Case Report

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Two young patients with extranodal natural killer/T-cell non-Hodgkin lymphoma, nasal-type (ENKTL-NT) masquerading inflammatory processes: A case series

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Abstract:

Extranodal natural-killer/T-cell lymphoma (ENKTL) is a rare type of non-Hodgkin lymphoma. However, it is common in Asia and South America. ENKTL, nasal type (ENKTL-NT), predominantly presents initial unspecific clinical manifestations involving the nasal cavity and its adjacent structures. We present two cases to increase the awareness of the ENKTL-NT cases masquerading inflammatory processes. Although the main clinical feature is a rapidly progressive facial destruction, none of these patients experienced the mentioned complaint. Its various manifestations frequently lead to misdiagnosis and delayed treatment, particularly in those with marked ocular, not nasal symptoms. Our patients were previously diagnosed with inflammatory conditions, namely sinusitis, idiopathic orbital inflammation, dacryocystitis, and orbital cellulitis. The combined approach of chemotherapy and radiotherapy has been proposed as the treatment of choice. Both cases showed young adults treated with combined therapy, yet showing poor outcomes. Clinicians should be aware of its existence and have to consider ENKTL-NT as one of the differential diagnoses in sinonasal or orbital inflammatory cases with unusually rapid progression or unresponsive to treatment.

Keywords:

Dacryocystorhinostomy, functional endoscopic sinus surgery, nasal type, non-Hodgkin lymphoma, orbital cellulitis, sinusitis

Introduction

Extranodal natural-killer/T-cell lymphoma (ENKTL) may be subdivided into "nasal-type" based on its primary anatomical involvement.[1] Among all recognized natural-killer (NK) cell proliferation, one of the most inferior outcomes come from ENKTL, nasal type (ENKTL-NT). ENKTL-NT is a rare, highly aggressive, Epstein–Barr virus (EBV) associated non-Hodgkin lymphoma which found slightly higher in men. This type of lymphoma encompasses only 5%–8% of head and neck extranodal lymphoma, with a higher incidence in East Asia and South and Central America.[2,3] It usually presented as initial nonspecific features, including nasal obstruction, purulent discharge, epistaxis, which then progressed into destructive lesions.[1,4-7] Recently, tremendous literature has discussed the clinical features, diagnosis, treatment, and prognosis of ENKTL-NT, yet its early recognition remains perplexing.[8] Furthermore, patients with marked ocular symptoms are more likely to be misdiagnosed than those with nasal symptoms. Thus, to diagnose ENKTL, particularly in ophthalmology clinic settings, need a high suspicion index.[8,9] We present two cases that expectantly promote the

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awareness of ENKTL-NT's various clinical presentations ended with unsatisfactory outcomes, although the combined approach has formerly given.

Case Reports

Case 1

A 34-year-old woman was referred to the Ocular Oncology Clinic of our tertiary hospital in Jakarta, Indonesia, with a complaint of a unilateral mass on her left eyelid for 1 month [Figure 1]. She had a history of functional endoscopic sinus surgery (FESS) before at the previous hospital due to left maxillary sinusitis, which confirmed only by paranasal sinus X-ray. One day after the FESS procedure, she complained of a painless, progressively enlarging mass extending from the lower to the upper left eyelid. She denied the history of redness, pain, bleeding, blurred vision, nasal congestion, nor epistaxis. Paranasal sinus multi-slice computed tomography (MSCT)-scan revealed a distinct border, hypodense lesion at the left inferior maxillary soft tissue, suggestive as soft-tissue tumor. Orbital magnetic resonance imaging (MRI) showed an oval ring-enhance cystic lesion with a size of 1.3 cm × 2.5 cm × 1.9 cm found in the inferior left eyelid, suspected as a chalazion [Figure 2].

Upon ophthalmological examination, there was a hyperemic, tender mass with a 3 cm diameter size on her left inferior eyelid. The examination and previous imaging modalities strongly suggested idiopathic orbital inflammation as the diagnosis. We decided to give the patient trial corticosteroid treatment for 2 weeks. Two weeks follow-up revealed unresponsiveness to the treatment, then we immediately performed an incisional biopsy and complete workup by the Internal Medicine Department. The laboratory tests later showed anemia (hemoglobin 10.8 g/dl and hematocrit 31.8%), leukocytopenia (3.3 × 103/μL), normal kidney and liver function test, nonreactive hepatitis B surface antigen, and Anti-hepatitis C virus [Figure 1a and b].

After a month, she represented with the extending mass to the left superior palpebra, with a size of 5 cm × 3 cm × 2 cm in the superior and 6 cm × 3 cm × 2 cm at the inferior palpebra. Histopathological examination later revealed diffuse, lymphocyte cells and eosinophilic cytoplasm with an indistinct edge, along with starry sky appearance and congestive vascular structure surrounding the mass. This presentation is indicative of a high grade non-Hodgkin malignant lymphoma [Figure 1c].

Immunohistochemistry showed positive results for CD3, Mum1, Ki67 95%, CD99, CD56, Perforin, Granzyme, lithocholic acid, and negative results for CD20, CD10, CD79a, Ccl6, and TdT, concluded as ENKTL-NT. *In situ* Epstein–barr coded RNA (EBER) hybridization showed positive results for the majority of cells. The patient was then confirmed as ENKTL-NT [Figure 3].

Systemic work-ups were done – reevaluation of laboratory examination showing persistent anemia and leukocytopenia. Echocardiography, thorax X-ray, abdominal ultrasound (USG), and bone marrow puncture were within the normal limits. However, thoracic MSCT-scan revealed a solid nodule found at the isthmus of the right thyroid lobule and dilatation of inferior vena cava, hepatic vein, and bilateral renal vein suspected of the inferior vena cava thrombus.

Three weeks after the diagnosis has been established, the patient was scheduled to undergo chemoradiotherapy, with radiation of 45 Gray (25 cycles of 1.8 Gray) and 5 cycles of chemotherapy with Cisplatin regimen 62 mg/weeks (40 g/m^2). After 14 cycles of 1.8 Gray radiotherapy and three cycles of cisplatin regimen, the mass became smaller without noticeable elevation [Figure 1d and e]. Nevertheless, the mass subsequently enlarges around 6 weeks after the patients completed chemoradiotherapy. There were also complaints of two lumps, each on the left thigh and the umbilicus. Fine-needle aspiration biopsy showed a positive result for non-Hodgkin malignant lymphoma for the sample aspirated from the femoral lymph node. The abdominal MSCT-scan revealed mild splenomegaly. The patient was then planned for adjuvant

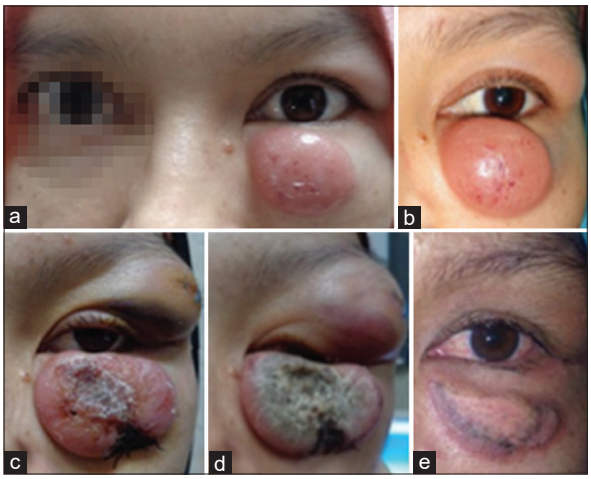

Figure 1: Case 1 Clinical presentations: (a) at the initial visit. (b) two weeks after systemic corticosteroid therapy. (c) post biopsy (one month after initial visit). (d) before chemoradiotherapy. (e) after complete chemoradiotherapy

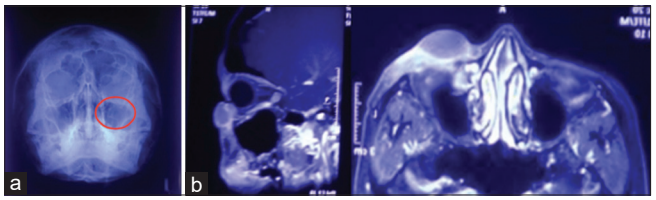

Figure 2: Case 1 Imaging Findings: (a) paranasal sinus x-ray suggested left maxillary sinusitis. (b) Orbital MRI revealed oval ring-enhanced cystic lesion suggested as chalazion

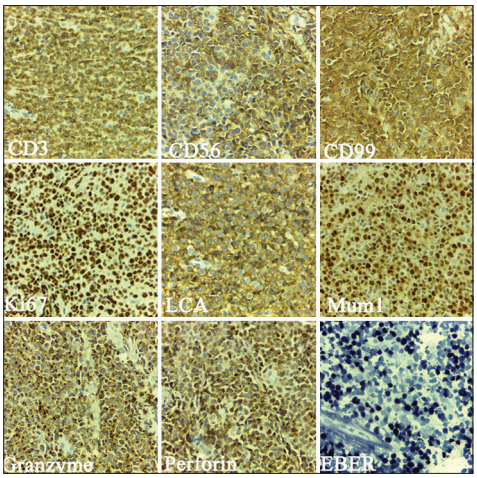

Figure 3: Case 1 Immunohistochemistry and *in situ* hybridization of ENKTL-NT showed positive results for CD3, CD56, CD99, Ki67 95%, LCA, Mum1, Perforin, Granzyme. *In situ* hybridization Epsteinn-Barr coded RNA (EBER) showed positive results for the majority of cells

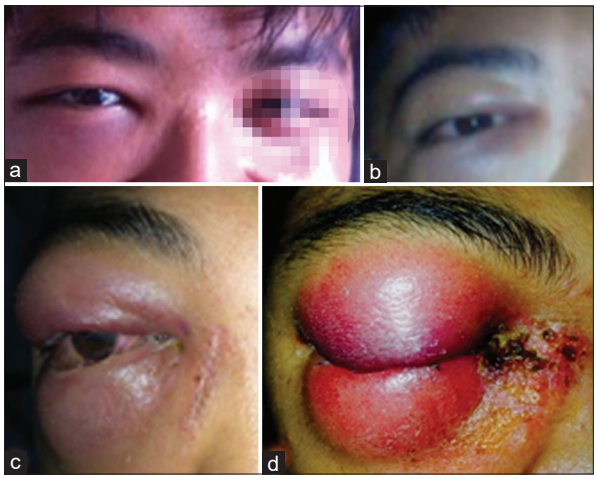

Figure 4: Case 2 Clinical Presentations: (a) RE mild swelling before DCR. (b) five days after DCR, swelling reappeared. (c) first visit to our hospital, two weeks after sinus debridement. (d) worsened eyelid swelling at second visit

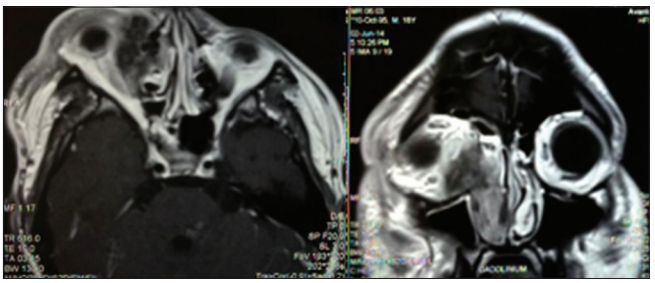

Figure 5: Case 2 Imaging Findings: Orbital MRI revealed edema and haziness of enhanced lesion concluded as inflammatory process

chemotherapy with the DEVIL regimen (carboplatin 280 mg, etoposide 90 mg, uromitexan 400 mg, ifosfamide 1400 mg, and uromitexan 1000 mg) per day for three consecutive days. Serial blood samples collection during inpatient admission revealed pancytopenia, for details: hemoglobin 9.1–10.7 mg/dl, hematocrit 29.2%–32.5%, leucocyte (3.08–4.92 × 103/μL), and thrombocyte (9.9–13.5 × 103/μL). Besides, there were also hyponatremia and hypomagnesemia at admission. The patient was lost to follow-up after completed adjuvant chemotherapy due to financial constraints. Unfortunately, at a 1-year follow-up, she died due to systemic involvement.

Case 2

An 18-year-old male came to the Emergency Department of Cipto Mangunkusumo Hospital, Jakarta, with a chief complaint of worsening right eyelid pain and swelling for 2 weeks before admission. He first experienced right eyelid pain, discharge, mild swelling, accompanied by high fever, and then decided to go to an eye hospital. The ophthalmologist suggested dacryocystorhinostomy (DCR) to be done without any confirmation by imaging modalities [Figure 4a].

The complaints of eyelid pain and swelling were immediately improved after the procedure but reappeared after 5 days. Computed tomography (CT) scan showed a mass suspicious of mucocele or polyp at the right maxillary sinus with the septum deviation. Besides, MRI revealed edema and haziness of enhanced lesion at the right medial orbit, concluded as an inflammatory process [Figure 5]. The patient was diagnosed with orbital cellulitis and suspicious of sinusitis [Figure 4b].

He was hospitalized for 5 days, given intravenous antibiotics, and suggested for sinus debridement. During surgery, the ear-nose-throat specialist found a mass at the sinus, and then proceed to biopsy. The pain and swollen eyelid were decreased for several days, but later getting worse. The Visual Analog Scale (VAS) score was 8 due to these complaints and high fever, he decided to go to our tertiary hospital's emergency department. Epistaxis was noted during the admission.

On his first visit, the ophthalmological examination showed the best-corrected visual acuity was 20/40 for the right eye (RE) and 20/20 for the left eye (LE). Intraocular pressure was 23.8 and 13.5 mmHg for RE and LE, respectively. The RE showed proptosis, periorbital swelling, hyperemia, and eyelid spasm. Restricted ocular motility in all directions was found. The inferotemporal conjunctiva was chemotic; pupils were normal. Fundus examination was within the normal limits. Sinus CT scan demonstrated enhanced soft-tissue lesion with an indistinct edge after contrast injection involving both superior and inferior palpebra, bilateral canthus, especially medial and reach cutis-subcutis. Extensions were seen in periorbita, anterior maxilla, and zygoma. The lesion pushed the inferior and medial rectus and also inferior oblique muscle with marked proptosis. There were no abnormalities of the optic nerve, extraocular muscles, and no bony erosion was found [Figure 4c].

The patient was suspected orbital cellulitis of the RE, then administered topical medications, including antibiotics, timolol 0.5%, and artificial tears. Besides, he also has given oral analgetic and intravenous steroid, metronidazole, and ceftriaxone. On the 2nd day of admission, the histopathological results from the previous hospital revealed diffuse tumors consisted of lymphoid cells with extensive necrosis and angioinvasion, suggestive a malignant non-Hodgkin lymphoma. Intravenous steroid injection was stopped, while others continued. On the 6th day of hospitalization, the patient was allowed to discharge.

After 3 days of discharge, the eyelid was getting swollen again, and he was readmitted to our hospital. Other than eyelid swelling, he experienced a severe headache and periorbital pain, eyelid hyperemia, and spasm [Figure 4d]. The previous inpatient treatment was given, except for the substitution of antibiotic therapy to intravenous amoxicillin-clavulanic acid. Immunohistochemistry study later showed neoplastic cell positive for CD56, CD16, perforin and granzyme, CD8, and Ki-67. *In situ* Epstein-Barr coded RNA (EBER) hybridization showed positive results. This result supported the diagnosis of ENKTL-NT. Unfortunately, due to medical record's limitation, data could not be presented. Abdominal USG showed splenomegaly; the lumbal puncture was within normal limit. The intravenous steroid was given for 5 days, which later switched to oral. This therapy resulted in decreased eyelid inflammation. After 3 weeks, he was allowed to discharge.

Shortly after, the patient underwent chemotherapy with cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP) regimen. Then, his general condition was weakened. Not so long after the second cycle, the patient presented to the emergency department with chemotherapy-induced nausea and vomiting (CINV), fever, and severe eyelid pain. He vomited more than twenty times in 2 days, which may explain hyponatremia. His condition was compounded by gum and gastrointestinal bleeding while hospitalized for a month. He died only 6 months since the onset due to multiple organ bleeding and respiratory failure.

Discussion

We reported two cases of ENKTL-NT in young patients, an 18-year-old male and a 34-year-old female. Presented cases showed different settings, the first case came in the early stage of disease, which then can be completely assessed. The later case presented in the emergency ward of his late stage, while some crucial examinations were already done in the previous hospital. Nevertheless, both cases surprisingly had the identical underlying conditions. This disease may occur in children but predominantly found in adults, with a mean age of 45 years.[5,10] Even though the age of presentation ranging from 19 to 80 years, both cases showed a lower age than the mean age reported.[10] Increased incidence is revealed in males.[10] The correlation between ENKTL-NT and EBV is remarkably strong that it will give rise to suspicious diagnosis for cases with a lack of EBV detection by *in situ* hybridization.[3,5] Epstein–Bar virus is a gammaherpesvirus that has infected at least 90% of the world's adult population. Infected patients frequently remained asymptomatic. Nevertheless, these asymptomatic conditions are correlated with the delayed primary infection that may predispose to infectious mononucleosis and EBV-associated malignancies.[11] Both patients showed positive results for EBV by *in situ* hybridization. Besides, a noninvasive, rapid serological EBV-specific polymerase chain reaction (PCR or prime flow EBER assay may be used to detect EBV infection, particularly for cases with unaccessible mass.[12] Nonetheless, it should be noted that this PCR approach may resulted in false positive due to contamination by plasma EBV DNA or infected B-cells. We did not assess the patients serologically due to insurance limitation and the sample for immunohistochemistry study has already taken for both samples to be examined, along with other pathological features.

Both patients did not manifest with the destructive lesion, then indeed alleged as inflammatory conditions. The first case showed a hyperemic, tender mass suggestive as idiopathic orbital inflammation. Other than physical examination, the previous imaging modalities supported the diagnosis of imaging of infections. Theoretically, a significant improvement will showed after trial corticosteroid treatment, but was not in this patient.[13] ENKTL-NT is typically presented in the nasopharynx, causing epistaxis, nasal obstruction, breathing difficulty which then progressed to a destructive mass.[3,10,14] A group of patients showed an extension to another extranodal sites, such as the skin, lungs, or testis.[1,3] However, an unusual presentation of ENKTL-NT cases was reported, and it is crucial to be rapidly recognized, considering its highly aggressive nature.[6,9,10,15] Delayed diagnosis may occur because of the clinical presentations of ENKTL-NT masquerading a variety of morphologies, as found in our patients. Besides, it has also formerly stated that patients with prominent ocular symptoms are more likely presented at the later stage, with periorbital swelling as the most common presentation.[16] Thus, the diagnosis of ENKTL-NT should be considered in patients who are presumably diagnosed with an ocular infection that has given adequate therapy, yet the symptoms do not improve or recurred. Mainly, if there is a swelling, roughness, erosion, or necrotic tissue in the nasal cavity.[8] It should be noted that a low suspicion index to its initial presentations may contribute to misdiagnosis, leading

to poor prognosis.[9] Although metastasis is uncommon, the lesion is commonly extending locoregionally to lymph nodes, orbits, and paranasal sinuses.[10] Our first case showed a metastasis both locoregionally and systematically that may predisposed to her worsened status.

Lymphoid malignancies are classified based on the cytotoxic lymphocytes, which could be confirmed through biopsy. ENKTL shows diffuse polymorphic lymphoid infiltrate, in conjunction with angiocentric and angiodestructive infiltration of NK cells or cytotoxic T-cells.[10,14] Based on the WHO 2016 classification, distinguishing pathologic features of ENKTL-NT are typically CD3−, CD3+, CD56+, CD16±, and germline T-cell receptor; subset of T cell origin; and clonal EBV NK/T cells.[5,17] Besides, imaging studies may become helpful modalities to suggest a diagnosis of ENKTL-NT. Previous reports showed that some patients initially recognized through nasal and paranasal sinus destruction.[9] Thus, nasal endoscopy and CT scans play an essential role in distinguishing ENKTL-NT from other etiology, causing similar symptoms.

Treatment is given based on the disease extension. For patients with localized type ENKTL, chemoradiotherapy is preferred.[5] Besides, combined chemotherapy and l-asparaginase is considered to be better for disseminated type.[14,18] Other reports suggested using the regimen of radiation therapy (RT) combined with CHOP chemotherapy, using cyclophosphamide, doxorubicin, vincristine, and prednisone (RT-CHOP). One of our patients was treated with this regimen, yet still showing a poor outcome. Recently, RT-2/3DeVIC using dexamethasone, VP16, ifosfamide, and carboplatin is recommended to replace the previous regimen.[10] However, the best possible treatment approach is still unknown.[5]

The survival of the patients is highly dependent on the stage at the time of diagnosis. The 5-year survival rate is around 40%–50%, with a risk of relapse in a 10-year follow-up.[2,19] The late diagnosis and treatment had previously been reported to result in poor prognosis.[9] In conclusion, it is noteworthy to consider ENKTL-NT for patients with ocular or sinonasal infections that rapidly progressed or refractory to treatment. An earlier diagnosis expectedly will result in a better prognosis.

Declaration of patient consent

The authors certify that they had obtained all appropriate patient consent forms. In the form, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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