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Case Report

Extranodal NK/T-cell lymphoma, nasal type extensively involving the bone marrow

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Abstract: Extranodal NK/T-cell lymphoma, nasal type, is an aggressive EBV-associated lymphoma that mainly involves the nasal cavity but has also been reported to involve other extranodal sites without nasal involvement. In contrast to aggressive NK cell leukemia (a marrow-based aggressive leukemia of NK-cell origin); extensive bone marrow and blood involvement is extremely uncommon by nasal type NK/T lymphoma. We report a patient with extranodal NK/T-cell lymphoma, nasal type that developed extensive bone marrow involvement during the course of her disease with some overlapping features with aggressive NK-cell leukemia.

Keywords: Nasal NK cell lymphoma, aggressive NK cell leukemia, bone marrow

Introduction

Extranodal NK/T-cell lymphoma, nasal type, is an aggressive lymphoma that was originally described to involve the midline facial area, mainly the nasal cavity. However, other extra nodal sites have been reported to be involved even without nasal involvement [1, 2]. It is more common in Asian and Latino patient population and shows a near 100% association with EBV, irrespective of the ethnic origin [1, 2]. Morphologically, an angiocentric lymphoid infiltrate with associated prominent necrosis and vascular destruction is the mainstay for establishing the diagnosis. Minimal involvement of the bone marrow and peripheral blood can occur but extensive involvement is extremely uncommon by nasal type NK/T lymphoma, which contrasts with aggressive NK cell leukemia (a marrow-based aggressive leukemia of NK-cell origin).

Case Report

Our patient is a 49 year-old Asian female with a past medical history of Graves' disease diagnosed in 2003 that was treated and controlled successfully with propylthiouracil. In April 2005, she developed severe sinusitis and an ulcerated

nasal mass, which was biopsied leading to initial reports of necrosis and vasculitis suggestive of an autoimmune disease. Bone marrow biopsy at the time showed normal marrow with active trilineage hematopoiesis. In November 2006, she developed a very rapidly growing groin mass that was diagnosed as extranodal nasal NK/T cell lymphoma (**Figure 1**). After reviewing the initial nasal mass at our institute and by other experts in the field, it was believed that the lesion represented focal infiltration by nasal NK/T lymphoma cells (**Figure 1**). In both specimens, the neoplastic cells were positive for CD2, CD3, CD4 (focal), CD56, Granzyme B, and TIA-1, and were negative for CD5, CD7, and CD8 by immunohistochemistry. In situ hybridization for EBV encoded RNA (EBER) was positive in both lesions. T-cell receptor gamma gene rearrangement studies performed on the nasal mass were negative and revealed a germline configuration. A bone marrow biopsy at the time (November 2006) showed an uninvolved marrow.

The patient received four cycles of chemotherapy (CHOP/Etoposide regimen) and went into remission. While undergoing stem cell collection in preparation for an autologous stem cell trans-

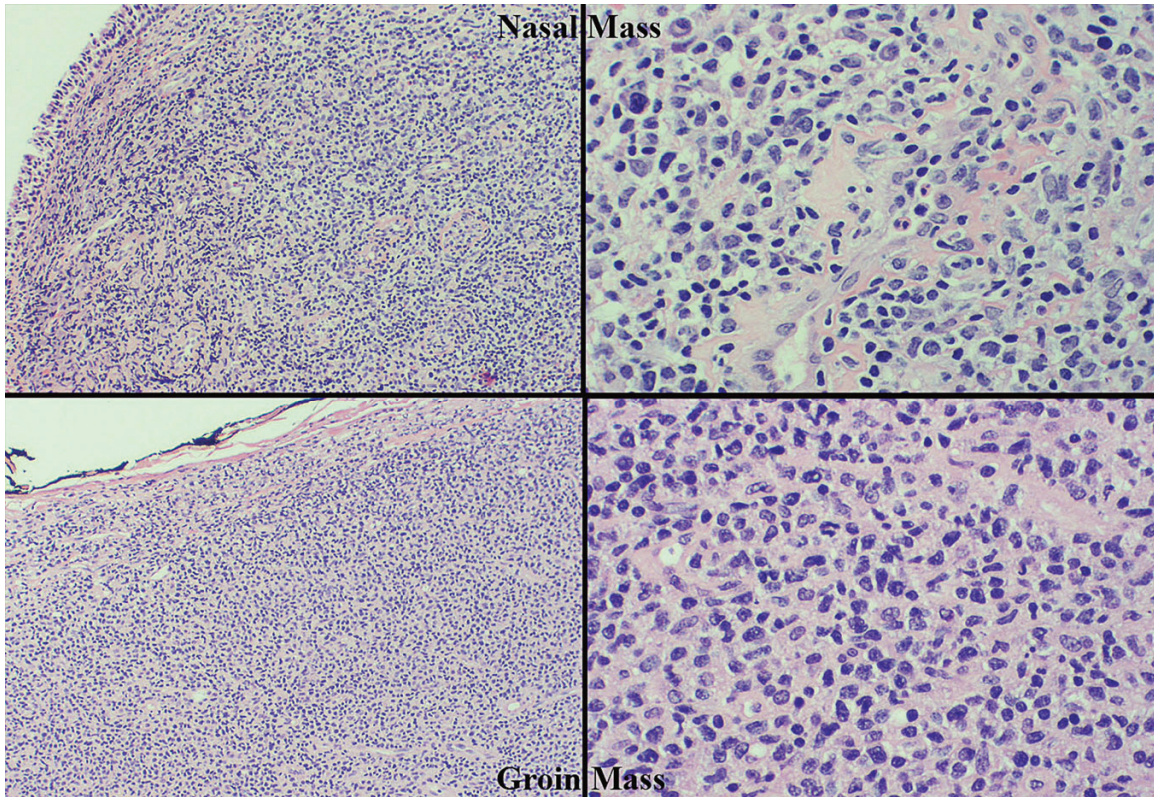


Figure 1. In the composite picture, the upper 2 pictures represent the original nasal mass at low (40x) and high magnification (600x). The lower 2 pictures represent the groin mass at low (40x) and high magnification (600x). In both masses, the neoplastic cells have a similar morphology and are medium-sized with slightly irregular nuclear contours and inconspicuous nucleoli.

plant, she developed Coombs-negative hemolytic anemia and rapidly progressive thrombocytopenia. A bone marrow biopsy was performed (April 2007), which revealed extensive involvement of the bone marrow by nasal NK/T cell lymphoma (**Figure 2**). The pattern of involvement was mainly diffuse with few vaguely nodular areas present. No evident hemophagocytic activity was noted. Scattered circulating lymphoma cells were identified in the peripheral blood. Flow cytometry was performed on the bone marrow aspirate and detected a population of NK/T cells (30%) that express CD2, CD7, and CD56 and are negative for surface CD3, CD5, CD16, CD4, and CD8. By immunohistochemistry, the neoplastic cells exhibited the same immunophenotype previously seen in the nasal and groin masses (**Figure 3**). EBER was also strongly positive (**Figure 4**). Chromosome analysis performed on the bone marrow sample showed abnormal complex female karyotype as follows: 46, XX, +3, dic(3;14)(p11;p11.2), i(3)

(p10), del(6)(q13q15), add(9)(p13).

Discussion

Nasal type NK/T cell lymphoma is a well-defined distinctive local disease, which may invade adjacent tissue, but rarely involves remote organs. It was originally described to almost exclusively involve the nasal area; however, it has been also shown to involve other extra nodal sites such as the skin, testis, soft tissue, and gastrointestinal tract [1, 2]. Secondary lymph node presentation has been reported in few cases [2]. Bone marrow involvement is rare and when it occurs, it is often minimal and is usually difficult to detect by routine morphologic examination.

Our case shows near total replacement of the bone marrow by sheets of CD56 and EBER positive lymphoma cells in a leukemic fashion, which is highly unusual for nasal NK/T lym-

Nasal NK/T cell lymphoma in the bone marrow

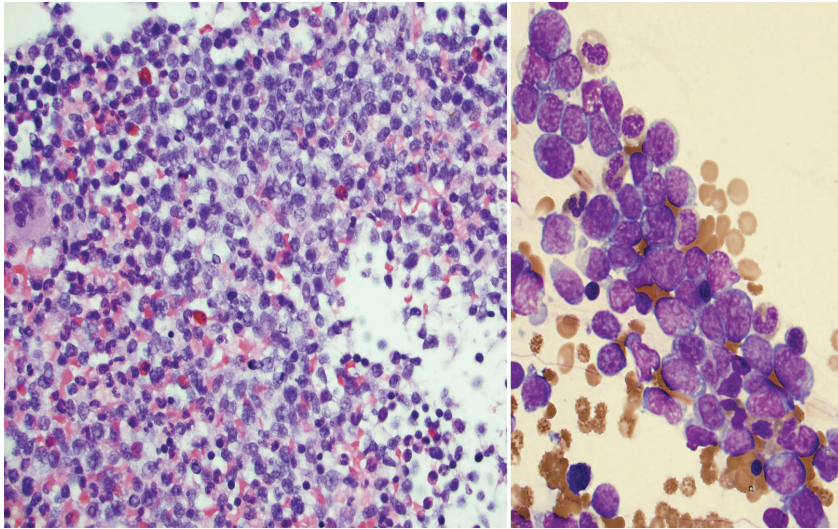


Figure 2. At high magnification (600x), the composite picture shows the clot biopsy section to the left with sheets of neoplastic cells with slightly irregular nuclear contours and inconspicuous nucleoli. Also seen are scattered admixed mature neutrophils, eosinophils, and a megakaryocyte. The aspirate smear to the right also shows sheets of immature-looking cells with slightly irregular nuclear contours, open chromatin, and inconspicuous to prominent nucleoli. No cytoplasmic granules are noted.

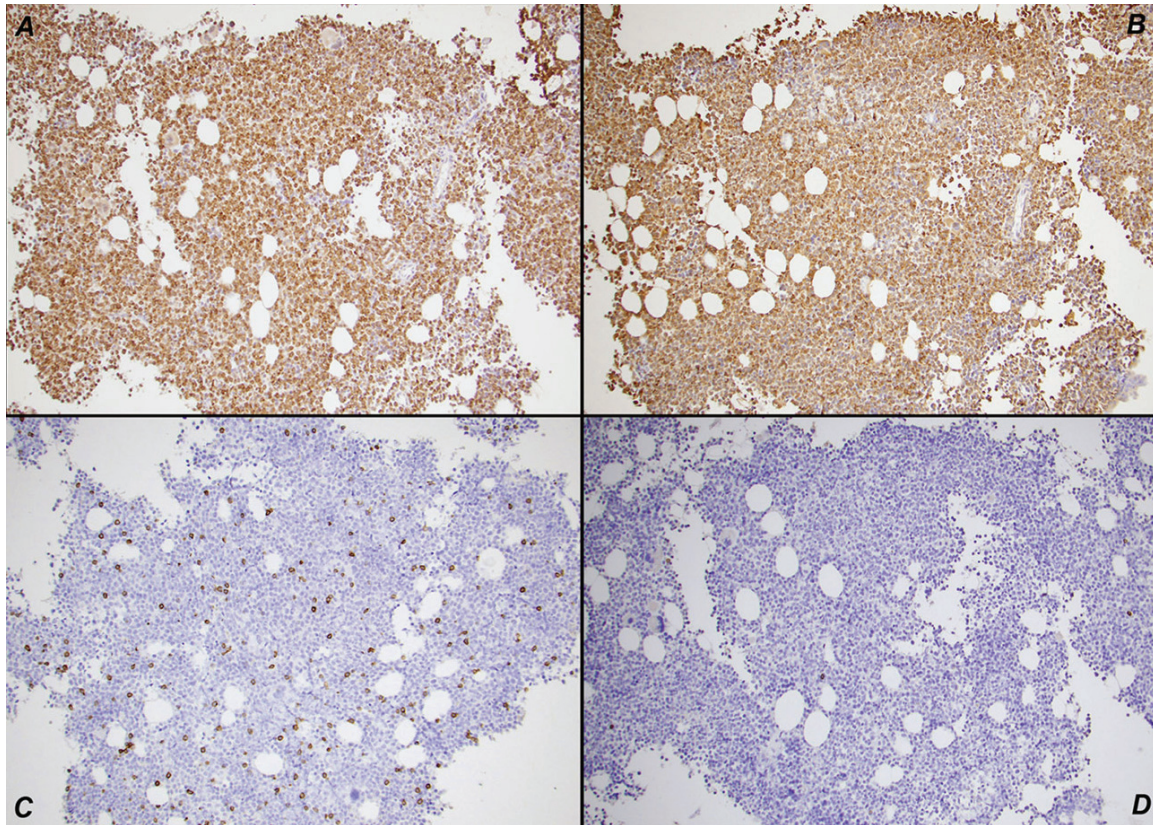


Figure 3. At low magnification (40x), the composite picture shows that the neoplastic cells clearly express CD3 (A) and CD56 (B) and are negative for CD5 (C) by immunohistochemistry. CD20 (D) only highlights rare B lymphocytes.

phoma patients to develop. These morphologic and immunophenotypic features are similar to those seen in *de novo* aggressive NK-cell leuke-

mia, which is defined in the World Health Organization (WHO) classification as systemic proliferation of NK cells with an aggressive and

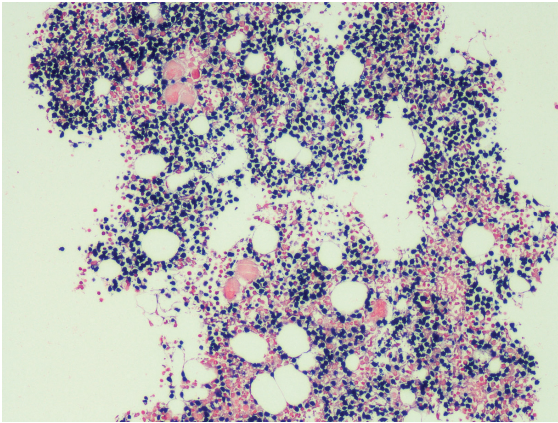


Figure 4. EBV is detected in the neoplastic cells of the bone marrow by in situ hybridization (EBER) using a 100x magnification.

often fatal clinical course [3]. Our case presentation may be concordant with the hypothesis that aggressive NK-cell leukemia may represent the leukemic counterpart of nasal NK/T cell lymphoma similar to the relationship between lymphoblastic lymphoma and acute lymphoblastic leukemia (ALL). This hypothesis is mainly based on the similar ethnic background (Asian), morphology, immunophenotype, and genotype (lack of T-cell receptor gene rearrangements) of both entities. Moreover, EBV is detected in over 75% of aggressive NK-cell leukemia cases and near 100% in nasal NK/T cell lymphoma [3,4]. Cytogenetic abnormalities were originally reported as being relatively similar in both entities with abnormalities in chromosomes 6, 7, 11, and 17 as the most frequently reported in addition to complex karyotypic abnormalities [4-6]. Despite these similarities, extensive bone marrow and peripheral blood involvement in a leukemic fashion as advanced stage of nasal type NK/T cell lymphoma is extremely rare.

Currently, the most accepted differentiating features between aggressive NK cell leukemia and disseminated nasal NK/T cell lymphoma are that the latter often presents at an older age (almost a decade older with a median age of 50 years-old), shows no manifestations of B symptoms, less frequency of hepatosplenic and bone marrow involvement, higher frequency of cutaneous involvement, less frequent expression of CD16, and usually does not disseminate at presentation but rather later on during the course of the disease [3,7-10]. Moreover, an

array-based comparative genomic hybridization (CGH) study has reported significance differences in genetic changes between the two disorders, where 6q- is more common in nasal NK cell lymphoma but rare in aggressive NK cell leukemia, while 7p-, 17p-, and 1q+ are more frequent in aggressive NK cell leukemia [11]. By applying these differentiating criteria to our patient, she is nearly 50 years old, showed no B symptoms, no definitive evidence of hepatosplenic involvement, and no expression of CD16, all are factors that are in line with a diagnosis of nasal NK cell lymphoma over aggressive NK cell leukemia. Although our patient showed a deletion in chromosome 6 by cytogenetic analysis, it has a different breakpoint than that proposed by Nakashima *et al* [11]. The unusual presentation for the patient is the extensive bone marrow involvement and its occurrence relatively early on during the course of the disease.

Some investigators have questioned the prognostic significance and the accuracy of bone marrow staging and whether, minimal bone marrow involvement can be missed by routine histological examination. Sung *et al* performed EBER in 40 bone marrow specimens from patients with extranodal nasal NK/T cell lymphoma, where they have detected marrow involvement in 3 cases, of which only one was recognized by H&E examination [12]. Another study by Wong *et al* showed occult marrow involvement in 2/25 nasal NK/T lymphoma patients demonstrated by CD56 and EBER expression [13]. Compared to CD56, EBER has been reported to possess more reliability and sensitivity in establishing the diagnosis of nasal NK/T cell lymphoma, and in detecting bone marrow involvement [14,15]. These studies, although show the superiority of ancillary studies over H&E histology in detecting occult disease, provide further evidence that bone marrow involvement is relatively uncommon in nasal NK/T cell lymphoma and when it occurs, it is often occult in nature rendering it hard to detect by morphology.

Although some investigators have reported that marrow involvement, whether at diagnosis or during relapse is associated with higher mortality rates [13,14], it is difficult to establish a definitive prognostic significance in nasal NK/T lymphoma patients with marrow involvement due to the scarcity of number of cases with

bone marrow involvement and the aggressive nature of the disease leading to a short survival time. Furthermore, the differentiation between advanced disseminated nasal NK/T cell lymphoma and aggressive NK cell leukemia can be hard due to the many overlapping features between the two entities and the lack of solid distinguishing criteria. Due to the complexity of the interrelationship between the two entities, additional studies are needed to further clarify whether they represent different clinical presentation of the same disease.

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