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Letter to the Editor

Orbital Inflammatory Lesion as an Initial Manifestation of Systemic Nasal Type NK/T-Cell Lymphoma

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TO THE EDITOR

Orbital mass lesions show several etiologies, ranging from benign inflammatory disease to malignant neoplasmic lesions.[1] The most common histopathology is lymphoma, accounting for approximately 20% of cases.[2] On the other hand, benign inflammatory disease, so-called inflammatory pseudotumor or idiopathic orbital inflammation, accounts for about 10% of cases.[2,3] Among cases with primary lymphoma, marginal zone lymphoma of mucosa-associated lymphoid tissue (MZL-MALT) is the most common pathologic type, accounting for more than 80% of cases.[4-6] Rarely, however, cases with natural killer/T-cell lymphoma (NKTL) have been reported among them, especially in Asian populations.[4,5,7,8] We encountered a case of NKTL of the orbita, which was initially misdiagnosed as a benign inflammatory lesion, but eventually progressed to systemic aggressive disease.

A 66-year-old Japanese female was admitted to our hospital because of fever and pancytopenia. Six months before admission, a tumor of the left orbita was noted at another hospital. She was referred to the hospital because of the left periorbital swelling. At that time, a T1-weighted magnetic resonance imaging (MRI) using gadolinium demonstrated an enhanced mass in the left orbita. Computed tomographic (CT) scans of the head, neck, chest, abdomen, and pelvis performed there did not reveal lymphadenopathy, hepatosplenomegaly, or other evidence of tumor. B symptoms or symptoms related to the nasal cavity were not present. Cytopenia was not seen and serum lactate dehydrogenase (LDH) level did not rise then. Bone marrow aspiration or biopsy was not carried out there. The left orbital mass was biopsied with the diagnosis of an inflammatory lesion. Corticosteroid pulse therapy was conducted and the size of the mass decreased by 50% compared with the initial lesion. Subsequently, treatment with oral prednisone was started, followed by tapering, continuing until her admission to our hospital. On admission, marked hepatosplenomegaly was seen without swollen lymph nodes. No skin rash was noted. Complete blood cell analysis revealed a white blood cell count of 900/μL, a platelet count of $4.8 \times 10^4/\mu$L, and hemoglobin concentration of 8.5 g/dL. An elevation of LDH up to 1,302 IU/L was observed (normal range, 110-225 IU/L). The serum ferritin value was as high as 48,134 ng/mL. Polymerase chain reaction (PCR) for Epstein-Barr virus (EBV) DNA using whole blood was positive, showing up to 3.4×10^5 copies/mL. Disseminated intravascular coagulation was present. A CT scan showed marked hepatosplenomegaly without swollen lymph nodes. MRI demonstrated a mass lesion in the left orbita. Bone marrow biopsy and aspiration revealed marked hypercellularity and fat necrosis, with abundant apoptotic findings and marked erythrohemophagocytosis (Fig. 1a). Infiltration by large atypical lymphoid cells was seen (Fig. 1b). These cells had pale or lightly basophilic cytoplasm containing azurophilic granules (Fig. 1c). Immunophenotyping using flow cytometry showed that these large cells were positive for cCD3, CD2, CD7, CD8, CD56, CD30, and CD38, and negative for sCD3, CD16, and TCR$\gamma\delta$. Immunohistochemically, tumor cells were positive for CD3, CD56, CD8, CD30, and granzyme B. *In situ* hybridization for EBER (EBV-encoded RNA) showed positivity in almost all of the tumor cells (Fig. 1d). These findings suggested a diagnosis of extranodal NK/T-cell lymphoma, nasal type (ENKTL). On the 4th hospital day, we began DeVIC (dexamethasone, VP16, iphosphamide, and carboplatine) therapy, but the patient died of multiorgan failure on the 6th hospital day. An autopsy was not allowed.

We reviewed the morphology of the left orbital mass biopsied at a previous hospital. Histological findings showed

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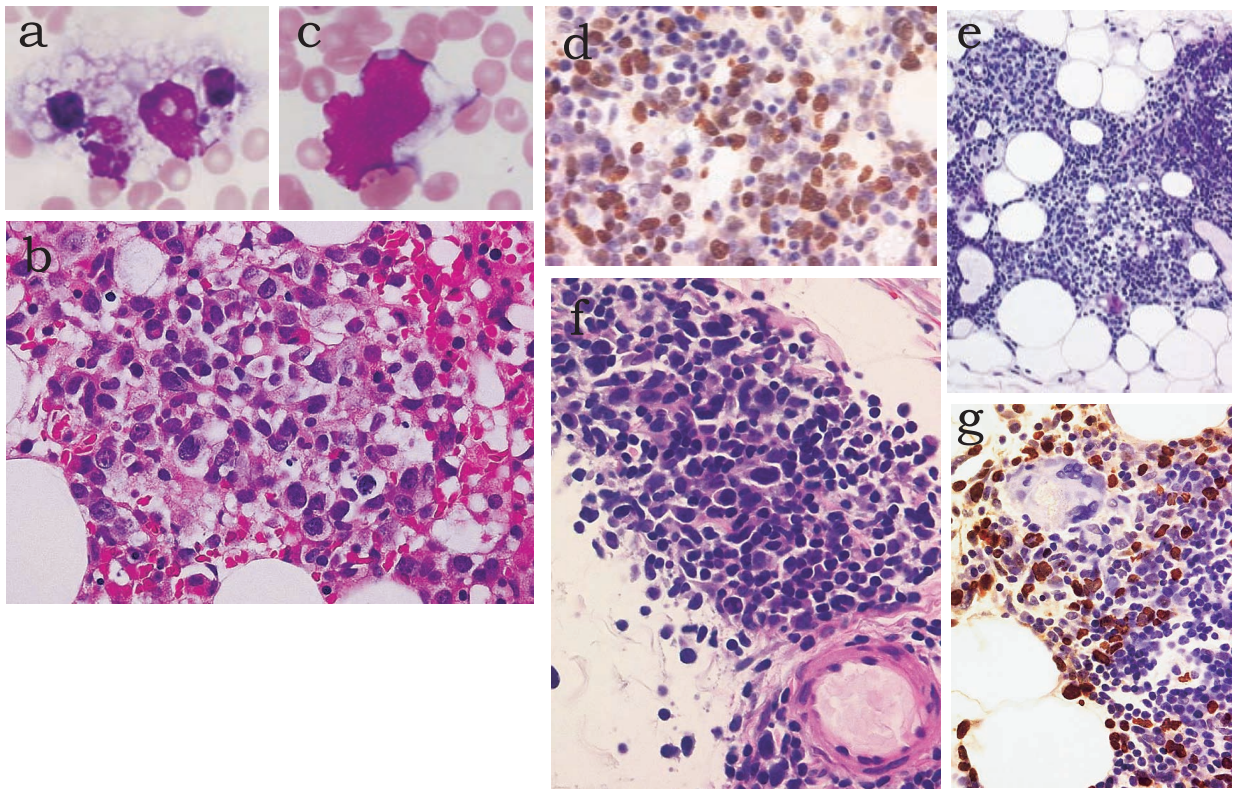

Fig. 1. Cytologic and histological findings. (***1a & 1c***) Bone marrow smear demonstrates erythrohemophagocytosis (*1a*) and large atypical lymphoid cells with azurophilic granules (*1c*). (***1b & 1d***) Histological findings of the bone marrow. Infiltration of large atypical lymphoid cells (*1b*). These tumor cells are positive for *in situ* hybridization for EBER (*1d*). (***1e, 1f & 1g***) Histological findings of the left orbital soft tissue mass. A feature of panniculitis (*1e*). Perivascular infiltration of large and slightly pleomorphic atypical lymphocytes (*1f*). Large atypical lymphocytes are positive for EBER (*1g*).

a feature of panniculitis and the perivascular infiltration of large and slightly pleomorphic atypical lymphocytes (Fig. 1e & 1f). Necrosis was not marked. It may be difficult to diagnose lymphoma definitively from only these findings. Immunohistochemically, however, large atypical cells were positive for CD3, CD56, CD8, CD30, granzyme B, and EBER (Fig. 1g), being identical to the specimens of BM biopsied at our hospital. However, retrospectively, considering the immunohistochemical findings, the orbital mass should have been diagnosed as NKTL, the same as the BM specimens at our hospital.

The diagnosis of ocular adnexal lymphoma (OAL) is sometimes difficult, and it can easily be misdiagnosed as an inflammation. Yi *et al*. reported that eight of 18 patients with biopsy-proven OAL were misdiagnosed with "inflammatory pseudotumor" before surgery.[4] MZL-MALT, the most common pathologic type among OAL, is sometimes pathologically and clinically confused with benign inflammation. Cases of NKTL are also sometimes difficult to diagnose definitively because tumor cells are often scarce and are obscured by surrounding inflammatory cells and necrosis. Contrary to indolent MZL-MALT, the misdiagnosis of NKTL leads to a poor clinical outcome. There is a report of a 41-year-old woman, although Caucasian, who was initially diagnosed with idiopathic orbital inflammation and later died of widespread ENKTL.[9] Another report demonstrated that NKTL comprises less than 1% of OAL in Western countries.[5] However, NKTL is often a fatal disease, especially when the diagnosis is delayed, as in our case, and has been shown to be more prevalent in East Asia than in Western countries.[7,8] In China, NKTL reportedly accounted for 11.9% of 18 patients with OAL.[4] Therefore, on encountering a case of orbital tumor, we should undertake careful examination to distinguish between malignant lymphoma and benign inflammation. NKTL should be considered as a differential diagnosis, especially in Japan.

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