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Natalie Wolkow, MD, PhD
Cogan Eye Pathology Laboratory
Massachusetts Eye and Ear Infirmary
243 Charles Street, Boston, MA 02114-3096
email: Natalie_Wolkow@meei.harvard.edu

"Is It Cellulitis?" (an unknown): Extranodal NK/T-cell lymphoma, Nasal Type

(Post-meeting protocol)

History and clinical findings:

A 94-year-old woman presented with 5-6 days of worsening right eyelid erythema, edema and pain. She also complained of tearing and purulent discharge from the right eye, as well as fevers, chills, nausea, vomiting and nasal congestion.

Her past medical history was notable for hypertension, gastroesophageal reflux disease and chronic right-sided sinus disease. The symptoms of sinusitis began 7 months prior to presentation. Initially she was treated by her primary care physician with levofloxacin, amoxicillin clavulanate and Flonase, but due to recurrent episodes was then referred to an otorhinolaryngologist.

Two months prior to presentation she was seen in consultation by an otorhinolaryngologist. A CT scan demonstrated complete opacification of the right maxillary, right ethmoid and right sphenoid sinuses (Figure 1). Nasal endoscopy revealed an obstruction of the right nasal cavity and functional endoscopic sinus surgery was recommended.

Two weeks prior to presentation she returned to the otorhinolaryngologist with acute-onset right upper and lower eyelid erythema, edema, pain and a fever. She was admitted for pre-septal cellulitis, started on IV antibiotics, and had functional endoscopic sinus surgery performed the following day. Histopathologic examination of the sinus contents revealed chronic inflammation and necrosis with bacterial overgrowth, but without fungi. Post-operatively the patient improved and was afebrile. She was discharged home on oral antibiotics.

She did well for several days but then returned with worsening periocular edema, erythema and pain, fevers, chills and nasal congestion. Examination revealed right upper and lower eyelid erythema and firm edema, right upper eyelid ptosis, and area of induration near the right lacrimal sac, decreased visual acuity on the right, restricted extraocular motility and right conjunctival chemosis. She was admitted for recurrent cellulitis, and started on IV antibiotics. After 3 days on IV antibiotics, she did not have significant improvement (Figure 2). A biopsy of the indurated skin overlying the right lacrimal sac was performed to aid in diagnosis.

Histopathologic findings:

See provided H&E slide, labeled WOLKOW, EOPS, 2018

Figures:

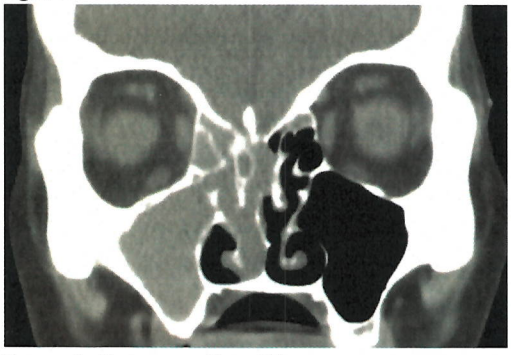

Figure 1: Pre-operative CT scan.

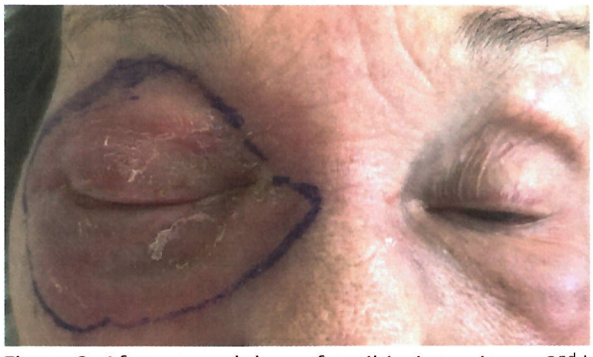

Figure 2: After several days of antibiotics, prior to 2nd biopsy.

Histopathologic findings, continued:

Hematoxylin-and-eosin-stained slides revealed a prominent infiltrate of small lymphoid cells, plasma cells and histiocytes in the dermis, among the striated muscle fibers and adipose tissue. Lymphoid cells and histocytes also appeared to infiltrate the wall of a large blood vessel. The lymphoid cells were mostly small and bland; some had irregular or angulated nuclei. Extensive necrosis was present and apoptotic cells were seen. The overall impression appeared to be that of a severe chronic inflammatory process.

Immunostaining revealed many scattered CD68-positive histiocytes, almost no CD20-positive B-lymphocytes, and many CD3-positve T lymphocytes. Further immunostains revealed that the CD3-positive cells were CD5-negative, CD4-negative and CD8-negative; however, most were CD56-positive. The immunostains confirmed that the lymphoid cells were almost all NK cells, and that there was a very small background of B-lymphocytes and T-lymphocytes. The NK cells immunostained positively for perforin and granzyme. They were also almost all positive for Epstein-Barr Virus RNA with in situ hybridization for EBV (EBER), confirming a diagnosis of extranodal NK/T-cell lymphoma, nasal type.

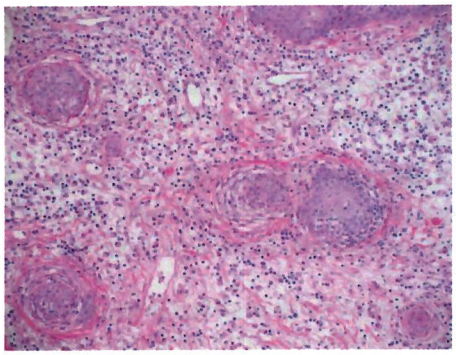

Figure 3: H&E, 20x

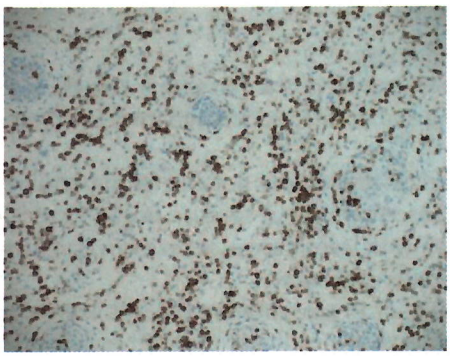

Figure 4: CD3, 20x

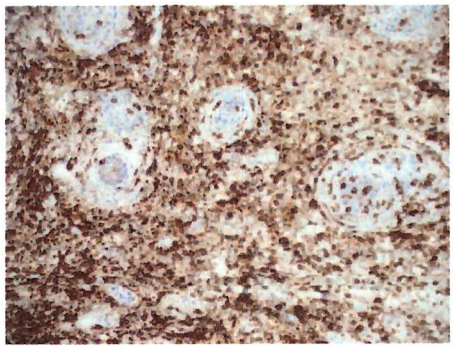

Figure 5: CD56, 20x

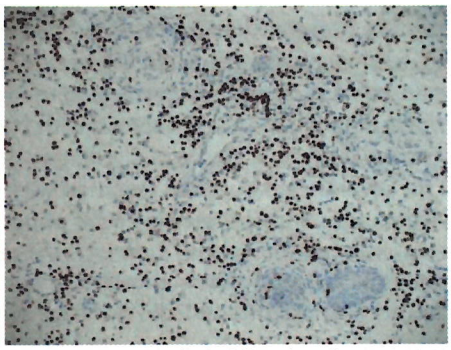

Figure 6: In situ hybridization for EBV RNA (EBER), 20x

Final diagnosis:

Extranodal NK/T-cell lymphoma, nasal type, with a predominance of small cells

Clinical course:

Soon after biopsy, the patient developed seizures. She was not a candidate for chemoradiation and after a discussion with her family, palliative care was elected. She died 3 weeks after the biopsy.

Discussion:

Extranodal NK/T-cell lymphoma, nasal type (ENKTCL) is uncommonly encountered in the orbit, representing fewer than 3% of orbital lymphoid tumors. ENKTCL most commonly is found in the nasal cavity, sinuses and pharynx. When present in the orbit, it typically represents extension of tumor from adjacent sinuses. True primary orbital ENKTCL is very rare. ENKTCL may clinically present as preseptal or orbital cellulitis, and can also mimic orbital inflammatory diseases, such as ANCA-associated vasculitides.

ENKTCL is more common in Asia, South America and Central America. It affects men more commonly than women, and is often found in the 45 to 55 year old age group. The current case was unusual in that the patient was elderly (94 years old) and Caucasian.

The histopathologic spectrum of ENKTCL varies widely. In most cases the lymphoma cells are medium or large and can have irregularly-folded nuclei. Approximately 7-20% of cases, however, are characterized by a predominance of lymphoma cells that are small in size and bland in appearance. These small cell-predominant lymphomas are often mistaken for inflammatory processes, particularly since the lymphoma cells may be accompanied by a mixture of inflammatory cells including histiocytes and plasma cells. A high degree of suspicion and immunostaining is critical in making a correct diagnosis.

ENKTCL often displays angiocentric and angiodestructive growth. Necrosis and apoptosis are commonly present. The lymphoma cells are positive for CD2 and CD56. On fresh and frozen sections they are negative for surface CD3; however, because they express cytoplasmic CD3-epsilon, in formalin-fixed tissues they are often positive for CD3. The tumor cells are typically CD5, CD4 and CD8-negative. They express cytotoxic molecules, such as granzyme B, perforin and TIA1. In situ hybridization for EBV-encoded small RNA (EBER) is almost always positive in most of the lymphoma cells. The association of EBV with ENKTCL is very strong, and if EBER is negative, alternative diagnoses should be strongly considered. Serum EBV titers can correlate with disease extent and response to therapy.

Historically, survival has been poor (30-40%), but has recently improved with advances in therapies. Treatment usually consists of a combination of chemotherapy and radiation. Currently used protocols include DeVIC (dexamethasone, etoposide, ifosfamide and carboplatin) and SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide).

The current case presented a challenge histopathologically because the lymphoma cells were small and bland appearing and intermixed with other inflammatory cells, resembling an inflammatory process. Familiarity with the patient's atypical clinical course and discussion with her clinical care team prompted a detailed immunohistochemical investigation, which yielded surprising results.

References:

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