American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2016; 17: 934-938
DOI: 10.12659/AJCR.899922

Received: 2016.06.06
Accepted: 2016.09.21
Published: 2016.12.09

Nasal Type Extranodal Natural Killer/T (NK/T) Cell Lymphoma Presenting as Periorbital Cellulitis: A Case Report

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Conflict of interest: None declared

Patient: Male, 25
Final Diagnosis: Nasal type • extra nodal NK/T-cell lymphoma
Symptoms: Left periorbital swelling • redness • pain for 25 days • yellowish eye discharge associated • headache • fever
Medication: —
Clinical Procedure: —
Specialty: Otolaryngology

Objective: Unusual clinical course

Background: Extranodal lymphoma of the paranasal sinuses is a rare clinical entity seen in only 5–8% of extranodal lymphomas of the head and neck. Nasal natural killer/T cell lymphoma (Nasal NKTCL), which is a subtype of peripheral T cell lymphoma, constitutes about 1.4% of all lymphomas. NKTCL is usually diagnosed at a late stage because it presents with nonspecific symptoms in the early stages.

Case Report: We report the case of a 25-year-old male patient who presented with periorbital swelling treated as fungal sinusitis but proven to have NKTCL. We review the literature and discuss the clinical manifestations of the disease, its relation to EBV virus, the histological and radiological characteristics, the prognostic indicators, and treatment options. This case report shows physicians that NKTCL lymphoma can present as periorbital cellulitis, although few similar cases are found in the literature.

Conclusions: NKTCL is a destructive midline tumor that should be kept in mind as a differential diagnosis of paranasal sinus lesions to help in early diagnosis, which can improve the prognosis.

MeSH Keywords: Granuloma, Lethal Midline • Nose Neoplasms • Orbital Cellulitis • Sinusitis

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/899922

Background

Non-Hodgkin lymphoma presents in extranodal sites in about 40% of patients [1,2]. Extranodal lymphoma of the paranasal sinuses is a rare clinical entity seen only in 5–8% of extranodal lymphomas of the head and neck [1]. Nasal NKTCL, which is a subtype of peripheral T cell lymphoma, constitutes about 1.4% of all lymphomas [2]. It is a locally destructive tumor mainly affecting the midface (the nose, oropharynx and hypopharynx), hence its old name "lethal midline granuloma" [1]. In general, NKTCL presents with nonspecific symptoms. The nasal variety can cause nasal obstruction, epistaxis, extensive midfacial structure, involvement of the orbit causing proptosis, and, occasionally, the hard palate [2]. Orbital cellulitis is a lethal condition that can lead to blindness; it can be caused by trauma, upper-respiratory infection, and sinus infection, and the latter is considered an important cause in its development, especially in children [3].

In this case report we discuss a 25-year-old male patient with NKTCL who presented with periorbital swelling that had been misdiagnosed as fungal sinusitis, and was treated accordingly. It is rare for NKTCL to present as periorbital cellulitis, and very few similar cases are reported in the literature. We report the clinical presentation and review the literature on NKTCL to alert physicians to this condition.

Case Report

A 25-year-old male patient came to our Otolaryngology Emergency Department complaining of progressive left periorbital swelling, redness, and pain for 25 days, with yellowish eye discharge associated with headache and fever. He did not have night sweats, change in weight or appetite, or change in vision. He sought medical advice from an ophthalmologist 1 week prior to coming to our department, who diagnosed him as having preseptal cellulitis, and was discharged on antibiotics, but the symptoms did not improve.

On examination the patient was febrile with temperature 38.2°C, pulse 108, respiratory rate 20, and blood pressure 115/75. He had left periorbital swelling and redness with intact visual acuity and normal extraocular muscle movement, and some discharge was seen from the nose. Throat examination was normal. Complete blood counts (CBC) and kidney function test results were normal. Liver function test was normal except for a high level of lactate dehydrogenase (LDH), which was about 2100 Units/Liter (normal level 240–480 Units/Liter). The computed tomography (CT) scan showed total opacification of the left maxillary sinus and left ethmoidal sinus, with left periorbital soft tissue swelling (Figure 1).

The patient was admitted under otolaryngology care as a case of preseptal cellulites secondary to left maxillary and ethmoidal sinusitis, and was started on cefepime hydrochloride 1 g intravenously (IV) twice daily and clindamycin 600 mg IV 3 times daily, but without any improvement. As the patient was not improving, we performed functional endoscopic sinus surgery. Middle meatal antrostomy and anterior and posterior ethmoidectomy were done, and tissue was sent for histology. After the surgery, the symptoms did not improve; therefore, Amphotericin and Moxifloxacin were started, but he developed an allergic reaction to Amphotericin, so it was shifted to Voriconazole 426 mg IV twice daily.

The histopathology result showed atypical lymphocytes, and no fungal organisms were identified. Immunohistochemical stains were performed to evaluate the atypical lymphocytes; it was positive for CD3, CD5, CD8, UCHL-1, Granzyme, and CD56, and

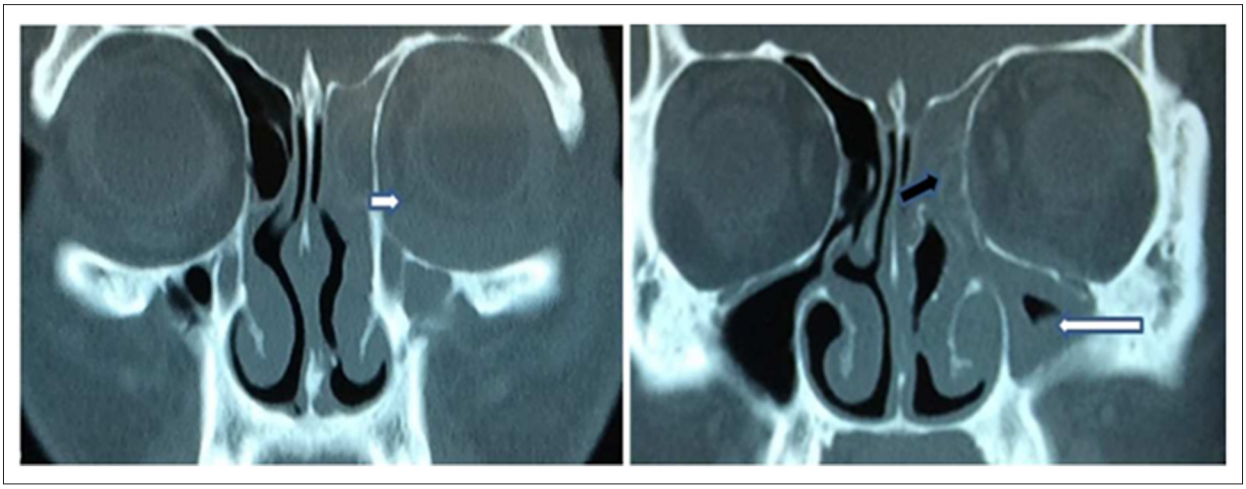

Figure 1. CT scan of paranasal sinuses demonstrating preseptal orbital edema (small white arrow), opacification of left maxillary (long white arrow), and anterior ethmoidal (black arrow) sinuses.

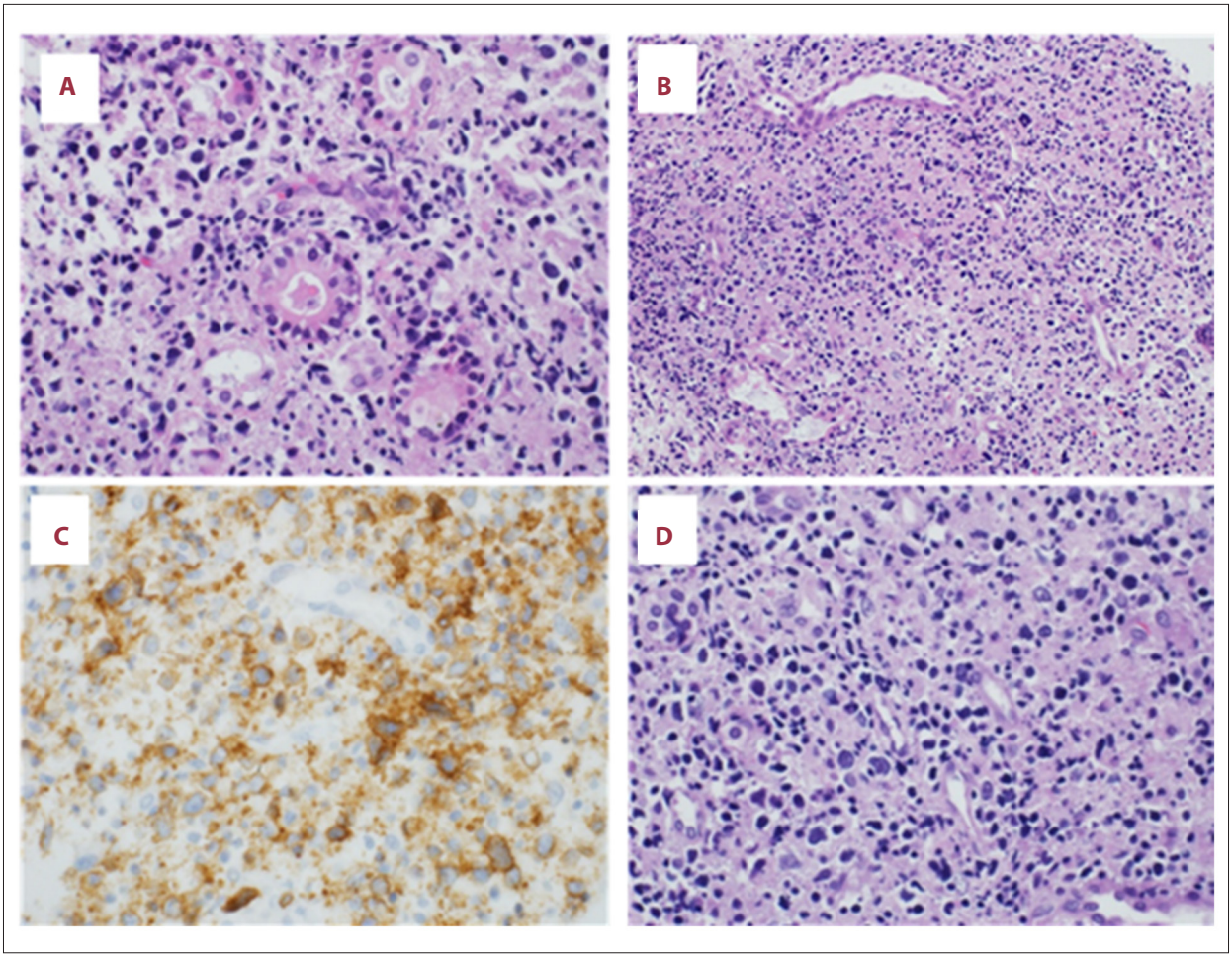

Figure 2. (**A**) 200×, H&E. Atypical lymphocytes with benign glands. (**B**) 100×, H&E. Infiltration of the mucosa with pleomorphic atypical lymphocytes. (**C**) 200×. IHC stain for CD56. (**D**) 200×, H&E. Pleomorphic atypical lymphocytes infiltrating the mucosa with occasional multinucleate cells.

negative for CK (AE/AE3), CD20, CD4, CD30, Alk, CD10, EBV, and CD43, and these features were consistent with NKTCL (angiocentric lymphoma) (Figure 2). The proliferation marker Ki-67 was not used on the specimen at the time.

The antimicrobial drugs were discontinued and a diagnosis of NKTCL was established. The patient was transferred to the oncology ward. CT scans of the chest and abdomen were normal. Bone marrow aspirate showed reactive hypercellular marrow with no obvious infiltration. No positron emission tomography (PET) scan was done.

SMILE protocol was started after a multidisciplinary team meeting with oncologists (Dexamethasone 40 mg day 2 to day 3, Methotrexate 2 g/m^2 day, Ifosfamide 1.5 g/m^2 from day 2 to day 4, along with Mesna and Etoposide 10 mg/m2 from day 2 to day 4). He also received intrathecal Methotrexate chemotherapy as a CNS prophylaxis. He tolerated the treatment very well. Granulocyte colony stimulating factor (G-CSF) was given after each cycle of chemotherapy. Before starting chemotherapy, quantitative polymerase chain reaction (PCR) for EBV on a peripheral blood specimen was positive (56457 International Unit/ml). After 2 cycles of treatment, a repeated CT scan showed complete resolution of the mass; he then received another 2 cycles of the treatment, and repeat EBV PCR was negative. No radiotherapy was performed.

Discussion

Extranodal NKTCL nasal type is an NK cell-derived neoplasm [4]. It usually affects the aerodigestive tract (e.g., nose, oropharynx, and larynx), but skin, gastrointestinal, and testis involvement can occur [5]. It is characterized by an angiocentric and angiodestructive pattern of growth with ulceration and necrosis [4], Superinfection can occur over these necrotic tissues, which can be misdiagnosed as an infectious process [5].

NKTCL is seen more in Asian and Latin-American countries, indicating some genetic association in its development [2,6]. It has a male-to-female ratio of 2: 1 to 3: 1 [2,6] and mainly affects patients in their 60s [6,7]. EBV also has a role in the development of this neoplasm [5]. The WHO requires both EBV-positivity and expression of cytotoxic granules for diagnosis of NKTCL [4].

In general, NKTCL presents with nonspecific symptoms. Weight loss, fever, night sweats, and anemia are usually only encountered in late stages [2]. Clinically, it can be divided into nasal and extranasal types [4]; the nasal variety commonly presents with nasal obstruction, but also it can cause epistaxis, extensive involvement of the midfacial structure, involvement of the orbit causing proptosis, and, occasionally, the hard palate [4,5,7]. Very few cases with periorbital cellulitis as the initial presentation of NKTCL have been reported in the literature, as we report in our case [8–10]. Termote et al. described 3 similar cases, all treated by chemo-radiotherapy, but they died within 5–35 months of diagnosis [8]. The other similar presentation was described by Kim JW et al. and was treated as sinusitis, but biopsies taken after relapses confirmed NKTCL diagnosis [9]. Three cases with periorbital involvement were reported by Charton et al; at first they were started on antibiotics until NKTCL diagnosis was confirmed by biopsy [10]. Skin is the most common site of extranasal involvement [7], but it can affect the gastrointestinal system, spleen, and testes [5]. Muscles and adrenal glands are rarely involved [4]. The extranasal type usually disseminates early in the course of the disease [4,5], but most were found to have occult nasal primaries [11].

Histologically, the neoplasm shows ulceration; angiocentric and angiodestructive growth is seen with areas of necrosis and lymphocytic infiltration with irregular nuclei on the surface of the epithelium and subepithelium, which is called polymorphic reticulosis [4]. The immunophenotypes of these tumors are CD2+, CD56+, and cytoplasmic CD3ε+. Cytotoxic molecules (Granzyme B, TIA-1, and Perforin) are positive [5], and often show negative expression of T cell antigen (e.g., CD4, CD5, and surface CD3) and negative for B cell marker CD20 [6]. The tumor tends to cause coagulative necrosis in the tissue, so a large biopsy should be taken [6,11]. Nasal panendoscopy should be done irrespective of the primary site of presentation [11].

Imaging can be useful in these tumors, and CT and magnetic resonance imaging (MRI) can demonstrate the extent of the disease; however, FLourine-18 fluorodeoxyglucose positron emission tomography computerized tomography (18-FDG PET-CT) has better sensitivity [2,4]. Quantification of Plasma EBV DNA level by PCR correlates with the disease status of the patient, and can be used as a marker for tumor load [5,11]; a high titer indicates extensive disease, poor response to therapy, and poor survival [5]. Serial EBV DNA can be used to monitor the response to treatment [11]. Many patients with NKTCL are hepatitis B carriers, and antiviral prophylaxis should be given during chemotherapy [11].

The prognosis of the disease is variable; it is generally poor, with a 30% 5-year survival rate, but it recently increased to 71% due to utilizing intensive therapy like up-front radiotherapy [5]. Multiple factors affect the prognosis: age of the patient, stage of disease, EBV DNA level, number of extranodal sites, LDH level, and regional lymphadenopathy [4,5,12]. Extranasal NKTCL in general has a worse prognosis than nasal type, as patients tend to have B symptoms (fever, night sweats, and weight loss) and involvement of the lymph nodes [13].

A combination of radiotherapy and chemotherapy is the best modality of treatment, especially for the early stages [14], because of the high recurrence rate when radiotherapy alone is used [4,6]; radiation alone has a 77–100% repose rate (RR) for localized early-stage nasal NKTCL, with 25–40% systemic relapse rates [11]. This tumor shows a poor response to CHOP regimen (Cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone), with a high relapse rate [11]. The RR for this regimen followed by radiotherapy is 58%, 3-year survival is 59% for early-stage nasal NKTCL [11], and CHOP with surgery has an RR of 69% if used to treat localized disease outside the nasal cavity [11]. Regimens like SMILE (Dexamethasone, Methotrexate with Leucovorin, Ifosfamide, L-asparaginase, and Etoposide) can be used instead, as it is based on non-P glycoprotein efflux chemotherapy agents like L-asparaginase, Ifosfamide, and Methotrexate [11]; it has an 86% RR. If radiotherapy is used, the RR increases to 89.7% and the response is durable [11]; it has 64% 4-year disease-free survival rate for early-stage nasal NKTCL [11]. Utilizing intrathecal Methotrexate as CNS prophylaxis in T cell lymphoma patients is controversial, and some authors do not recommend it because CNS relapses are rare in T cell lymphoma and there is insufficient data to show its efficacy in preventing CNS events [15]. Some studies found that intrathecal Methotrexate injection may add more toxicity to the patients, especially when compared to its efficacy [16].

Conclusions

NKTCL is a rare and destructive midline tumor that can be easily misdiagnosed as other more common inflammatory processes, and this can delay the treatment. The prognosis is usually poor because of the destructive nature of the disease and delayed diagnosis. The differential diagnosis of NKTCL should always be kept in mind for any lesion of the paranasal sinuses with atypical presentation and non-responsive to conventional treatments.

Conflict(s) of Interest

None.

Financial support

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

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