

Case Report

Aggressive natural killer/T-cell lymphoma masquerading as acute orbital hemorrhage: a case report

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Abstract: Natural killer T-cell lymphoma (NKTCL) is a highly aggressive tumor that usually affects the nasal cavity and/or paranasal sinuses. Primary orbital NKTCL is extremely rare, with only a few cases reported in the literature. The clinical presentation of orbital involvement by NKTCL is atypical and usually misdiagnosed as orbital cellulitis or orbital pseudotumor. A 23-year-old male patient was admitted to our hospital complaining of severe eye pain and manifested as acute orbital hemorrhage. Isolated orbital natural killer T-cell lymphoma (NKTCL) was confirmed by biopsy. This patient's orbital NKTCL did not respond to CHOP (cyclophosphamide, epirubicin, vincristine, prednisone) chemotherapy, but shrank significantly after receiving 1 cycle of C-SMILE (chidamide, steroid, methotrexate, isophosphamide, L-pegasparase, etoposide). However, he still died after 3 cycles of C-SMILE chemotherapy at a follow-up time of 4 months. Primary orbital NKTCL can present clinically as a rare acute orbital hemorrhage, and the disease is aggressive and has a poor prognosis.

Keywords: Nasal natural killer/T-cell lymphoma, orbital hemorrhage, orbital lymphoma, SMILE regimen

Introduction

Non-Hodgkin's lymphoma (NHL) is the most common malignant orbital tumor in adults. The majority of orbital lymphomas are mucosa-associated lymphoid tissue (MALT) lymphomas, followed by follicular lymphoma (FL) and invasive lymphomas such as diffuse large B-cell lymphoma (DLBL) and mantle cell lymphoma (MCL) [1]. Natural killer T-cell lymphoma (NKTCL) is one of the rare types of orbital NHL. It may present as extranodal NKTCL (or nasal type) or aggressive natural killer cell leukemia [2, 3]. Nasal NKTCL is highly malignant, progresses poorly, and develops rapidly [4, 5]. It is usually found in the nasal cavity and/or paranasal sinuses. Other common sites of involvement include the skin [6, 7]. Primary orbital involvement of nasal NKTCL is extremely rare and challenging to diagnose clinically. Atypical clinical manifestations of NKTCL presenting with red eyelids, edema, proptosis, and restricted eye movements may be misdiagnosed as orbital cellulitis or orbital pseudotumor [8-12]. We present here a case of orbital nasal NKTCL

in a young patient, with a rare clinical presentation of acute orbital hemorrhage that rapidly progressed and had a poor prognosis.

Case report

A 23-year-old male patient was admitted to the ophthalmology emergency department with worsening periorbital pain, exophthalmos, and severe ptosis of the left eye for two days. Two months ago, he had a history of alternating conjunctival redness and swelling in both eyes, which subsided after treatment with antibiotics and dexamethasone (DXM). The upper and lower eyelids of the left eye were markedly red and swollen. The visual acuity of the left eye was only light perception and positioning was not accurate. The intraocular condition of the left eye could not be assessed due to severe ptosis and high orbital pressure (**Figure 1A**). On emergency admission, a diagnosis of acute orbital hemorrhage was considered, and emergency orbital decompression surgery was planned. However, an emergency orbital computed tomography (CT) scan showed dense

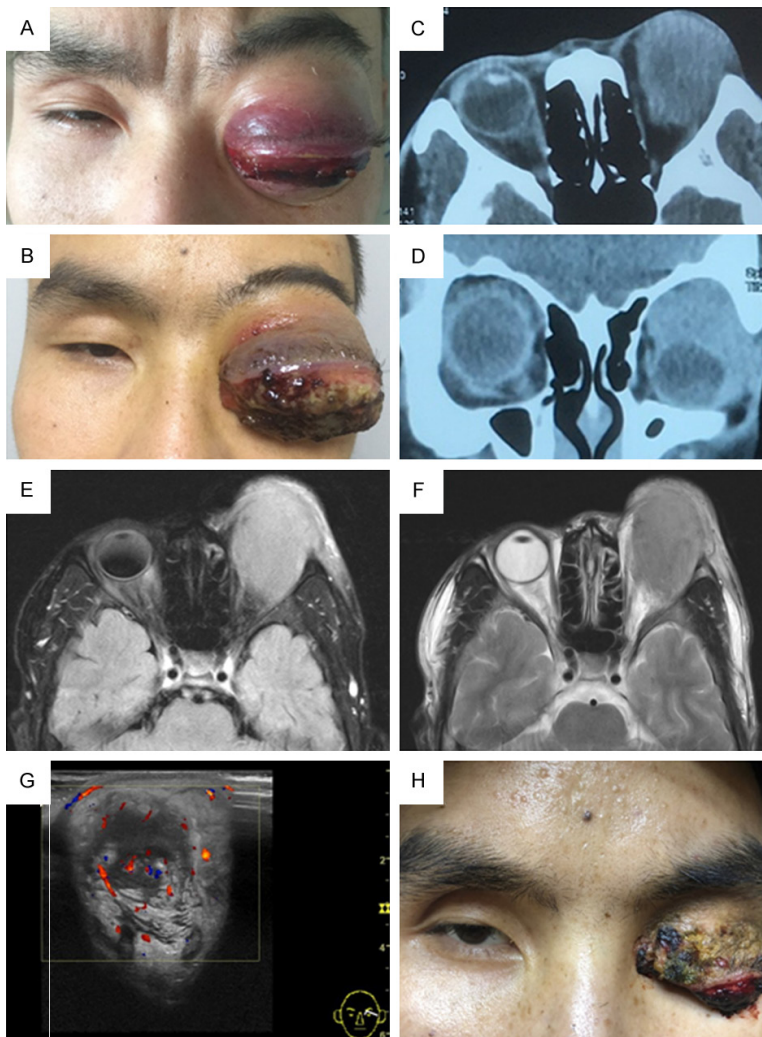


Figure 1. A. Initial presentation with exophthalmos, ptosis, redness and swelling of left eye; B. The mass enlarged with ulceration and necrotic tissues at two weeks after admission to the hospital; C and D. Orbital CT scan (axial and coronal view); E and F. Magnetic resonance T1 and T2 imaging (axial view); G. Ocular color Doppler ultrasound; H. The patient received 3 cycles of C-SMILE (chidamide, steroid, methotrexate, Isophosphamide, L-pegaspargase, etoposide) chemotherapy treatment.

packing of the left orbit by soft tissue (**Figure 1C** and **1D**). Emergency ocular color Doppler ultrasound showed a 39*35 mm irregular hypoechoic mass in the left eye containing abundant blood flow signals (**Figure 1G**). Considering the left orbital mass, orbital decompression surgery was cancelled. Then orbital magnetic resonance imaging (MRI) showed homogeneous high signal intensity on T1-weighted images (T1WI) and homogeneous low signal intensity on T2-weighted images (T2WI) of the soft tissue mass in the left eye (**Figure 1E** and **1F**). An incisional biopsy was performed. The results of immunohistochemical staining sh-

owed that the tumor cells were strongly and diffusely positive for CD3, CD56, and granzyme B (**Figure 2B** and **2C**). The positive rates of Ki-67 and c-myc by tumor cells were 70% and 30%, respectively. In situ hybridization for Epstein-Barr virus (EBV)-encoded mRNA (EBER) was strongly positive (**Figure 2D**). The final diagnosis was extranodal NK/T-cell lymphoma of nasal type.

The patient was transferred to the hematology department for further treatment. There was no enlargement of systemic lymph nodes. Bone marrow biopsy and lumbar puncture did not reveal any metastasis. Tumor had no infiltration of nasal cavity and brain. A positron emission tomography computed tomography (PET-CT) scan revealed a hypermetabolic mass involving the left orbitopathy and adjacent skin, liver, spleen, pelvic bone marrow, cervical spine, thoracic spine, and lumbar spine. The patient was started on one cycle of CHOP (cyclophosphamide, epirubicin, vincristine, prednisone) chemotherapy but did not respond well. The chemotherapy regimen was then changed to C-SMILE (chidamide, steroid, methotrexate, Isoph-

osphamide, L-pegaspargase, etoposide), and the tumor shrank significantly after one cycle of treatment (**Figure 1H**). However, he still died 4 months after the initial diagnosis and 3 cycles of C-SMILE treatment.

Discussion

Extranodal NKTCL usually occurs in Asian, native American, and Hispanic patients [4]. A study found that only 3 of 84 patients with extranodal NKTCL had primary orbital involvement, and no nasal infiltration was detected in these patients [13]. Meel et al. [9] reviewed 16 case reports of isolated orbital NKTCL from

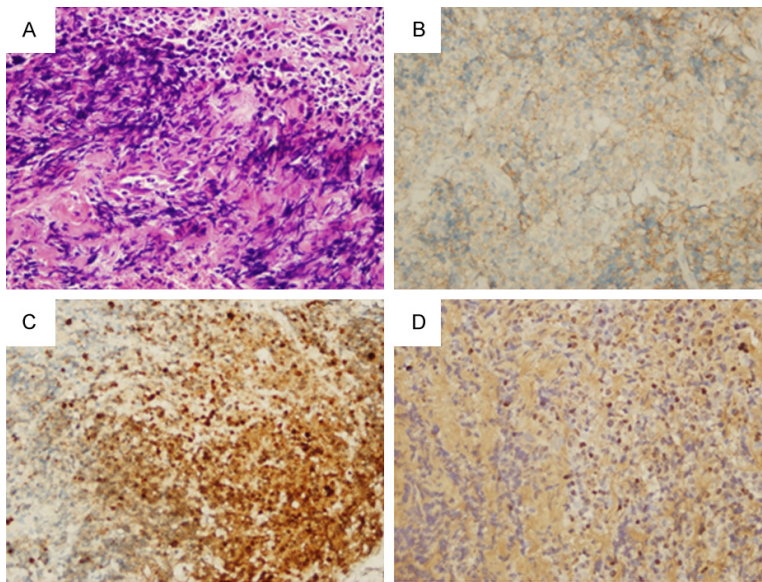


Figure 2. A. Hematoxylin and eosin staining shows abundant lymphocytes and necrotic tissue ($\times 40$); B. The tumor cells are positive for CD56 ($\times 40$); C. The tumor cells are positive for Granzyme B ($\times 40$); D. The tumor cells are positive for EBER ($\times 40$).

1999 to 2016. The age of the patients was 51.63 ± 17.97 (22, 81) years, the male to female ratio was 1:1, and most of the patients had unilateral eye involvement. Our patient was a 23-year-old man with monocular involvement, who was younger than previously reported in the literature.

The ocular clinical manifestations of NKTCL are based on infiltration of the eye or orbit. Intraocular infiltration of NKTCL, also named “camouflage syndrome”, manifests as uveitis or endophthalmitis, and might lead to macular holes, and retinal detachment. Orbital expansion of the NKTCL results in painful conjunctival chemosis, proptosis, and restricted extraocular movements that might masquerade as orbital cellulitis, orbital inflammatory pseudotumor, or inflammatory myositis [14]. Marchino et al. reported a patient with primary orbital NKTCL, initially regarded as left orbital cellulitis due to presentation with left periorbital pain, eyelid edema and erythema, proptosis, restricted extraocular movements, and fever [5]. Kiratli et al. [12] described a 57-year-old man with conjunctival NKTCL who presented with diffuse growth of a salmon colored mass under the entire bulbar conjunctiva. Meel et al. [9] showed a young woman with solitary orbital NKTCL who presented with plump lower eyelid and tearing, initially presumed to have an orbital pseudotumor. Orbital NKTCL should be consid-

ered if the patient presents with proptosis, restricted extraocular movements, decreased visual acuity, and signs of ocular/orbital inflammation, but does not respond well to antibiotics or steroids.

In our case, this young patient had swollen red eyelids and a dramatic increase in orbital pressure initially thought to be a spontaneous acute orbital hemorrhage. He was scheduled for emergency orbital decompression surgery. However, imaging showed a diffuse mass located around the entire eyeball, and the extraocular muscles and optic nerve were not clear. The mass grew so fast outside the upper eyelid and fornix that the eyeball was completely covered,

resulting in complete loss of vision. A previous study reported a high rate (25%) of sight-threatening complications in 24 patients with nasal T/NK lymphoma [15]. The orbital lesion grew so rapidly in our patient that we felt even urgent orbital decompression surgery could not save vision.

Not only is orbital NKTCL difficult to diagnose based on clinical presentation, but pathologic biopsy diagnosis is also a challenge. Extranodal NKTCL is a cytotoxic lymphocytic lymphoma characterized by vascular destruction and necrosis. Ulcer lesions with chronic inflammation and necrosis can obscure the visibility of tumor cells [4, 17]. The EB virus was found to be associated with this disease and was detected in almost every patient [18]. Diagnosis of extranodal NKTCL according to WHO classification criteria [2] requires the presence of EB virus in tumor cells.

There is no standard treatment for primary orbital NKTCL. Yang et al. [7] performed surgical resection of orbital NKTCL in 7 patients. They found that the tumor could not be completely resected due to clinical features such as indistinct tumor borders, friability, easy bleeding, and much necrotic tissue. But they still recommend removing the tumor as much as possible when performing biopsy to confirm the diagnosis. Chemotherapy combined with radiotherapy sequential or concomitant therapy has

become the mainstay of treatment for orbital NKTCL [19-22]. Conventional CHOP chemotherapy regimens have poor results and high mortality. The currently recommended SMILE chemotherapy regimen has good efficacy even for patients with stage IV relapse or refractory disease, with an overall response rate of 79% [23]. Meel et al. [9] reported a case of primary orbital NKTCL in a young woman who responded very well to chemotherapy with the SMILE regimen in combination with radiotherapy, and the patient was in remission at 2-year follow-up. However, the prognosis of extranodal NKTCL with primary orbital involvement is very unfavorable due to tumor progression and/or recurrence, and systemic chemotherapy adverse effects. Kiratli et al. [12] reported a 57-year-old man with extranodal NKTCL who initially responded well to chemotherapy and local radiotherapy, but died 11 months later due to systemic dissemination. Marchino et al. [5] reported a 67-year-old woman with non-nasal primary orbital NKTCL who received 2 cycles of CHOP and 2 cycles of SMILE chemotherapy without clinical response and died 10 months later. Hematopoietic stem cell transplantation has been mentioned as a consideration for patients who fail to respond to chemoradiotherapy or achieve a stable response [24, 25]. Our patient presented clinically with localized orbital lesions, but PET-CT showed multiple hypermetabolic lesions throughout the body. The patient did not respond to initial CHOP therapy, and the tumor rapidly regressed after switching to the C-SMILE regimen, but the patient still died 4 months later, which is consistent with previous studies showing poor NKTCL survival [26]. Thirteen patients with isolated orbital NKTCL died at 5.75 ± 4.05 (1, 14) months, and only three patients reported survival of 8, 24, and 64 months, respectively [8].

Primary extranodal orbital NKTCL is a rare disease with high malignancy and poor prognosis. We report a case of atypical clinical presentation that could be acute orbital hemorrhage and requires the attention of ophthalmologists and oncologists.

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Disclosure of conflict of interest

None.

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