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Case Report Open Access

A case of extra-nodal natural killer/T cell lymphoma presenting as rhinorrhea and blindness

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Extra-nodal natural killer/T cell lymphoma (EN-NK/T) is a highly uncommon, aggressive, mature T or NK-cell lymphoma with a high fatality rate. It has a propensity for infiltrating tissues and spreading to the eye. EN-NK/T-NT is marked by polymorphic clinical characteristics, which can make diagnosis difficult and cause delayed management. This report details a 63-year-old Iranian woman who presented initially with left ocular involvement of unknown cause. Ethmoidal sinusitis, upper nasal obstruction, right proptosis, dacryocystitis, and pulmonary nodules developed later as her disease progressed. Biopsies of the orbit, ethmoidal sinus, and pulmonary nodules were significant for EN-NK/T cell lymphoma. The patient developed and was treated for Covid-19. Due to the progressive lymphoma, chemotherapy was initiated after recovery from Covid-19. After starting the first course of chemotherapy, the patient's condition deteriorated rapidly with the possibility of pulmonary embolism, and she expired inAugust, 2021 2021. This case highlights the diagnostic difficulty of EN-NK/T cell lymphoma and demonstrates its rarity and ability to mimic other diseases.

Keywords: Natural Killer cells; T Cells; NK/T Cell Lymphoma; Lymphoma

Introduction

Extra-nodal natural killer/T-cell lymphoma (ENKTL) is an uncommon type of non-Hodgkin lymphoma (NHL) [1]. ENKTL, nasal type, and aggressive NK-cell leukemia are the two pathological forms of malignancy. Lymphoma occurs most frequently (80%) in the nasal cavity and nasopharynx [2-4], less frequently (20%) in non-nasal regions (skin, gastrointestinal tract, testis, salivary gland), and rarely as disseminated disease with a leukemic phase [5]. The prevalence of ENKTL varies significantly acrossthe world, and it is higher in Asian countries than in Western countries [3, 6]. According to a study in 20117, the incidence rate is higher in Asia and Latin America (accounting for 10% of all non-lymphoma Hodgkin cases) than in Europe and North America (accounting for < 1%) [4]. ENKTL can invade the orbit and globe due to their anatomic proximity, which might cause ocular symptoms [7], leading to ocular complications which, however, are rarely reported in pathologically diagnosed patients [8]. Nasal ENKTL diffusion or invasion is the most common form of ocular tissue NKTL; however, intraocular ENKTL has been described in a few cases. Orbital cellulitis, dacryoadenitis, uveitis, and myositis constitute some of the early ocular symptoms [9,

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10]. Very few studies have reported intraocular NKTL presenting as posterior, intermediate, or pan uveitis. Several of those cases were misdiagnosed as other inflammatory conditions, such as unspecific intraocular inflammation or viral-related uveitis, but they did not respond to corticosteroid and/or antimicrobial therapy. Patient survival is dependent upon disease type and its stage [7, 11-14]. Herein, we present a case of ENKTL in a 63-year-old Iranian woman who presented with ophthalmic involvement and multiple pulmonary nodules.

Case presentation

A 63-year-old woman was referred to our hospital with chief complaints of right dacryocystitis and proptosis. She had a 15-year history of papillary thyroid carcinoma (PTC) treated with total thyroidectomy and radioactive iodine. The patient first developed arthralgia, an indurative skin lesion on the skin of the nose and right dacryocystitis. Nasal skin lesion biopsy revealed lobular panniculitis of the lymphohistiocytic type. The patient was treated with prednisolone 5 mg/d and hydroxychloroquine (HCQ) 200 mg/d and diagnosed with sarcoidosis. The patient's clinical symptoms improved after treatment with prednisolone and HCQ, but she subsequently developed dacryocystitis in her left eye. Methotrexate was added to her treatment, and because of the lack of response to methotrexate, adalimumab 40 mg every 2 weeks was added to the therapeutic regimen. Signs of the disease were fully recovered in the patient's left eye, but the vision in the left eye gradually deteriorated. Four months later, the patient experienced erythema and periorbital edema of the right eye. She stopped using Adalimumab but suffered from nasal mucosal ulcers, rhinorrhea, epistaxis, weakness, and weight loss for one year. She had no fever, sweating, coughing, or dyspnea. Her symptoms progressed, however, and a paranasal sinus computed tomography (CT) scan, brain and orbit magnetic resonance imaging (MRI) were performed. A CT scan of the patient's paranasal sinuses revealed bilateral concha bullosa in the middle concha, opacity in the frontal and right ethmoid sinuses, mucosal thickening and remodeling in the right sphenoid, ethmoid, frontal and maxillary sinus, widening and obliteration of the right osteomeatal complex (OMC) (Figure 1). Furthermore, significant signal foci in the periventricular, centrum semiovale, and subcortical white matter were discovered on the brain MRI, indicating chronic small vessel ischemia (Figure 2).

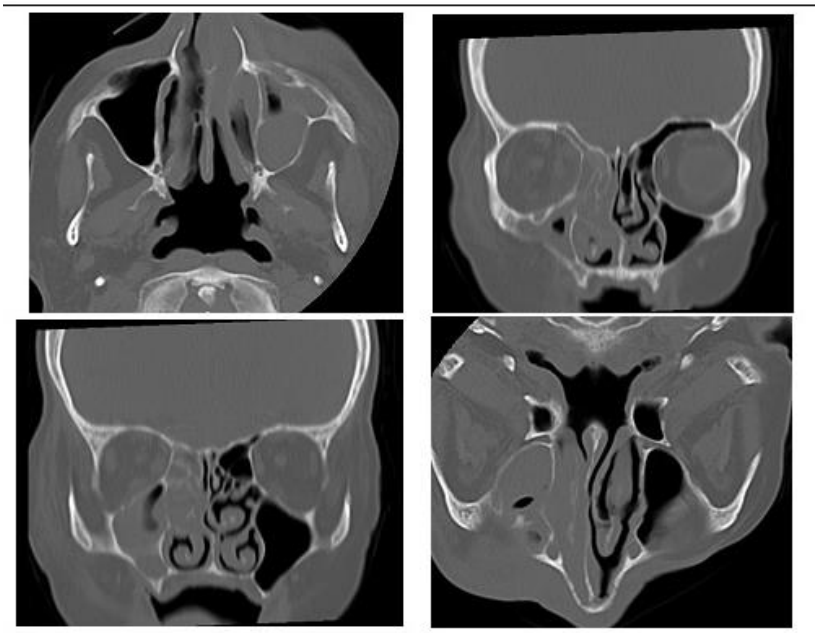

Figure 1. Computed tomography maxillofacial without contrast showing opacity in the frontal and right ethmoid sinuses, mucosal thickening and remodeling in the right sphenoid, ethmoid, frontal and maxillary sinus, and widening and obliteration of the right osteomeatal complex.

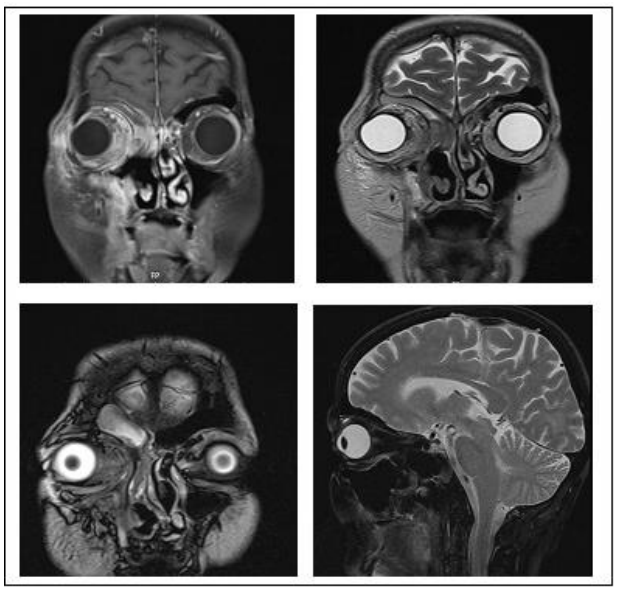

Figure 2. Brain and orbit magneic resonance imaging with and without contrast showing significant signal foci in n the periventricular, centrum semiovale and subcortical white matter indicating chronic small vessel ischemia

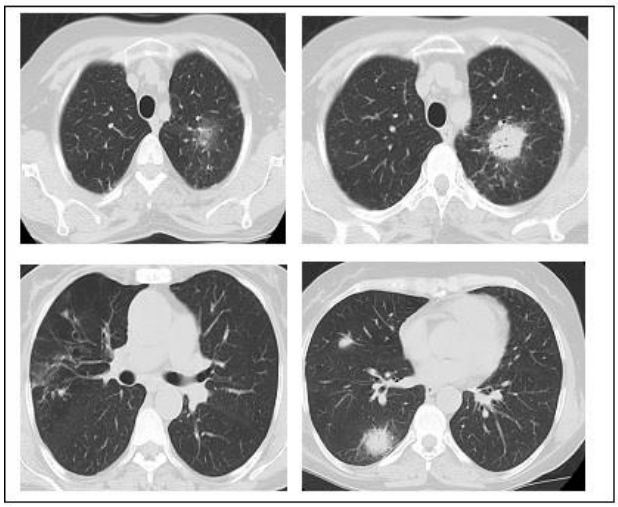

Figure 3. Computed tomographic scans of the chest showing dense consolidated areas in the right lower lobe and left upper lobe of the lungs

Due to her progressive symptoms, the patient was referred to Loghman Hospital for further diagnostic evaluation. On admission, her vital signs included blood pressure of 130/70 mmHg, pulse rate of 74 beats/min, respiratory rate of 20 breaths/min, and body temperature of 38.6 °C. Examination demonstrated elevation, depression, and abduction impairments on the right eye with proptosis, peri-orbital edema, erythema, and ulcerative lesion corresponding to the lacrimal fossa. Moreover, a normal appearance and a decrease in vision were observed in the left eye. There was an erythematous lesion on the nose skin, nasal congestion, and mucous discharges, particularly in the right nasal cavity. In the oral cavity, candida-associated lesions (CALs) were discovered. No palpable lymph nodes were found on the neck or supraclavicular area. Changes consistent with hand osteoarthritis were seen. The following results were obtained in paraclinical studies:

Chest CT scan found multiple solid masses (37 × 40 mm) in the right lower and left upper lobes of the lungs. Fibrosis-related changes were discovered in the lungs' lower lobes. Reticular turbidity with honeycombing bronchiectasis seen in the lower half of the right upper lobe suggested chronic inflammatory alterations. In addition, two hypodense lesions in the liver (52 × 55 mm) were discovered (Figure 3). In segments 2, 6, and 7 of

the liver, three echogenic lesions without noticeable vascularity but with distinct boundaries (24 mm, 12 mm, and 40 × 60 mm) were identified with high probability. Vasculitic diseases like granulomatosis with polyangiitis (GPA) due to the involvement of paranasal sinuses and lung lesions were included in the patient's differential diagnosis. Serological analyses of rheumatic diseases and tissue biopsy were used to confirm the diagnosis.

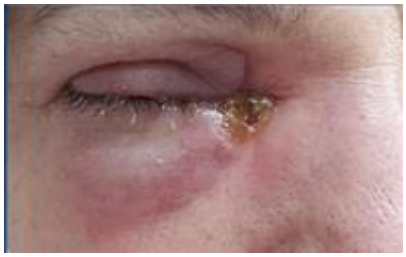

Figure 4. Dacryocystitis in the right eye

Laboratory findings revealed the following: white blood cell count: 7000/mm^3, hemoglobin: 13.0 g/dl, platelet count: 96,000/mm^3, ESR: 26 mm/hr., C-reactive protein: 25 mg/dl, aspartate aminotransferase: 24 IU/L, alanine amino-transferase: 21 IU/L, alkaline phosphatase: 119 IU/L, total bilirubin: 0.8 mg/dl, BUN: 34 mg/dL, Cr: 0.9 mg/dL, CPK: 37 µg/L, and LDH: 949 IU/L. ANA, Anti-Ds DNA, RF, anti CCP, ACE, C-ANCA, and P-ANCA were negative.

According to an ophthalmology consultation, chemosis, positive Marcus Gunn signs and pink–blurred-elevate optic disc were found in the patient's right eye, however, a pink left optic disc with a clear border was detected, and the left eye's vision hadnon-light perception. Decompression and antibiotic therapy were recommended due to erosion of the lower wall and an abscess in the medial wall of the right orbit. Sinus endoscopy and right orbital decompression surgery were conducted following consultation with an ears, nose, and throat (ENT) specialist and consideration of the possibility of a subperiosteal abscess. According to the functional endoscopic sinus surgery (FESS) report, the middle turbinate appeared pale and brittle. The middle turbine was resected properly. The procedure included an enterostomy, anterior and posterior ethmoidectomy, sphenoidotomy, and a biopsy that was figure sent for further investigation. Despite antibiotic administration and orbit decompression, the patient reported reduced right ocular vision. The reduced right ocular vision was linked to a previous subperiosteal abscess, according to several ophthalmology consultations. According to the orbit MRI, there was a compressive effect on the posterior section of the orbital nerve, indicating a re-need for abscess draining. There were no retrobulbar optic neuritis manifestations. From an ophthalmological stand-point, there was no rationale for the loss of left vision, and no neurological causes for vision loss were found in the normal LP, normal brain MRI, or MRV. Pathological evaluation of the right middle turbinate and right nasal sinus mass biopsy showed atypical lymphoid infiltrate with an angiocentric pattern and extensive necrosis suspicious for EN-NK/T cell lymphoma. On immunohistochemistry staining (IHC), the atypical cells were found to be positive for CD3, CD5, leucocyte common antigen (LCA), Ki67, CD68, BCL-2, Cyclin D1, but negative for CD20, BCL-6, CD79a, PCK, CD45, CD56, Melan A, synaptophysin, and chromogranin. A lung lesion biopsy revealed significant necrosis and vascular and parenchymal infiltration of atypical lymphoid cells. These findings were in line with a diagnosis of high-grade NK/T cell lymphoma.

The patient was referred to Imam Hossein Medical Center due to the persistence of erythema and edema in the right orbit and gradual vision loss in the right eye. The patient received meropenem-vancomycin antibiotic therapy and orbitotomy surgery, and the sample was sent for pathology. Heparin treatment was given due to tachypnea, and a CT angiography resulted in a diagnosis of pulmonary embolism. Furthermore, because of ground-glass opacity and a positive Covid-19 PCR, treatment for Covid-19 pneumonia was suggested. According to the definitive pathology result based on EN-NK/T cell lymphoma and due to the rapid progression of the disease, the first course of chemotherapy was started after the patient showed relative improvement from COVID-19. The patient then became a candidate for the CHOP regimenand received the first and lowest dose of vincristine. Unfortunately, before receiving cyclophosphamide, the patient experienced cardiac arrest and expired.

Discussion

ENKTL is a tumor that most commonly forms ulcerative and necrotic lesions in the sinuses and

nasal cavities (70%), although it can also arise everywhere [15]. According to Wang et al., the upper aerodigestive tract is the most prevalent site of ENKTL-nasal type involvement (75.5%) [16], which is in line with prior studies [2, 3]. Patients can also developed rhinorrhea, nasal obstruction, and epistaxis due to the tumor or ulceration in the affected locations [16]. In a large series of 24 cases with primary nasal and paranasal sinus ENKTL, six patients with uveitis/vitritis and orbital involvement suffered from vision-threatening complications, including one with rhegmatogenous retinal detachment (RRD) and one with a macular hole [17]. ENKTL primarily affects people in their fourth and fifth decades of age [18] and more frequently in men [19, 20].

ENK/T-polymorphic NT's clinical features explain the disease's commonly delayed treatment, as the disease's clinical presentation is non-specific and can sometimes be misleading, resulting in an inaccurate diagnosis. In most patients, an aggressive tumor invading the sinuses, palate, and nasal cavities induces a localized lesion with nasal obstruction. Symptoms include dysphagia, hemifacial pain, and facial edema as well as non-specific nasal symptoms (epistaxis, nasal obstruction, and discharge) [21, 22]. In 8% to 12% of cases, tumor cells release cytokines, which cause systemic symptoms like weight loss and fever [5]. Several biopsies are required to confirm the diagnosis of ENKTL [11]. In the case presented herein, the patient had ocular involvement. The globe or ocular adnexa are infrequently invaded by NK/T-cell lymphoma, which accounts for around 1% to 3% of all lymphoproliferative tumors in the ocular site; thus, it can be mistaken because of the wide range of diagnoses (11).

As a result of advances in IHC and molecular biology, ENKTL has become more precisely characterized [23]. NK/T-cell lymphoma has the same histopathological findings independent of the location of the lesion [24] and is comprised of sheets of atypical Sternberg-like cells of various sizes (small, medium, large, or huge) [3]. The formation of vascular lesions with tumor cells grouped in perivascular (angiocentric) cuffs, with occasional penetration of these cells across the arterial wall and proliferation in the lumen, resulting in vascular thrombi, is the defining characteristic of ENKTL (angio-destructive lesions). The nasal mucosa exhibits necrosis, fibrosis and marginal pseudo epitheliomatous hyperplasia [25]. Despite advances in IHC and molecular biology, ENKTL remains an exclusionary diagnosis due to the lack of distinct clinical and histological characteristics. Many disorders, including GPA, various malignant tumors, syphilis, and cocaine usage, can induce mid-facial and nasal ulceration and destruction remarkably similar to that caused by ENKTL [26]. ENKTL represents polymorphic clinical features that lead to diagnostic challenges. A CT scan is required for the investigation of ENKTL. Establishing the tumor site, the presence of osteolysis, and the possibility of extension to neighboring structures allow for accurate staging of the lesions [27]. It is also necessary to perform pre-treatment assessment, therapy response evaluation, and follow-up. Soft tissue invasion can be more accurately demonstrated with MRI, because it can separate inflammation and soft tissue edema from tumor invasion. The laboratory workup is non-specific and in-effective for confirming a positive diagnosis of this disease [28, 29].

Before any treatment, a staging assessment must be completed, which includes a physical examination for superficial lymph nodes, splenomegaly, or hepatomegaly, abdominal ultrasound, a chest x-ray, chest and abdomen CT, gastrointestinal endoscopy, bone marrow biopsy, and possibly lumbar puncture if a lesion of the skull base is present [30]. ENKTL is a complicated condition to treat. Surgical resection of the lesions has been suggested, mainly for diagnostic goals and facilitating necrotic cavity drainage. According to prior research, surgery is ineffective and may exacerbate the lesions by accelerating the disease's course. For localized stages (stages I and II), external beam radiotherapy is suggested[31]. According to Mikhaeel and Spittle, even in localized phases, this lymphoma's aggressive behavior necessitates extensive chemotherapy [32]. Aggressive chemotherapy is the only therapeutic modality for severe stages (stages III and IV), anda complete response occurs in less than 15% of cases[33]. Hatta et al. discovered that CHOP treatment combined with radiation for advanced ENKTL over stage IIE and stage B NK/T-cell lymphoma is ineffective [34, 35].

Previous research revealed the mechanisms of

ENKTL pathogenic genes, such as EZH2, H3K27, c-Myc, STAT3, PD-L1, and CD30. These genes could be crucial in developing future targeted therapies [36-38]. Furthermore, future progress in the disease will depend on more reliable diagnostic criteria and repeatable molecular markers [16].

ENKTL is associated with a poor prognosis, including extra-nodal propagation, macrophage activation syndrome induction, and a high local recurrence rate. The 5-year overall survival rate for the tumor ranges between 10% to 45% [19]. Furthermore, patients with stage I ENKTL have better outcomes. Individuals in stage I had a better prognosis than patients in stages II and IV, according to previous studies [16]. Other factors, including advanced-stage disease (stage III or IV) and bone or skin invasion, were thought to be associated with patient prognosis. Wang et al., on the other hand, discovered no relationship between clinical stage and survival rate [16].

Conclusion

The clinicopathological aspects of a patient with ENKTL were detailed in this case report. This paper may add to the growing body of evidence that ocular problems can occur in patients with ENKTL, but such cases are still uncommon. A complete review of clinicopathological characteristics, immunophenotypic data, and molecular results supports the diagnosis of ENKTL. Although the prognosis is poor, remission is still possible with intensive chemotherapy and radiotherapy. Moreover, ENKTL-related ocular complications require ophthalmic treatment as well as baseline and ongoing ophthalmology evaluations. Finally, to enhance the prognosis of ENKTL, interdisciplinary collaboration between radiotherapists, otorhinolaryngologists, medical oncologists, and nutritionists is necessary for optimal management .

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Declaration of Conflicting Interests

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