative Epstein Barr DNA titers. ENKTL is a rare disease initially misdiagnosed in our elderly patient, who demonstrated adequate response with a modified therapeutic regime. [P R Health Sci J 2023;42(4):328-331]**

*Key words: Maxillary lymphoma, Non-Hodgkin lymphoma, T-cell lymphomas*

**E**xtranodal Natural Killer/T-cell lymphoma (ENKTCL) is a subtype of Non-Hodgkin's lymphoma associated to Epstein Bar Virus infection (EBV) (1,2). It is a rare NHL subtype and represents approximately 1% of cases in the United States and Europe. A higher incidence has been described in other geographic locations including Asia and South America where it can comprise up to 10% of cases (2). Theories regarding the lower incidence of NK cell lymphoma in the United States compared to Asia and other continents, includes misclassification with other Non-Hodgkin's Lymphoma subtypes or malignancies, granulomatous diseases and misdiagnosis of an invasive infectious process (3-6). Epidemiology registries show a higher predominance in young to middle age men (2). This entity presents as a localized disease with tissue and extranodal involvement. Primary disease commonly arises from nasal cavity, upper aerodigestive tract, lung and GI tract with an angio-invasive behavior (7). Disease is characterized by malignant transformation of Natural Killer overexpressing antigens, including cytoplasmic CD3e1, CD56, perforins, granzyme B and T-cell markers (7).

Diagnostic criteria require the presence of EBV to avoid misclassification (7). Survival at 5 years ranges from 37.9% to 45.3% and prognosis of disease relies on the stage at diagnosis with advanced disease presenting very poor prognosis (8). There is also a known risk of relapse or recurrence for which continuous surveillance is recommended. Suzuki et. al studied plasma EBV-DNA levels in patients with ENKTCL and found this test as a valuable prognostic marker and indicator of treatment response (9).

## Case report

An 85-year-old Hispanic male with medical history of hypertension and hypothyroidism, presented to his primary care physician with chronic history of anorexia, vertigo, epistaxis, twitching and involuntary movements of facial muscles. Supportive treatment with oral anti-spasmodic agents provided no relief, for which a Brain Magnetic Resonance Imaging (MRI) and Brain angiography (MRA) were performed for further evaluation, interpreted as within normal limits. Physical examination and direct nasal endoscopy were normal without evidence of epistaxis, polyps or masses. After Neurology evaluation, based on examination and imaging studies, patient was diagnosed with hemifacial spasms and started with Onabotulinum toxin A injections.

In this case, the patient presented with a series of non-specific symptoms affecting his upper respiratory tract, facial muscles and cranial nerves. His initial workup and imaging studies did not reveal a structural or anatomic finding that could explain the clinical presentation. After no evidence to suggest otherwise, he

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*The authors have no conflict of interest to disclose.*

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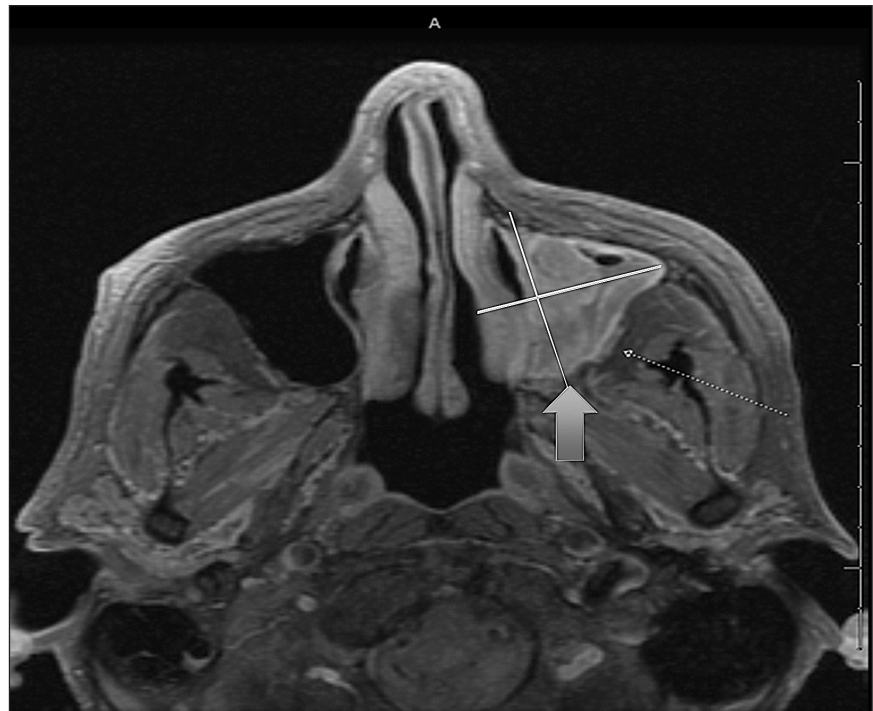
received a diagnosis of muscle spasm, which is a common diagnosis in the primary care setting.

Treatment according to the initial diagnostic impression was provided for 9 months. The patient continued with severe pain and persistent symptoms. A Sinus Computer Tomography (CT) scan revealed a left maxillary sinus expansible soft tissue lesion that measured 4.1 x 4.3 cm. The lesion was not present on prior studies and extended to left middle turbinate and reached the nasal septum with possible involvement of the maxillary bone. A sinus Magnetic Resonance Imaging (MRI) confirmed above findings (Figure 1). Nasal endoscopy with direct visualization was repeated, and a polyp medial to the middle turbinate with increased vascularity over the sphenoid-ethmoidal area was detected and biopsied.

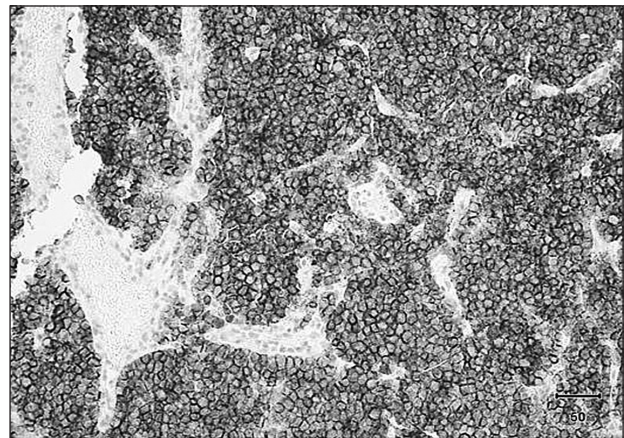
Poor response to treatment and worsening of symptoms in this particular case was a major indication for re-assessment of diagnosis and perform new imaging studies. A structural disease with mass effect affecting facial muscles and cranial nerves was in the initial differential diagnoses. Nonetheless it was initially disregarded based on imaging studies. Based on new imaging findings, tissue diagnosis was needed to further characterize the etiology of the lesion.

Nasal polyp biopsy showed a proliferation of large lymphocytes with positive markers for CD3, CD4, CD56, CD10 and Granzyme B; and negative results for CD5, CD20, and BCL-2 (Figure 2 and 3). In addition, biopsy showed a positive Epstein Bar Virus status in more than 90% of the cells, but negative EBV plasma levels. Interestingly, biopsy results confirmed the diagnosis of Extranodal NK/T cell lymphoma, nasal type. Polymerase Chain Reaction for Plasma EBV DNA resulted in less than 200 copies.

In this case, NK lymphoma was found to be localized in the left maxillary sinus/ethmoid area with surrounding inflammatory edema. Bone marrow biopsy showed no lymphoma involvement. A positron emission tomography (PET/CT) scan confirmed opacification of left frontal, ethmoidal, nasal and maxillary sinuses without increase in metabolic activity in other parts of the body. Eastern Cooperative Oncology Group (ECOG) performance status score was 1 (strenuous physical activity restricted; fully ambulatory and able to carry out light work). The prognostic index of NK cell lymphoma with EBV DNA resulted in an intermediate risk score considering patient's age (>60 years old) and presence of EBV DNA on tumor cells. According to tissue diagnosis, comorbidities, age, functional



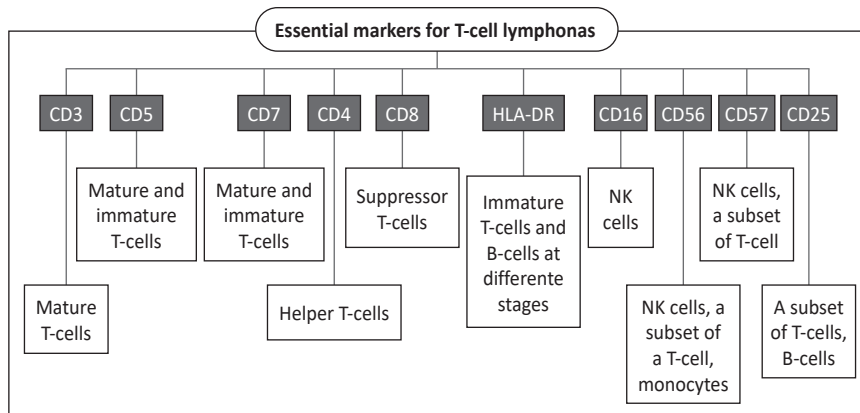
**Figure 1.** Sinus MRI showing a left maxillary sinus expansible soft tissue lesion measuring 4.1 x 4.3 cm extending to nasal septum.



**Figure 2.** Maxillary sinus mass positive for CD56, a marker for Natural Killer cells.

status and current guidelines, combination of chemotherapy and radiotherapy was recommended.

The patient received 2 cycles of Gemcitabine with oxaliplatin (GEMOX) and 20 sessions of radiation 180 cGy each followed by 2 additional cycles of GEMOX as consolidation therapy. Patient tolerated treatment adequately with only transient thrombocytopenia before cycle 2 of chemotherapy. Follow up PET/CT Scan showed no evidence of residual disease. 18 months post chemotherapy the patient is asymptomatic with overall clinical improvement and active surveillance with negative EBV DNA PCR and a normal PET/CT scan.



**Figure 3.** Large lymphocytes had positive molecular markers for CD3, CD4, CD56, CD10 and Granzyme B; and negative results for CD5, CD20, and BCL-2,confirming the diagnosis of an Extranodal Natural Killer/T cell lymphoma.

factors for EBV infection, has negative plasma EBV levels with a high viral burden in tumor. Due to advanced age of the patient, we adjusted successfully the treatment permitting excellent tolerance with minimal toxicity or morbidity.

This case presents the effective use of a less toxic chemotherapeutic treatment in which Asparaginase was not included. Compared to other established regimens in which Asparaginase was a common component of treatment, we were able to provide a safer approach with complete response. Newer options with use of immunotherapy are been explored in this disease as to improve cure with drugs that have less toxicity (14).

### Discussion

Studies have compared Overall Response Rate (ORR) and Complete Remission (CR) with single or combined therapies and show that NK lymphoma is a known radiosensitive malignancy (7). Several chemotherapy agents have been studied, including CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone), SMILE (Dexamethasone, Methotrexate, Ifosfamide, L-Asparaginase, and Etoposide), and P-GEMOX/GELOX1,10-12. Xi-wen et. al specifically compared treatment regimens in elderly patients which represents a lower percentage of affected patients with NK lymphoma, but with significant mortality<sup>10</sup>. Important prognostic factors in this population include performance status, age, Ann Arbor Stage, natural killer/T-cell lymphoma prognostic index, B symptoms and LDH<sup>10</sup>. Elderly patients are limited to receive some chemotherapy agents due to toxicity and mortality effects (13). The results published in their article showed that elderly patients have superior response to treatment with combination of radiotherapy and PGEMOX based in OS and PFS, as it provides a good response with less toxicity. In these studies, most patients had an ECOG between 0-1 and a median age of 65. The recommendation before choosing a treatment strategy is to evaluate patient’s comorbidities, clinical presentation, stage and physical status<sup>13</sup>. Based on this publication, which shows the largest study of ENKTL in elderly patients, Peg-Asparaginase was not included in our treatment approach due to comorbidities, age and risk for toxicity. Follow up for persistent or recurrent disease based on plasma EBV levels, as proposed by Suzuki et. al was not possible in this patient due to positive EBV DNA on tumor cells only, and not in peripheral blood.

In conclusion, here we present a rare case of NK lymphoma in a Puerto Rican patient, where to our knowledge, at present there is only one other case at present in a young patient in the Island. Our patient is an elderly man with good performance status but several comorbidities, placing him at risk of higher toxicity and mortality with treatment. The patient does not have known risk

### Resumen

El linfoma NK/T-cell (ENKTL), es raro en Occidente con menos de 1% en Estados Unidos a 8% en Asia entre todos los linfomas Non-Hodgkin. Es agresivo, con pobre pronóstico y el tratamiento óptimo no está bien definido. Una terapia de combinacion que incluye Peg-Asparaginasa se ha utilizado en pacientes jóvenes. Un paciente de 85 años se presentó con anorexia, epistaxis, vertigo y movimientos faciales involuntarios. Fue tratado con la toxina A Onabotulinum por sospecha de un espasmo hemifacial. Sin embargo, una tomografía computarizada (CT) demostró una lesion maxilar izquierda que se extendía a la turbina medial con una biopsia consistente con ENKTL. Ajustamos el tratamiento debido a edad y estado funcional del paciente, recibiendo Gemcitabina-Oxaliplatino (Gemox) con radioterapia obteniendo una respuesta completa. ENKTL es una enfermedad rara que en nuestro paciente inicialmente no fue identificada, eventualmente demostrando respuesta adecuada a un regimen terapéutico modificado.

### Legend

- ENKTL:** Extranodal Natural Killer Cell lymphoma
- EBV:** Epstein Barr Virus
- PET/CT:** Positron emission tomography
- NK:** Natural Killer
- RT:** radiotherapy
- NHL:** Non-Hodgkin lymphoma
- MRI:** Magnetic Resonance Imaging
- ORR:** Overall Response Rate
- OS:** Overall Survival
- LDH:** Lactate Dehydrogenase
- PFS:** Progression free survival
- CR:** Complete Remission
- ECOG:** Eastern Cooperative Oncology Group
- MRA:** Magnetic resonance angiography

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