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Case Report

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PEG-Asparaginase Based Multidrug Chemotherapy is Effective for Refractory Disseminated Extranodal NK/T-Cell Lymphoma With Leptomentigeal Involvement: A Clinical Case Report and Review of Literature

Hong Cheng[a, d], Tatyana Feldman[b], Kar F. Chow[a], Anthony Mato[b], David Panush[c], Xiao Yan Yang[a], Andre Goy[b], Fermina M. Mazzella[d], Pritish K. Bhattacharyya[a, e]

Abstract

Extranodal natural killer/T-cell lymphoma, nasal type (ENKTL) is an Epstein-Barr virus (EBV)-associated lymphoid malignancy derived from natural killer or cytotoxic T-cells. While many patients with early stage ENKTL can achieve complete remission after radiochemotherapy, patients with advanced stage, relapsed or refractory ENKTL usually respond poorly to conventional treatment. We present a case of ENKTL which did not respond to regular radiochemotherapy. One month after treatment, the disease progressed with dissemination to the mesenteric lymph nodes as well as central nervous system (CNS). However, the disease was effectively controlled by the addition of pegylated asparaginase (PEG-asparaginase), dexamethasone, and methotrexate to the regiment. Our data suggest that PEG-asparaginase based multidrug chemotherapy is a promising strategy to treat refractory and disseminated ENKTL involving the CNS.

Keywords: Extranodal NK/T-cell lymphoma; PEG-asparaginase; Central nervous system

Introduction

Extranodal NK/T-cell lymphoma, nasal type (ENKTL) is a rare and aggressive lymphoma derived from natural killer (NK) cell or, occasionally, cytotoxic T cells [1, 2]. It is more prevalent in Asia and Latin America than in Europe and North America. Epidemiological studies indicate pesticides and chemical solvents can be causative, but HLA antigen may also contribute to the geographic predisposition [3]. While the mechanism underlying ENKTL development is poorly understood, its close association with Epstein–Barr virus (EBV) in a clonal episomal form suggests a probable pathogenic role of the virus [4, 5]. A proposed model of ENKTL pathogenesis involves the deregulated P53 tumor suppressor function [6], activation of nuclear factor kappa B (NF-κB) pathways [7] and other pathways, such as Myc and STAT3 pathways, possibly driven by EBV LMP-1. The cumulative consequence of these oncogenic pathways results in up-regulation of proliferation and anti-apoptotic signals in tumor cells [8-10].

The most commonly involved site in ENKTL is the upper aerodigestive tract, including nasal cavity, nasopharynx, paranasal sinuses, and palate, with the nasal cavity considered as the prototypic site. The disease may rapidly disseminate to skin, gastrointestinal tract, testis, or cervical lymph nodes [11, 12]. Central nervous system (CNS) involvement is extremely rare and always associated with advanced stage and poor prognosis [13-16].

Microscopically, ENKTL is characterized by a predominantly extranodal lymphocytic infiltrate with an angiocentric and angiodestructive pattern of growth. There is often prominent necrosis. The neoplastic lymphocytes are usually medium to large in size cells. The nuclei are often irregularly folded and elongated with granular chromatin. Nucleoli are generally inconspicuous or small. The classical phenotype includes CD56 and cytoplasmic CD3ε expression and an activated cytotoxic profile with perforin, granzyme B, and TIA-1 expression [17].

The differential diagnosis for ENKTL includes lymphomatoid granulomatosis, Wegener's granulomatosis, diffuse large B-cell lymphoma (DLBCL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), and CD56-positive peripheral T-cell lymphoma [18]. The first three entities are of B-cell origin and are unlikely to be misdiagnosed as ENKTL. While BPDCN can express NK-cell markers such as CD2,

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[a]Department of Pathology, Hackensack University Medical Center, Hackensack, NJ 07601, USA
[b]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ 07601, USA
[c]Department of Radiology, Hackensack University Medical Center, Hackensack, NJ 07601, USA
[d]Department of Pathology and Laboratory Medicine, University of Medicine and Dentistry of New Jersey - New Jersey Medical School, Newark, NJ 07103, USA
[e]Corresponding author: Pritish K. Bhattacharyya, Hematopathology and Molecular Pathology, Hackensack University Medical Center, 30 Prospect Avenue, Hackensack, New Jersey 07601, USA.
Email: pbhattacharyya@hackensackumc.org

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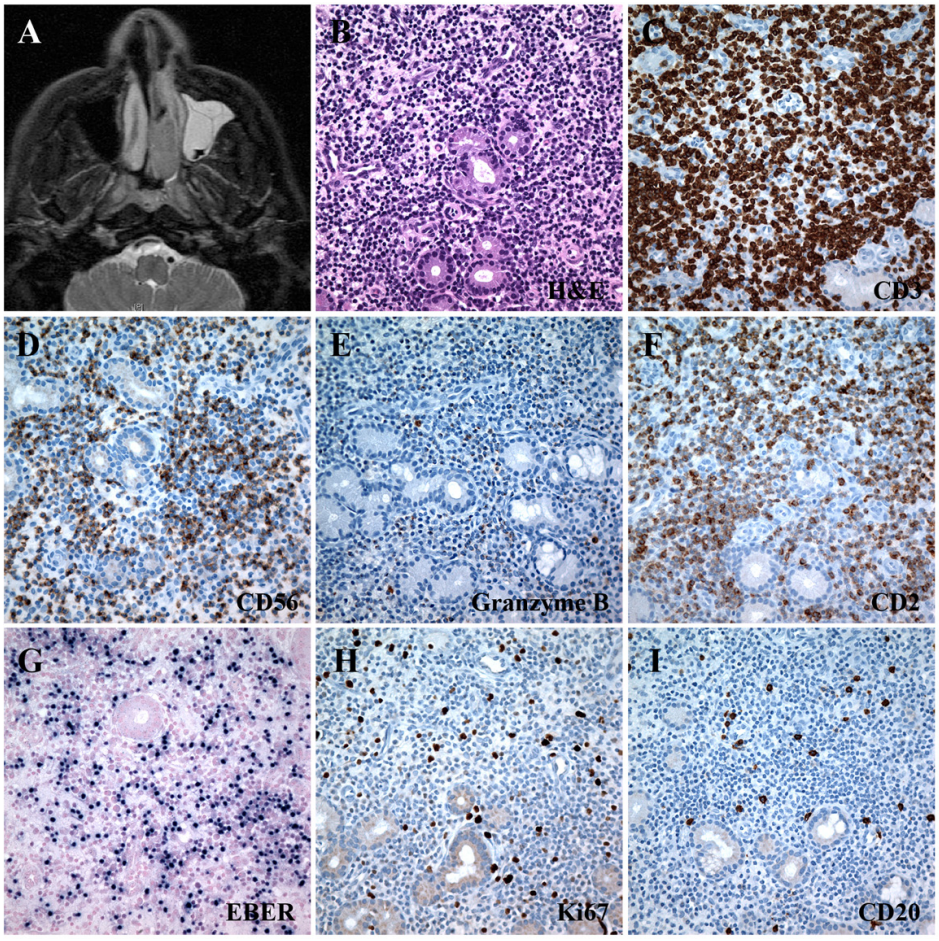

Figure 1. MRI and immunohistochemistry for the nasal mass. A: Initial MRI of the head revealed a nasal mass in the left nasal cavity. B: Microscopic image of the mass on H&E stain. C-I: Immunohistochemistry of the mass revealed the phenotype of extranodal NK/T-cell lymphoma, nasal type.

CD7, and CD56, they are invariably positive for plasmacytoid dendritic cell markers including CD123 and TCL1. A subset of BPDCN's is also positive for myeloid (CD33) and lymphoid (TdT) markers, which are not detected in ENKTL [19]. Peripheral T-cell lymphomas with CD56 expression will often show surface CD3 and T-cell receptor (TCR) by flow cytometry, as well as TCR gene rearrangement by PCR clonality analysis, none of which are seen in ENKTL [20, 21].

ENKTL with local involvement often respond to radiochemotherapy and 70-80% of the patients achieve complete remission. However, patients with disseminated, relapsed or refractory ENKTL usually respond poorly to conventional therapy [22]. We present a case of ENKTL case in which the patient did not response to initial radiochemotherapy. The disease progressed with dissemination to the mesenteric lymph nodes as well as CNS. However, the disease was effectively controlled by the PEG-asparaginase based multidrug chemotherapy.

Case Report

The patient was a 52-year-old man originally from Dominican Republic who presented with nasal obstruction and persistent epistaxis. Initial MRI of his head revealed a mass in the right nasal cavity (Fig. 1A) that showed mucosal ulceration on direct examination. Microscopic examination revealed infiltration of the nasal mucosa by an atypical population of small to medium-sized lymphoid cells with scant cytoplasm, irregular nuclear contours, clumped chromatin, and indistinct nucleoli (Fig. 1B). A prominent angiocentric and angiodestructive growth pattern with focal necrosis was also present. Immunostaining showed the lymphocytes negative for CD 20, positive for CD2, CD3, CD56, and granzyme B (weak). The proliferation index as assessed by Ki67 was approximately 5-10%. In situ hybridization for EBV-encoded RNA (EBER-ISH) was positive in the atypical lymphocytes (Fig. 1C-I). No cytogenetic aberration was detected. The diagnosis of ENKTL, nasal type was made based on the

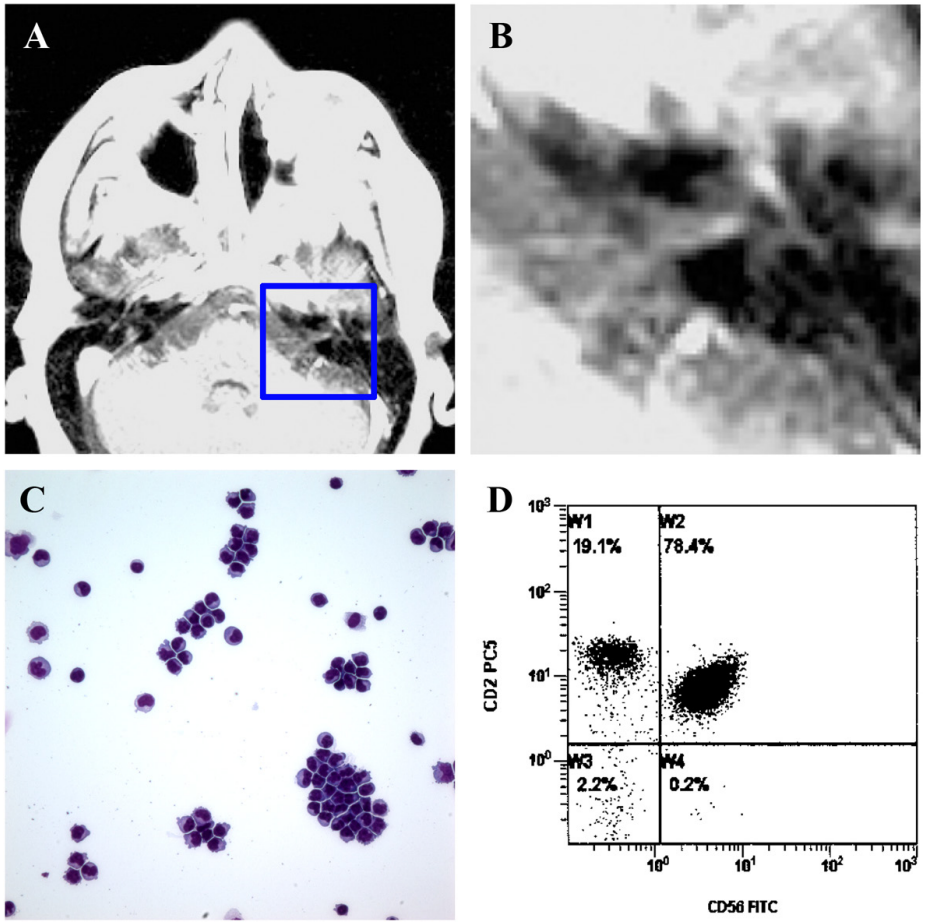

Figure 2. Dissemination of ENKTL, nasal type with leptomentigeal Involvement. A and B: Repeat MRI of head revealed a faint enhancement in the course of left 7th nerve. B is the enlarged image of outlined area in A. C: Cytology of cerebrospinal fluid. D. Flow cytometry of CSF showed around 80% of CD45 positive cells positive for CD2 and CD56.

clinical and histological feature, as well as the immunophenotype. Both the bone marrow biopsy and additional imaging studies were negative, consistent with Stage I disease.

The patient was treated with radiotherapy (5040cGR involved field) and weekly Cisplatin followed by VIPD (etoposide, ifosfamide, cisplatin, and dexamethasone) chemotherapy. One month after completion of the last cycle of chemotherapy, he presented with sudden onset of severe left shoulder pain progressing to weakness of dorsiflextion in his left 4th and 5th fingers and left-sided Bell's palsy. Repeat head and spine MRI was unrevealing except for faint enhancement in the course of left 7th cranial nerve (Fig. 2A, B).

His cerebrospinal fluid (CSF) was significant for an increased white blood cell (WBC) count and elevated protein levels. Microscopic analysis showed the presence of atypical lymphocytes (Fig. 2C). PCR for EBV DNA detected very high levels in the CSF (195,000 copies per mL), but not in the serum. Flow cytometry of the CSF identified a population of lymphoid cells that account for 80% of the cellularity and were positive for CD45, CD2, and CD56, confirming CNS involvement by ENKTL (Fig. 2D). PET scan also showed new small lymphadenopathy in mesenteric area (Fig. 3A, B). Bone marrow was uninvolved. The patient was then treated with several cycles of biweekly high dose dexamethasone, intrathecal methothrexate and high dose methotrexate followed by the addition of PEG-asparaginase (2,500 units per m^2). His Bell's palsy and shoulder pain immediately resolved but dorsiflexion of the left hand remained impaired. Repeat imaging studies and CSF analysis showed clearance of the disease systemically (Fig. 3C, D), as well as in CSF (data not shown). One month after the initial usage of PEG-asparaginase, the patient expired from complications of acute pancreatitis prior to the planned allogenic transplant.

Discussion

The nasal cavity is the most frequently involved site for EN-

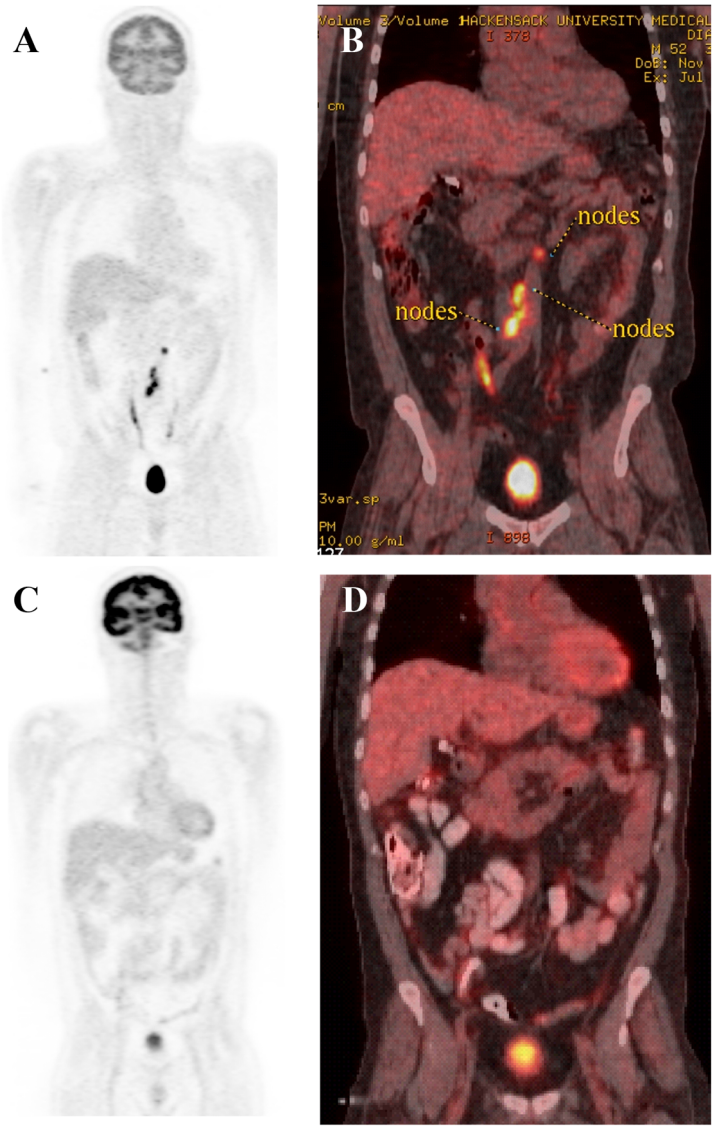

Figure 3. PET scan of body before and after PEG-asparaginase based multidrug chemotherapy. A and B: PET scan before the treatment. C and D: PET scan after the treatment.

KTL. Interestingly, although the CNS and the nasal cavity are anatomically close, CNS involvement by ENKTL is extremely rare [14]. Effective maintenance of the blood brain barrier (BBB) may play an important role in prevention of CNS involvement during the earliest stage of oncogenesis. In addition, the lack of significant lymphatic drainage and the low expression of major histocompatibility complex molecules in normal brain tissue may also contribute to the low incidence of CNS dissemination [23]. However, once the BBB is breached, the prognosis is grim because refractory ENKTL with CNS involvement is usually difficult to treat [13-16]. Thus, CNS prophylaxis should be considered in stage III or IV disease [24].

Due to the overall low incidence of ENKTL, there has been no randomized controlled trial and most treatment protocols are consensus-guided [25]. While localized NK/T-cell lymphomas often respond to radiotherapy [26, 27] or to concurrent radiochemotherapy [28], relapse is common. Current treatment strategies, such as VIPD or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), are clearly sub-optimal and chemoresistance is common [28, 29]. The expression of P-glycoproteins or multidrug resistance gene (MDR) [30], up-regulation of positive regulatory domain I (PRDM 1) [31] by tumor cells, and the absence of granzyme B inhibitor P19 [32] may all account for the chemoresistance and poor prognosis.

Clinical trials and several case reports have demonstrated that asparaginase-based multidrug chemotherapy is ef-

fective in the management of newly diagnosed and relapsed ENKTL [33-35]. Our report further suggests that this regimen may effectively control refractory ENKTL, even with CNS dissemination. The antitumoral mechanism of asparaginase is not affected by MDR. Since NK cells lack asparagine synthase activity, asparaginase can effectively induce apoptosis in these neoplastic cells [36]. PEG-asparaginase, a chemically modified form of asparaginase, has a significantly prolonged half-life with decreased immunogenicity [37]. The main adverse effects of asparaginase include liver dysfunction, myelosuppression, and hypersensitivity reactions. Neutralizing antibodies are also commonly identified due to the need for frequent administration. Less common but potentially more serious side effects are acute pancreatitis and bleeding or thrombotic events secondary to suppression of coagulation protein production by the liver [38]. Most multi-agent chemotherapy regimens also include methotrexate and dexamethasone [33, 35]. Methotrexate shows synergistic effect with asparaginase and is insensitive to the multidrug resistance pathway. The addition of dexamethasone seems to be associated with a lower risk of thrombosis when given with asparaginase [39]. Unfortunately, despite its efficacy, our patient ultimately succumbed to acute pancreatitis, which is likely secondary to PEG-asparaginase.

In summary, refractory ENKTL with CNS involvement is rare and often difficult to treat. PEG-asparaginase based multidrug chemotherapy appears to effectively control disease and should be considered in advanced stage disease.

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