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LETTER TO THE EDITOR

Non-nasal natural killer cell lymphoma: not non-nasal after all

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Dear Editor,

Natural killer (NK) cell lymphoma, or extranodal NK/T-cell lymphoma, nasal type, according to the World Health Organization classification, is a rare neoplasm affecting preferentially Asian and South American populations, being extremely unusual in Western patients [1]. There are two clinical forms, nasal and non-nasal (extranasal) [2]. In nasal NK-cell lymphoma, the nasal and upper aerodigestive areas are initially involved. Dissemination to the skin, gut, testis, salivary glands or marrow occurs in advanced diseases. In non-nasal NK-cell lymphomas, however, the skin, gut, testis, salivary glands or marrow are the primary sites. Non-nasal NK-cell lymphomas have been reported to have a worse prognosis [3].

A 59-year-old man presented with bone pain, jaundice and fever. There were no lymphadenopathy or organomegaly. Investigations showed hemoglobin: 11.4 g/dL, white cell count: 1.4×10^9/L with no abnormal circulating cells, platelet count: 45×10^9/L, bilirubin: 67 (7–19) μmol/L, alkaline phosphatase: 510 (49–138) U/L, alanine aminotransferase: 407 (6–53) U/L, aspartate aminotransferase: 336 (13–33) U/L and lactate dehydrogenase (LDH): 1,200 (107–218) U/L. A positron emission tomography/computerized tomography (PET/CT) showed hyper-metabolic lesions confined exclusively to the bone marrow (Fig. 1a). Histologic examination of the marrow showed diffuse infiltration by medium-sized lymphoid cells with irregular nuclei, clumped chromatin and cytoplasm with fine azurophilic granules, associated with florid hemophagocytosis (Fig. 1b). The neoplastic cells were surface CD3–, CD2+, CD7+, CD56+, and strongly positive for Epstein Barr virus encoded RNA on in situ hybridization (Fig. 1c). A nasal panendoscopy showed normal nasal, nasopharyngeal and oropharyngeal areas. Overall features were consistent with non-nasal NK-cell lymphoma.

He was treated with methotrexate 2 g/m^2 (day 1), and ifosamide 1.5 g/m^2/day, etoposide 100 mg/m^2/day, dexamethasone 40 mg/day (days 2 to 4) [4]. He responded with normalization of temperature and LDH. On day 8, however, he developed fever, nasal pain and obstruction with epistaxis. A CT scan showed a 2-cm rim-enhancing irregular lesion in the nasopharynx, a site which was uninvolved initially (Fig. 1d). Biopsy of the lesion confirmed NK-cell lymphoma infiltration (Fig. 1e). Treatment with L-asparaginase (6,000U/m^2/alternate daily×7) induced complete resolution of symptoms. Following normalization of blood counts and liver function, a marrow examination showed complete morphologic remission. Nasal panendoscopy with random nasopharyngeal biopsies also showed normal findings.

Although NK-cell lymphomas are considered aggressive [1], stage I/II nasal NK-cell lymphomas have a favorable prognosis with radiotherapy and chemotherapy [5], whereas stage III/IV nasal NK-cell lymphomas fare much worse with few survivors. Conversely, non-nasal NK-cell lym-

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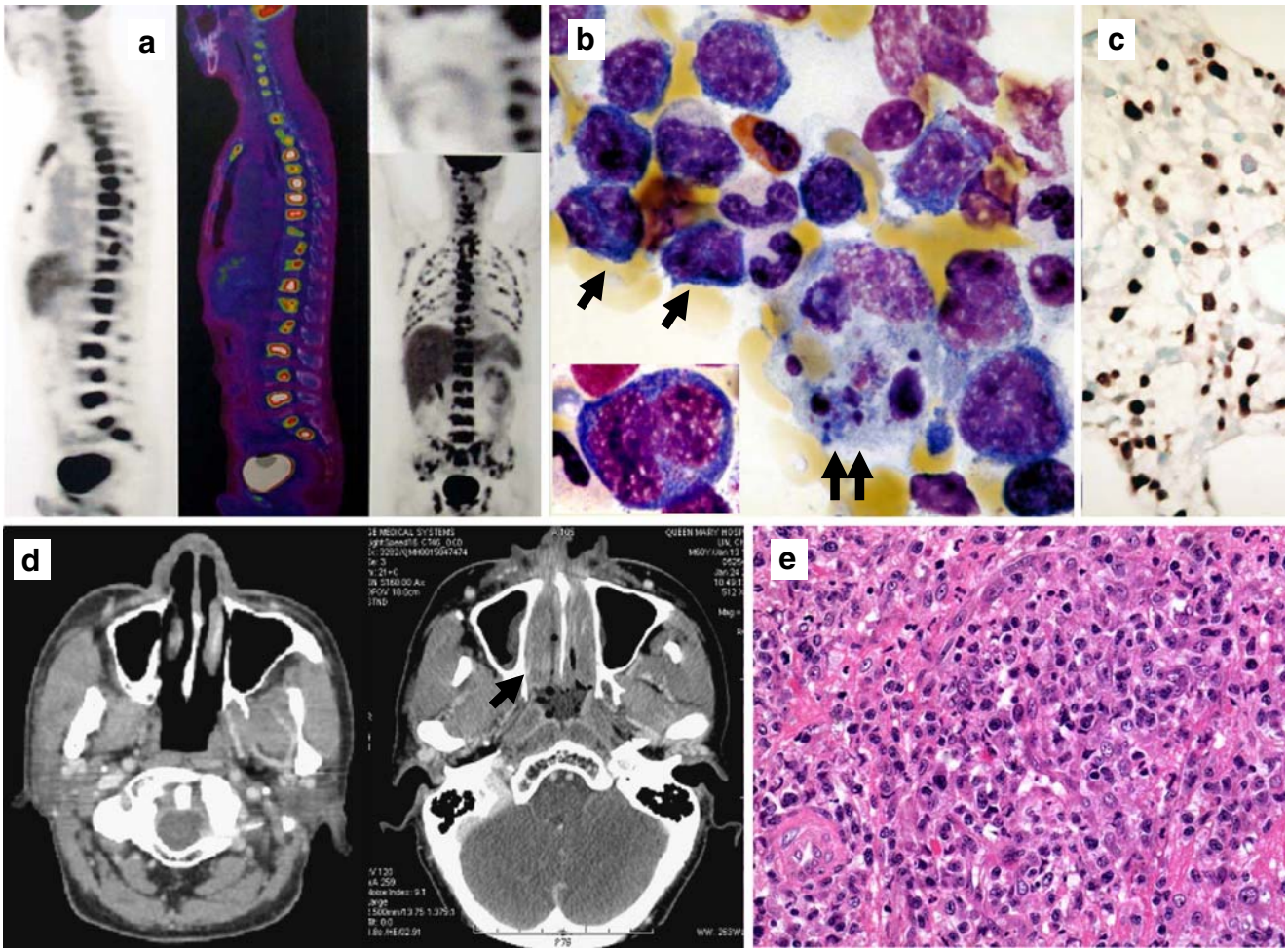

Fig. 1 A patient with natural killer (NK) cell lymphoma. **a** Positron emission tomographic/computerized tomographic (PET/CT) scan showing hyper-metabolic lesions confined solely to the bone marrow. The nasopharynx (*right uppermost panel*) did not show any hyper-metabolic lesions. **b** Bone marrow aspirate, showing infiltration by neoplastic lymphoid cells (arrows) with fine azurophilic granules (magnified in the *insert*). There was active hemophagocytosis (*double arrow*) (Wright Giemsa stain, original magnification 1000x). **c** In situ hybridization for Epstein Barr Virus encoded RNA, showing numerous positive cells in the bone marrow trephine biopsy (original magnification 1000×). **d** PET scan of the nasal cavity. *Left panel* apparently normal scan initially at diagnosis. *Right panel* a mass lesion with rim enhancement (*arrow*) 8 days afterwards. **e** Histologic examination of the nasal mass, showing infiltration by pleomorphic neoplastic lymphoid cells. These cells had the same immunophenotype as the bone marrow neoplastic NK cells

phomas at any stage have been reported to have uniformly poor prognoses [3]. An important caveat in diagnosing non-nasal NK-cell lymphoma is that few if any studies of these patients actually examined the nasal areas carefully with panendoscopy, random biopsies or state-of-the-art imaging techniques. Therefore, many "non-nasal" NK-cell lymphomas might conceivably represent in fact disseminated nasal NK-cell lymphomas, particularly when the primary sites of "non-nasal" NK-cell lymphomas are precisely the sites where nasal NK-cell lymphomas will metastasize to. This is well illustrated in our patient, who would have been diagnosed to have a "non-nasal" NK-cell lymphoma, because even an initial thorough examination with PET/CT scan and pan-endoscopy, a rigorous evaluation absent in any of the previous studies of "non-nasal" NK-cell lymphomas [3], did not show nasal involvement. The subsequent rapid appearance of a nasopharyngeal lesion highly suggested that there was initial occult nasal involvement undetectable despite stringent investigations. Therefore, unless results from pathologic, biologic or molecular studies indicate otherwise, "nasal" and "non-nasal" NK-cell lymphomas should be considered different clinical forms of the same disease process.

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