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Angiocentric Centrofacial Lymphoma as a Challenging Diagnosis in an Elderly Man

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 72
Final Diagnosis: Angiocentric centrofacial lymphoma
Symptoms: Nasal obstruction • night sweats • occasional cough and pharyngeal dryness • rhinorrhea
Medication: —
Clinical Procedure: Nasal endoscopic biopsy
Specialty: Otolaryngology

Objective: Unusual clinical course

Background: Angiocentric centrofacial lymphomas, now known as nasal-type extranodal natural killer T-cell lymphomas, are neoplasms of highly destructive characteristics that mainly affect the nasal cavity and palate. The most frequent clinical presentation includes fever, weight loss, nasal obstruction, epistaxis, nasal or facial edema, as well as necrotic ulcers in the nasal cavity, gums, and palate. It has been found to have an important association with the Epstein-Barr virus. Diagnostic pathology could be difficult due to the typical widespread tissue necrosis.

Case Report: A 72-year-old Caucasian male sought medical attention with a chief complaint of nasal obstruction for the past 3 years, which only responded partially to unspecific treatment. He also presented with intermittent fever and nocturnal hyperhidrosis. Physical examination with rhinoscopy demonstrated a deviated septum, congestive turbines, and fragile and pale mucous membrane with yellowish, thick mucus. The pathology report described an angiocentric centrofacial lymphoma and a positive serology for Epstein-Barr virus.

Conclusions: The objective of this case report was to show that this illness represents a diagnostic challenge for the treating physician. It may be concluded that despite the poor prognosis of the disease, this particular case showed slower evolution and the patient remained stable despite multiple consecutive complications.

MeSH Keywords: Herpesvirus 4, Human • Lymphoma, Extranodal NK-T-Cell • Nasal Obstruction

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/913856

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Background

Angiocentric centrofacial lymphoma, now known as nasal-type extranodal natural killer T cell lymphoma (ENK/TL-NT) by the World Health Organization (WHO) since the year 2001 [1,2], is a neoplasm of destructive characteristics, but low incidence. It tends to affect mainly the nasal cavity and palate [3]. According to the 2016 WHO classification, ENK/TL-NT is considered within the category of mature T and NK neoplasms [1,4]. The ENK/TL-NT is known as "NK/T" (instead of "NK") although most cases derive from NK cells, they lack of T-cell receptor (TCR) gene rearrangement; there is a small proportion that may originate from cytotoxic T cells (αβ or γδ phenotype) [5–7] and another variety of the disease in about 20% of the cases, that might occur in extra nasal sites, with the most frequently affected locations described as the skin, pharynx, testicles, gastrointestinal tract, and kidneys [8,9].

It usually affects males with a median age group of 56 years and is found in populations from Asian territories and Native Americans from Central and South America [5,10]. The most frequent clinical features include fever, weight loss, nasal obstruction, bloody rhinorrhea, nasal or facial edema, and necrotic ulcer lesions in the nasal cavity, gums and palate [11].

It has been sturdily associated with Epstein-Barr virus (EBV) since it has been detected in up to 95% of studied cases by either polymerase chain reaction (PCR) or the detection of cell-free EBV-DNA in serum or plasma [12–14]; these are also useful methods for quantification of tumor burden and estimation of residual disease [15,16]. It is also known that neoplastic cells harbor clonal episomal EBV [5,17], which can be detected by EBV-encoded RNA (EBER) *in situ* hybridization, is an important diagnostic indicator [10].

Diagnostic pathology could be difficult due to widespread tissue necrosis. NK/T-cell lymphomas show a classic histological pattern characterized by prominent angiocentric and angiodestructive growth associated with zonal tissue necrosis and ulceration [5,18,19]. The immunophenotype of neoplastic cells is crucial in order to differentiate T-cell from NK-cell lymphoma. Additionally, there are several phenotypic markers expressed in EBV which are also represented in the phenotype of normal T-cells [5].

In addition to the use of histopathology and immunohistochemistry as tools for the diagnosis of the disease, computed tomography (CT) could be useful for the evaluation of prognosis for overall survival (OS) and disease-free survival (DFS) [20,21].

To differentiate NK-cells from T-cell lymphoma it is useful to evaluate the expression of sCD3, CD5, or T-cell receptors (TCRs) on the lymphoma cells [6]. CD30 is considered to be an indicator of "activated" B cells but it is also expressed in T cells and NK cells [14]. In addition, it has been reported that CD30 is frequently expressed in ENK/TL, perhaps due to the presence of EBV infection. Some studies have correlated CD30 expression with a better prognosis [16]. Its role, however, as a prognostic biomarker remains controversial but might be a potential therapeutic molecular target. In our patient, positivity for CD30 and positive EBV serology support the previous statement that this cluster of differentiation could be expressed.

Systemic chemotherapy is the first choice of treatment [13]. Radiotherapy may be effective in localized disease [9], despite this, it cannot prevent recurrence outside of the radiation field [4]. New treatment protocols have been reported in trials to improve outcomes [9]. Regardless, these neoplasms have a relatively poor prognosis [22], with 5-year survival rate between 38% and 64% [5,12].

Case Report

A 72-year-old Caucasian male sought medical attention with a 3-year history of nasal obstruction. The medical interview highlighted a maternal family history for breast cancer, diabetes mellitus, hypertension, and rheumatoid arthritis, as well as an aunt with stomach and kidney cancer.

The patient denied a history of smoking and drinking but referred to occupational exposure to formaldehyde in an electric workshop, and to starch and sulfur in a corn processing plant for 18 years. He had also been diagnosed with macular degeneration and hypertension, treated now with an angiotensin receptor blocker. Surgical history only included previous cholecystectomy.

The main objective of this article was to focus on reporting a case with an atypical progression yet the expected complications and features of the ailment to raise awareness and prevent a late stage diagnosis.

The patient arrived at the ENT (Ear, Nose and Throat) service with a chief complaint of nasal obstruction during the past 3 years. Initially, he was treated for rhinosinusitis by conventional medicine only once, and alternative medicine for 1 year. The symptoms intermittently improved for a couple of days and then returned with the same characteristics. He had also related his condition to exposure to air conditioning with an exacerbation of the clinical features, causing cough and pharyngeal dryness, opposed to temperate climates which would improve his condition.

The examination was positive for the presence of nasal crusts that caused discrete bleeding when detached, however, it was

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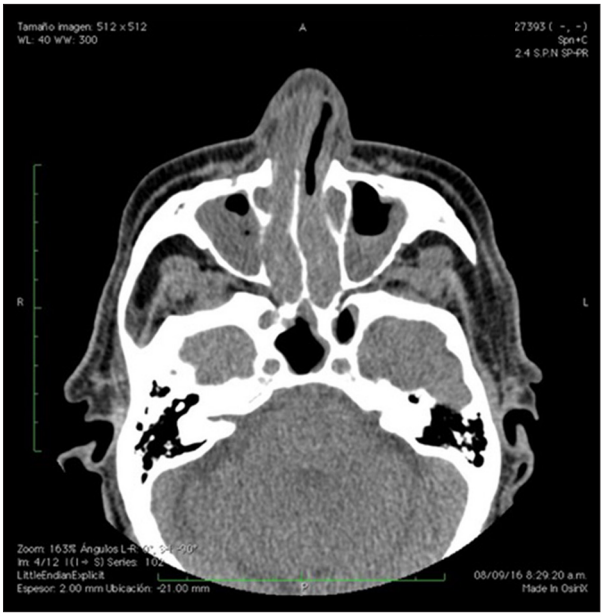

Figure 1. Axial computed tomography (CT) scan before diagnosis. Complete obstruction of right nasal duct and partial obstruction of bilateral paranasal sinus and left nasal duct.

negative for epistaxis. The patient complained of watery rhinorrhea associated with nasal edema without any specific triggers. He also reported violaceous macules located in the upper extremities, which can be attributed to capillary fragility. He would then present sporadic fever, which he did not quantify, and profuse nocturnal perspiration.

Rhinoscopy demonstrated a deviated septum, congestive turbines, and fragile and pale mucous tissue with yellowish, thick mucus. Paranasal sinus CT scan was ordered. Differential diagnoses considered at this point were Wegener Disease, Churg-Strauss, Kartagener's, sarcoidosis, rhinitis, and structural nasal defects (deviated septum, fracture, polyps).

Figure 1 shows the presence of complete obstruction of the maxillary sinus and partial obstruction of the nasal ducts. The Radiology Department reported an inflammatory change in nasal ducts and maxillary sinuses. Imaging was not clear enough to rule out the presence of nasal polyps nor granulomatosis diseases, although there were not erosive changes in any structure of the nasal septum nor paranasal cavities. The patient denied paranasal sinus pain, headache, epiphora, and odynophagia (Figure 1).

Treatment was instated with oral antibiotics, ciprofloxacin, and clavulanate-amoxicillin, and steroid-antihistaminic therapy with betamethasone and dexchlorpheniramine. The patient reported symptomatic improvement during the treatment, but once finalized, he relapsed.

Table 1. Immunohistochemical report: Antibodies associated to angiocentric centrofacial lymphoma are positive.

Immunohistochemical report		
Primary antibody	**Case D1705869**	**Witness**
CD30	Positive focal in immunoblasts (nonspecific labeling in plasma cells)	Adequate
TIA-1	Positive in T lymphocytes +++	Adequate
EBER	Positive in distribution corresponding to the T cell population +++	Adequate
PD1	Positive focal	Adequate
CD2	Positive	Adequate
CD25	Negative	Adequate
Primary antibody	**Case D1705869**	**Witness**
CD3	Positive +++	Adequate
CD20	Positive focal +	Adequate
CD4	Positive ++	Adequate
CD8	Positive ++	Adequate
CD7	Positive ++	Adequate
CD5	Positive +++	Adequate
CD56	Negative	Adequate
CD10	Negative	Adequate
Ki67	Positive	Adequate

Nasal endoscopic biopsy of the white tissue that was causing the nasal obstruction was performed whilst continuing treatment for the obstructive symptoms, with antihistaminic and mucolytic drugs. The Pathology Department reported an angiocentric centrofacial lymphoma along with a positive serologic result for Epstein-Barr virus. The patient denied knowledge of previous exposure or any treatment for this infection. Because of the atypical presentation of the disease, the sample was analyzed by several pathologists whom concluded the same diagnosis.

Immunohistochemical report showed positivity for CD30, CD2, CD3, and CD5 which are highly suggestive for angiocentric centrofacial lymphoma (Table 1).

The patient was referred to Hematology Service and started oral corticoid therapy with dexamethasone 4 mg half a day,

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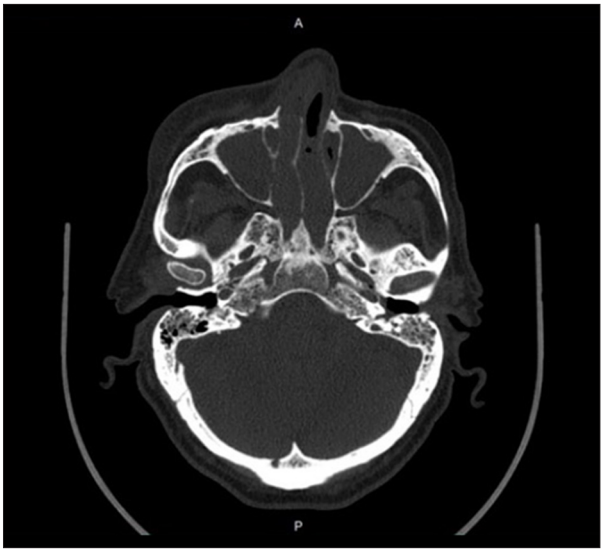

Figure 2. Axial computed tomography (CT) scan during hospitalization. Complete obstruction of right nasal duct and bilateral paranasal sinus, and periorbital edema of right eye.

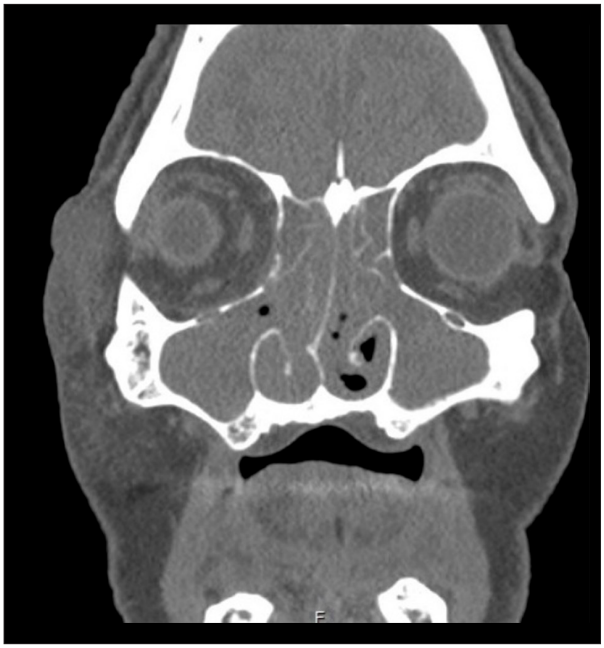

Figure 3. Coronal computed tomography (CT) scan during hospitalization. Complete obstruction of right nasal duct and bilateral paranasal sinus.

thalidomide 100 mg once a day, potassium once a day for 7 days, proton pump inhibitor 40 mg once a day, acetylsalicylic acid 100 mg once a day, vitamin B12 twice a day, sennosides in case of constipation and trimethoprim-sulfamethoxazole, eventually suspending the last one because of hypersensitivity reaction. Two months later, he suspended corticoid therapy because of the adverse effects (nephrotoxicity) and no significant improvement of the symptoms. Two weeks later without the treatment, a periorbital edema appeared and was promptly diagnosed as periorbital abscess and cellulitis at the hospital.

During his hospitalization, laboratory tests and imaging studies were taken. The most remarkable abnormal values at the first hematological biometry were leukocytosis, neutrophilia, and lymphopenia. But the second one, taken the next day, demonstrated a reduction of leukocytosis (14.64 to 11.34), a mild normocytic and normochromic anemia with a hemoglobin of 11.81 g/dL, hematocrit (Ht) 33.51%, mean corpuscular volume (MCV) 87.18 fl and mean cell hemoglobin concentration (MCHC) 35.24 g/dL. Neutrophils increased value to 84% (previously 77%). Blood chemistry was within the normal parameters, except for CRP, measured at 84.6 mg/L (reference lab value 0–10 mg/L). The next day it increased to 142.1 mg/L.

Paranasal sinus CT scan was ordered. Figures 2 and 3 showed in the transverse section, periorbital edema in the right eye, severe pansinusitis and complete obstruction of the right nasal duct and partial obstruction of the left side. Samples of the secretion from the abscess were taken for culture and antibiogram, which showed *Staphylococcus aureus* resistant to penicillin and ampicillin. Intravenous (IV) antibiotics (meropenem 20 mg/kg) were instated during his hospitalization. After hospital discharge, the patient went home with oral antibiotics (amoxicillin-clavulanate 875/125 mg bid (twice a day), loratadine-betamethasone 100/5 mg bid for 3 weeks, and gargles with nystatin 250 000 IU qid (4 times a day)) because of oral candidiasis. After a few months of intermittent antibiotic treatment (3 weeks with antibiotic therapy and 2 weeks of rest), the attending of Infectious Diseases Specialist changed treatment to clindamycin 300 mg and dicloxacillin 500 mg qid to prevent antibiotic resistance, with loxoprofen 60 mg tid (three times a day). The patient had an important improvement shown in the Figures 4–6.

The patient presented in 2 consecutive episodes a periorbital abscess in the same facial region, treated both times with the same therapy and drainage. Currently, his symptoms are under control without antibiotic therapy; and he has not presented any other complication since the last abscess.

Discussion

The case reported here was a nasal-type extranodal natural killer T-Cell lymphoma (ENKTL-NT), a rare neoplastic disease of destructive characteristics that first presents in the nose and/or paranasal area [4]. The common presentation of the disease occurs mostly in males at middle-age, and the compatible clinical features are predominantly nasal symptoms [23]. These are unspecific, because it could look like a sinonasal

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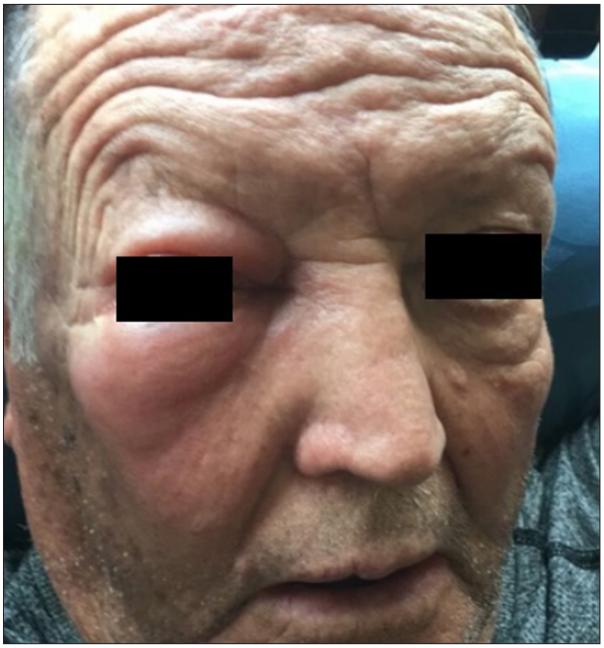

Figure 4. Patient with a periorbital abscess before hospitalization and treatment.

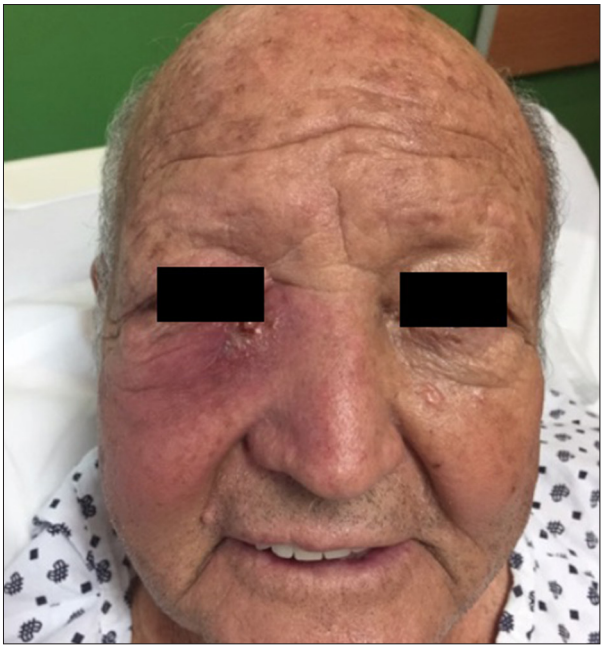

Figure 5. Patient during hospitalization and treatment for the abscess.

infection [24]. In most cases, the patient refers nasal obstruction, rhinorrhea, epistaxis, and nasal or facial edema [8]. This particular case had shown nasal obstruction and discharge for 3 years, but never facial edema or epistaxis.

The disease tends to be very localized initially, although dissemination is common. In the case of our patient, he had not had any invasion to adjacent tissues nor destructive lesions of the nasal skin or nasopharynx. ENK/TL-NT has been associated to EBV, a virus from the *Herpesviridae* family. It is generally transmitted through saliva and infects more than 90% of all adults. If the primary infection is acquired at an early age it might or might not cause symptoms, on the other hand, if it occurs later in life it may cause infectious mononucleosis [9]. Our patient presented positive serology for EBV, but it had not been previously detected or treated, which suggested an asymptomatic infection.

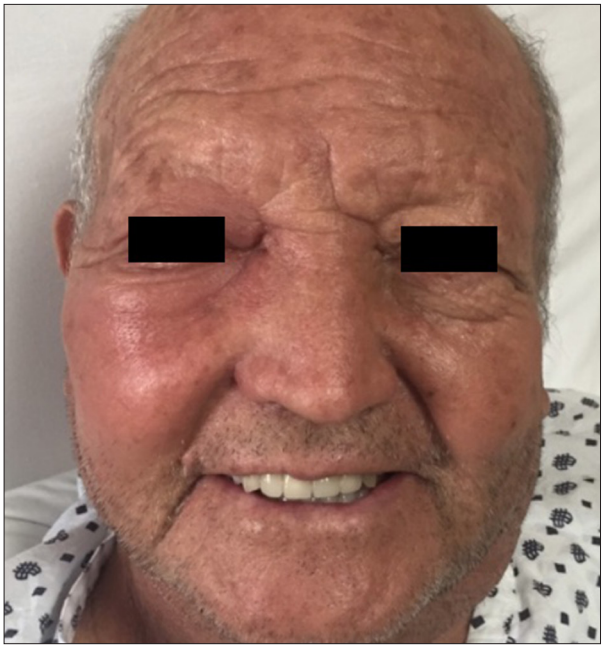

Figure 6. Patient after treatment for the abscess.

It is important to mention that this disease does not always behave as expected. Frequently, histological diagnosis is difficult and multiple biopsies might be required to confirm the diagnosis [25], in this case, the samples of the patient were analyzed by several pathologists in order to confirm the diagnosis. The common immunophenotype of neoplastic cells is characterized by the expression of CD2, CD56 (principal marker of NK cell lineage) [12], cytoplasmic CD3ε without surface CD3 (sCD3), cytotoxic proteins (granzyme B, perforin), and T cell-restricted intracellular antigen (TiA1) [6–8]. Immunophenotype testing shown in Table 1, was positive for CD2, CD3, CD5, and CD30, but not for CD56, which are the main markers for NK cell lineage [26].

Even though there should be radiological features in these patients, just a few limited studies have investigated the radiological findings. Some of them suggest that local invasiveness is an important prognostic factor for poor overall survival (OS) and disease-free survival (DFS) in patients with ENK/TL-NT. On the other hand, a superficial infiltrative pattern predicts

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favorable OS and DFS in patients without local invasion [14]. In our patient, only occupation of the nasal sinuses with mucus was shown, but there was no evidence of invasiveness to adjacent structures such as zonal tissue of necrosis nor destruction.

Although the prognosis of this disease is somber, some studies suggest that in early stages of disease there is good response to radiation therapy [27], and systemic chemotherapy holds as the first choice of treatment [13]. The patient of this case did not need chemotherapy nor radiotherapy; he was controlled only with antibiotics and sinusitis treatment. Since his last hospitalization, the patient has used therapeutic control under temporary antibiotics, with the objective to prevent the recurrence of complications by the paranasal obstruction (periorbital cellulitis and abscess) [28–30], as well as with nasal decongestants to control and decrease obstruction symptoms.

Conclusions

Angiocentric centrofacial lymphoma, known as natural killer (NK) T-cell lymphoma, is a rare neoplasm that affects primarily the nasal cavity and paranasal sinuses. Despite being more common in middle-aged men, it should be considered as a possible diagnosis in elderly men with recurrent nasal affection. Regardless of its poor prognosis due to its invasive and destructive characteristics, this type of lymphoma is usually misdiagnosed at the beginning because of its similarity with other common inflammatory affections of the nasal and paranasal area. This type of lymphoma must be considered in any patient with atypical presentation and evolution despite of the conventional treatments.

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Conflicts of interest

None.

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