Case Report

Anaplastic lymphoma kinase-positive diffuse large B-cell lymphoma presenting in nasal cavity: a case report and review of literature

Ji Chen, Xiaoli Feng, Mei Dong

Introduction

Anaplastic lymphoma kinase (ALK)-positive diffuse large B-cell lymphoma (DLBCL) is a rare subtype of non-Hodgkin’s lymphoma (NHL) with distinct morphologic and immunohistochemical features. It was first reported in 1997 by Delsol [1], and no more than 100 cases have been reported up to now. It has been identified in all age groups with a male-to-female ratio of approximately 3:5:1 [2, 3]. Although ALK-positive DLBCL primarily involves lymph nodes [3-5], extra-nodal presentations such as the tongue, nasopharynx [6], ovary [2], liver, breast and bone [7] have also been reported. Immunohistochemically ALK-positive DLBCL is characterized by the presence of ALK-positive neoplastic B cells but lack of B (CD20, CD79a), T (CD3, CD5) cell markers and CD30. The aberrant expression of ALK in these tumors usually comes from the results of rearrangement of ALK to other gene’s promoters [8-11]. This disease exhibits a more aggressive clinical course and worse prognosis than typical diffuse large B-cell lymphoma [2]. It shows poor response to standard therapies, such as former standard CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy treatment. In this article, we reported a 57-year-old woman with extra-nodal ALK-positive DLBCL presenting in the nasal region. This type of tumor is rarely reported to be presented in the nasal cavity [2, 7], and to our knowledge, our case is the fifth case reported in this area.

Case report

Clinical history

A 57-year-old female patient with symptoms of constant headaches, left nasal obstruction and bleeding for three months was admitted to the hospital. She had past histories of hypertension for 5 years but was taking medications to keep it under control and her ECOG performance status was 0. Physical examination revealed bleeding secretions in her left nasal area with swelling of nasal root. The mass pushed her left...
ALK-positive DLBCL in nasal cavity

Figure 1. Radiological and morphologic features of the nasal mass. A. CT scan of the nasopharyngeal region showed an irregular, homogeneous mass in the left nasal cavity. B. The immunoblastic/plasmablastic morphology tumor cells were presented with large round nuclei containing prominent nucleoli and rich cytoplasm (H&E, original magnification 400 ×).

The biopsy tissues were formalin fixed and paraffin embedded. H&E sections were made according to standard methods. Immunohistochemical analyses were performed using the ChemMate Envision/HRP Kit (Dako, Glostrup, Denmark). Antibodies used in this study were CK, CK5/6, MUM1, PAX5, P63, Syn, CgA, NSE, s-100, HMB45, Melan-a, Vimentin, CD2, CD3, CD5, CD7, CD4, CD8, CD56, CD30, CD38, ALK, GrB, LCA, CD20, CD79a, CD138, CD56, CgA, and ki-67. The antibodies were purchased from Dako Cytomation (Carpinteria, CA) and Santa Cruz Biotechnology (Santa Cruz, CA). In situ hybridization was performed using an anti-sense probe of Epstein-Barr virus (EBV)-encoded RNA (EBER). However, in this case, the patient complained that biopsy in the nasal area was too painful, so we did not perform biopsy a second time. Therefore, we did not get enough tissue to complete the FISH evaluation for the ALK gene rearrangement. It is unfortunate that this significant test was not performed.

Results

Pathological findings

The tumor cells were large and exhibited the immunoblastic/plasmablastic morphology. The eyeball to the side and outwards, as the result, her vision became blurred and she was always tearing. She felt headaches and numbness in her left cheek. However, she did not present any B symptoms, and her LDH level, hematologic, kidney as well as liver functions were also tested normal. Computed tomography (CT) scan showed an irregular, homogeneous mass in her left nasal cavity which invaded the left ethmoid sinus, extended into left maxillary sinus and sphenoid sinus in the back (Figure 1A). Multiple small lymph nodes as large as 1 cm were found in the bilateral cervical area. CT scans of the head, chest, abdomen, and pelvis were negative. Bone marrow biopsy was also negative for lymphoma. Serum protein electrophoresis (SPEP) did not show a monoclonal spike. Histological examination of the nasal mass revealed a plasmablastic morphology tumor cells. According to the above observations the neoplasm was subsequently classified as stage IAE and her IPI score was 0. After four cycles of CHOEP (cyclophosphamide, epirubicin, vincristine, prednisone, and etoposide) treatment, the tumor in her left cavity disappeared and the symptoms of headache, nasal obstruction and bleeding were greatly relieved. After chemotherapy, the patient achieved complete response, proven by PET-CT scan and following radiotherapy was given to the originally involved area. The patient had successfully completed all of the intended treatment and was advised to follow up regularly.
ALK-positive DLBCL in nasal cavity

Figure 2. Immunohistochemical findings of some characteristic proteins expression in this tumor. Tumor cells were showed restricted cytoplasmic coarsely granular staining pattern of ALK expression (A). Tumor cells were positive for markers suggesting plasmacytic differentiation like MUM1 (B), CD138 (C) but negative for CD56 (D), CD30 (E) and weekly positive for PAX5 (F) (original magnification 400 ×).

neoplastic cells contained large round nuclei with prominent nucleoli and rich cytoplasm (Figure 1B). Immunohistochemically, the neoplastic cells were positive for cytoplasmic ALK (Figure 2A), LCA, CD38, CD4, MUM1 (Figure 2B), CD138 (Figure 2C), and Vimentin, but negative for CD56 (Figure 2D), CD30 (Figure 2E), CK, CK5/6, PAX5 (Figure 2F), P63, Syn, CgA, NSE, s-100, HMB45, and Melan-a. Interestingly, the ALK staining was found to be a restricted cytoplasmic coarsely granular pattern in tumor cells. The neoplastic cells failed to express mature B cells markers such as CD79a (Figure 3A), CD20 (Figure 3B) and T cells markers such as CD2, CD3, CD5 (Figure 3C), CD7 (Figure 3D) and CD8. Ki67 was expressed in nearly 80% of the tumor cells. In situ hybridization analyses revealed that the neoplastic cells were nega-
ALK-positive DLBCL in nasal cavity

tive for EBER. According to these results, a diagnosis of ALK-positive LBCL was made.

Discussion

ALK-positive DLBCL is a rare subtype of non-Hodgkin’s lymphoma (NHL) with distinct morphologic and immunohistochemical features. It was recognized as a distinct entity by the latest WHO classification of Tumors of hematologic malignancies and Lymphoid Tissues. Its confusing morphologic and immunophenotypic features may lead to misdiagnosis with other malignancies. Although ALK-positive DLBCL primarily involves lymph nodes, scattered extranodal presentation have also been reported [2, 3], including the epidural space, ovaries [2], skeleton, nasopharyngeal [6], tongue, brain, and stomach [12]. To our knowledge, very few cases with ALK-positive DLBCL in the nasal cavity have been reported before [2, 7]. As our case was detected in the nasal cavity, the main differential diagnostic considerations should include Extra-nodal NK/T-cell lymphoma, nasal type, and Olfactory neuroblastoma. Extra-nodal NK/T-cell lymphoma, nasal type is the most common tumor in the nasal cavity in East Asian population [13] and usually occurs in the upper respiratory tract, especially the nasal region. It is characterized by generalized necrotizing vasculitis and rapid destruction of the nose and face (midline) by necrotic and granulomatous lesions. It is closely associated with EBV. Extra-nodal NK/T-cell lymphoma, nasal type shows good response to radiotherapy treatment [13]. Another malignant neoplasm that is commonly observed in the nasal cavity is Olfactory neuroblastoma [14]. Surgical resection alone or sur-

Figure 3. Immunohistochemical findings of other characteristic proteins negatively expressed in this tumor. Neoplastic cells failed to express mature B cells markers like CD79a (A), CD20 (B) (original magnification 400 ×) and T cells markers like CD5 (C), CD7 (D) (original magnification 400 ×).
ALK-positive DLBCL in nasal cavity

gery followed by radiation was usually used in the treatment of patients with advanced olfactory neuroblastoma [14]. It shows negative response to CHOP or CHOP-derived chemotherapy treatment. These characteristics can help us distinguish them from ALK-positive DLBCL.

ALK-positive DLBCL also needs to be distinguished from anaplastic variant of DLBCL, ALK-positive anaplastic large cell lymphoma (ALCL), and plasmablastic lymphoma. Histopathological and immunohistochemical analyses can help us make an accurate diagnosis. In ALK-positive DLBCL, the B-cell related antigens such as CD20 (Figure 3A) and CD79a (Figure 3B) and T-cell markers such as CD2, CD3, CD5 (Figure 3C), CD7 (Figure 3D), CD8 and CD30 were undetected. The absence of these antigens can lead us to distinguish ALK-positive DLBCL from anaplastic variant of DLBCL. For the latter is signified by B cell markers such as CD20+, CD79a+, CD30+/-, and ALK- [15]. Another important biomarker is CD30, which was negative in all ALK-positive DLBCL cases. The negativity of biomarker CD30 can be used to differentiate from ALK-positive ALCL, which is positive for ALK, CD30, and T-cell markers but negative for plasma cell marker CD138 and immunoglobulin light chain [16]. In this case, the tumors were positive for biomarkers suggesting plasmacytic differentiation like MUM1 (Figure 2B), EMA, CD138 (Figure 2C). These observations suggest that the tumors might be derived from post-germinal B-cell lymphocytes. However the positivity of ALK expression can aid us to differentiate with the plasmablastic myeloma, which is also CD138 positive but ALK negative [17]. The EBV expression in tumor was also helpful in differential diagnosis. For ALK-positive DLBCL does not seem to be associated with EBV. While the extra-nodal NK/T cell lymphoma, nasal type is highly associated with EBV and CD56+ [13]. Plasmablastic lymphoma mainly occurs in immunodeficient patients and is always EBV+ [17]. All of these immunohistochemical characteristics can help us in making the correct diagnosis.

According to previous studies, the aberrant expression of ALK is implicated in the pathogenesis of this unusual lymphoma. ALK gene is located on chromosome 2p23 and encodes a tyrosine kinase of the insulin receptor superfamily. Normally ALK is not expressed in lymphoid cells. The aberrant expression of ALK in DLBCL results from the fusion of the ALK tyrosine kinase domain and the 5' region of partners, which provides a promoter that is involved in the constitutive activation of the ALK kinase. The 17q23 Clathrin (CLTC) [8, 9] and the 5q35 nucleophosmin (NPM) [10, 11] are the two most commonly observed fusion partners in ALK-positive DLBCL, though other rare translocations could also be detected [18, 19]. In our case, the restricted cytoplasmic coarsely granular staining pattern for ALK expression was observed. This observation suggested the probability of underlying cytogenetic translocation of this tumor. In each tumor case, the ALK staining pattern is unique from each other, and this is because of the underlying cytogenetic translocation each tumor bears [2, 8-11]. Malignant cells carrying the CLTC-ALK/t (2; 17) translocation show distinct cytoplasmic and granular ALK staining pattern [8, 9]. Because the gene clathrin encodes a coated vesicle protein involved in endocytic activity of the cell [20, 21]. In contrast, cases with NPM-ALK/t (2; 5) translocation show a characteristic cytoplasmic and nuclear staining pattern [10, 11]. For the gene NPM1 encodes for nucleophosmin which is subsequently transported from the cytoplasm to the nucleus [22]. Further fluorescence in situ hybridization is needed to confirm the presence of CLTC-ALK/t (2; 17) translocation. However, in this case we were unable to obtain enough tissue to perform this test.

Previous studies showed the overall survival of ALK-positive DLBCL patients were strongly associated with the clinical stages [2, 23]. Early-stage patients tended to achieve longer overall survival than advanced-stage patients [2, 23]. The median survival time and overall survival of advanced-stage patients were only 12.2 months and 20.3 months, respectively [2]. There is not a standard treatment for this kind of disease, however, the combination of radiotherapy and chemotherapy of the localized aggressive non-Hodgkin's lymphoma (NHL) has been widely accepted. Therefore, the patient in this case was treated with chemotherapy and sequential radiation therapy. According to past researches, patients diagnosed with this disease were always treated with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-derived chemotherapy [2, 9]. Considering the classic
ALK-positive DLBCL in nasal cavity

CHOP regimen might be insufficient to treat this lymphoma, we chose CHOP plus etoposide to treat our patient. As CD20 expression was negative in the patient’s tumor, the rituximab was not used in our treatment. After four cycles of CHOEP (cyclophosphamide 1.2 g d1, epirubicin 70 mg d1-2, vincristine 2 mg d1, prednisone 100 mg d1-5, and etoposide 200 mg d1, 100 mg d2, q21d) treatment, the patient achieved CR (complete response) of the tumor. Her headaches and nasal bleeding had completely disappeared. After that she received radiation therapy for the involved area. In the radiation treatment planning, the clinical target volume (CTV) one including: bilateral frontal sinus, maxillary sinus, ethmoid sinus, sphenoid sinus, nasopharynx, part section of oropharynx, bilateral superior parts of cervical lymphatics. The CTV two including: bilateral inferior parts of cervical lymphatics, the CTV was expanded by 0.3 cm to form the planning target volume (PTV). The 6MV-X-ray 9F-IMRT was used and the radiation dose was 95% PTV1 40Gy/2Gy/20f and 95% PTV2 30Gy/1.5Gy/20f. Then she was advised come back to the hospital for regular check-ups. Until now the patient has been free of the disease for seven months. Due to the fact that ALK-positive DLBCL is more aggressive than ALK-negative DLBCL and it has a poor prognosis with conventional therapies, researchers have been trying to find a new way to treat this disease. Rearrangement of a gene EML4-ALK translocation and ALK kinase and lacking the 2; 5 translocation. Crizotinib is a new small-molecule ALK kinase inhibitors. The use of Crizotinib has shown great success in the treatment of NSCLC with EML4-ALK translocation [27, 28] and ALK-positive ALCL [29]. Cerchietti and his colleagues established the first CLTC-ALK positive DLBCL cell line and xenotransplant tumor mouse [30]. In the in vivo studies in the mouse showed that CLTC-ALK positive B-cell lymphomas respond well to ALK inhibitors [30]. Recently Sara Redaelli reported to have administered Crizotinib 250 mg bid for treatment of eleven ALK-positive lymphoma patients who were resistant to cytotoxic-therapy [31]. Nine of the patients were ALK-positive ALCL and two were ALK-positive DLBCL. All of the patients presented B symptoms, had multiple sites of the disease, and their ECOG score were 1-4, but they responded well to Crizotinib. The overall response rate was 10/11 which included 9 CR and 1 PR (partial response) [31]. Maxi Wass also reported that Crizotinib was used to treat a stage IV ALK-positive DLBCL patient who relapsed soon after 6 cycles of standard chemotherapy with CHOP and autologous stem-cell transplantation [32]. The patient achieved partial response to Crizotinib but soon relapsed again [32]. So further basic and clinical researches are needed to understand the mechanisms of ALK-positive DLBCL and to develop new therapeutic method for this disease.

In brief, we reported a rare ALK-positive DLBCL case in the nasal cavity and the patient responded well to the CHOEP treatment and radiation therapy. Considering the patient was treated in the early stage of the disease, future prognosis should be good.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Mei Dong, Department of Medical Oncology, Cancer (Institute) Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, 17 Panjiayuan Nanli, Chaoyang District, Beijing, People’s Republic of China. Tel: (0086) 13811929322; Fax: (0086) 10-87788631; E-mail: Dongmei030224@163.com

References


ALK-positive DLBCL in nasal cavity


ALK-positive DLBCL in nasal cavity


