Int J Clin Exp Pathol 2015;8(2):2123-2130
www.ijcep.com /ISSN:1936-2625/IJCEP0004161

Case Report

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

Ji Chen[1], Xiaoli Feng[2], Mei Dong[3]

[1]Department of Medical Oncology, The Seventh People's Hospital of Chengdu, Chengdu Cancer Hospital, Chengdu 610041, China; Departments of [2]Pathology, [3]Medical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China

Received November 26, 2014; Accepted January 28, 2015; Epub February 1, 2015; Published February 15, 2015

Abstract: 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. We reported a 57-year-old female with ALK-positive DLBCL in her left nasal cavity. Histologically, the tumor cells were characterized by plasmablastic morphology and tested positive for ALK in a cytoplasmic granular staining pattern. The neoplastic cells were positive for CD38, CD4, MUM1, CD138 and Vimentin. However, they failed to express CD56, CD30, as well as mature B cells markers, such as CD79a, CD20 and T cells markers such as CD2, CD3, CD5, CD7 and CD8. The patient achieved complete response after four cycles of CHOEP (cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide) treatment. Then she received radiotherapy of the originally involved area. This case represented a rare ALK-positive DLBCL in the nasal region.

Keywords: Anaplastic lymphoma kinase (ALK), diffuse large B-cell lymphoma, nasal cavity

Introduction

Anaplastic lymphoma kinase (ALK)-positive diffuse large B-cell lymphoma (DLBCL) is a rare subtype of non-Hodgkin's B-cell lymphoma, which is characterized by plasmablastic or immunoblastic morphology. 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, and 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

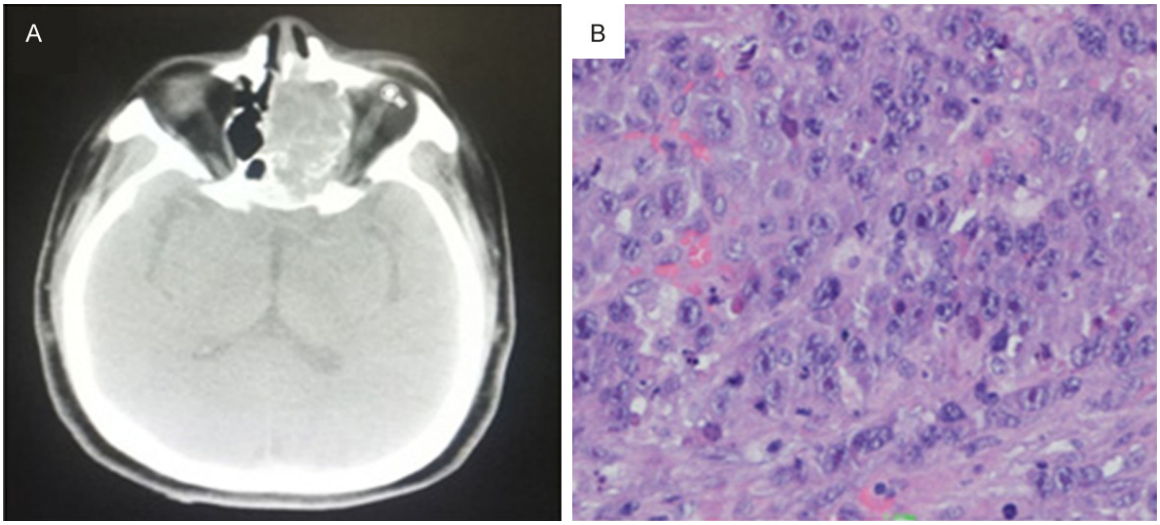

Figure 1. Radiological and morphologic features of the nasal mass. A. CT scan of the nasopharyngeal region showed an irregular, homogeneous mass in the left nasal cavity. B. The immunoblastic/plasmablastic morphology tumor cells were presented with large round nuclei containing prominent nucleoli and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

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.

Immunohistochemistry and In situ hybridization

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 Epstain-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

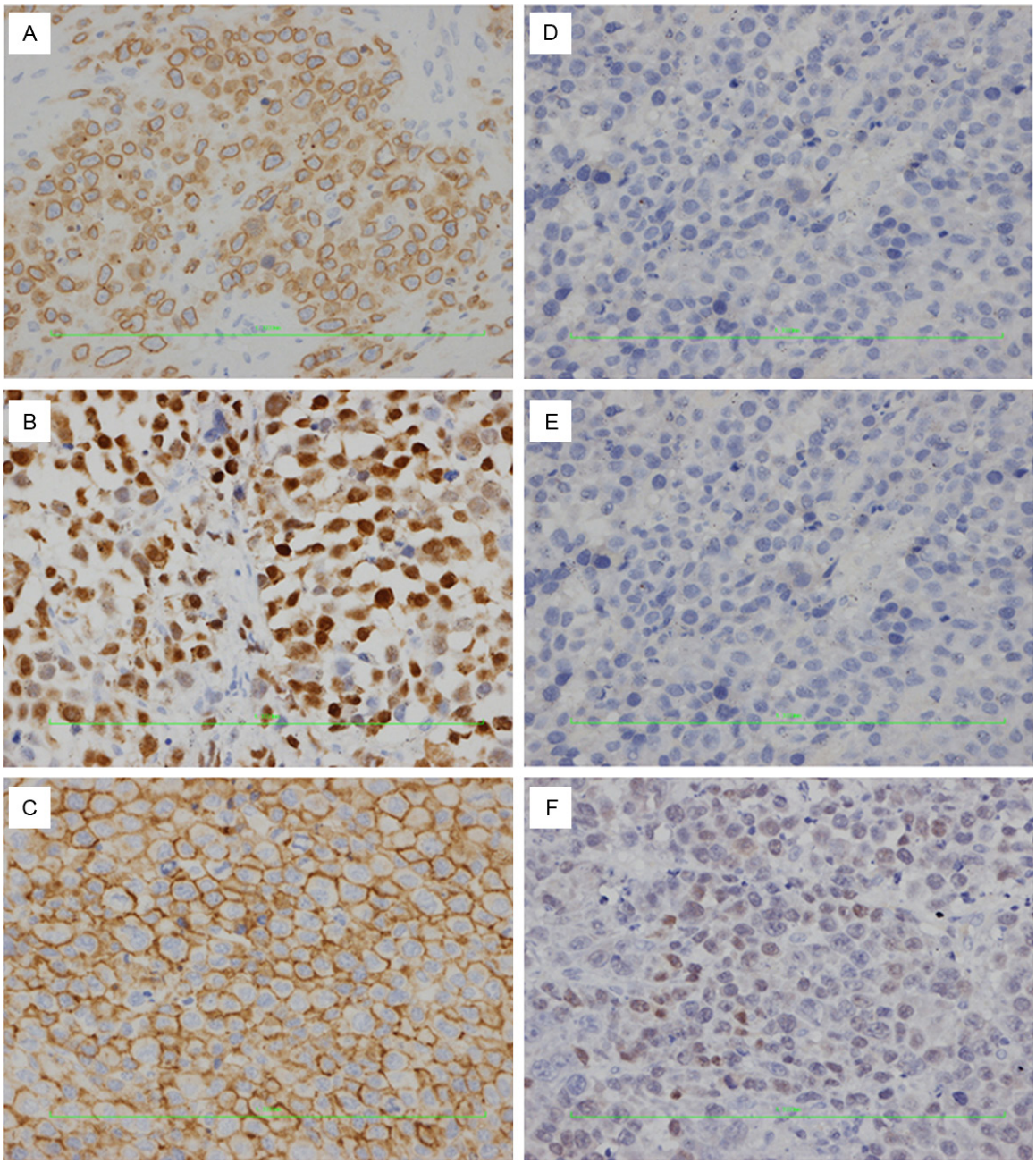

Figure 2. Immunohistochemical findings of some characteristic proteins expression in this tumor. Tumor cells were showed restricted cytoplasmic coarsely granular staining pattern of ALK expression (A). Tumor cells were positive for markers suggesting plasmacytic differentiation like MUM1 (B), CD138 (C) 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-

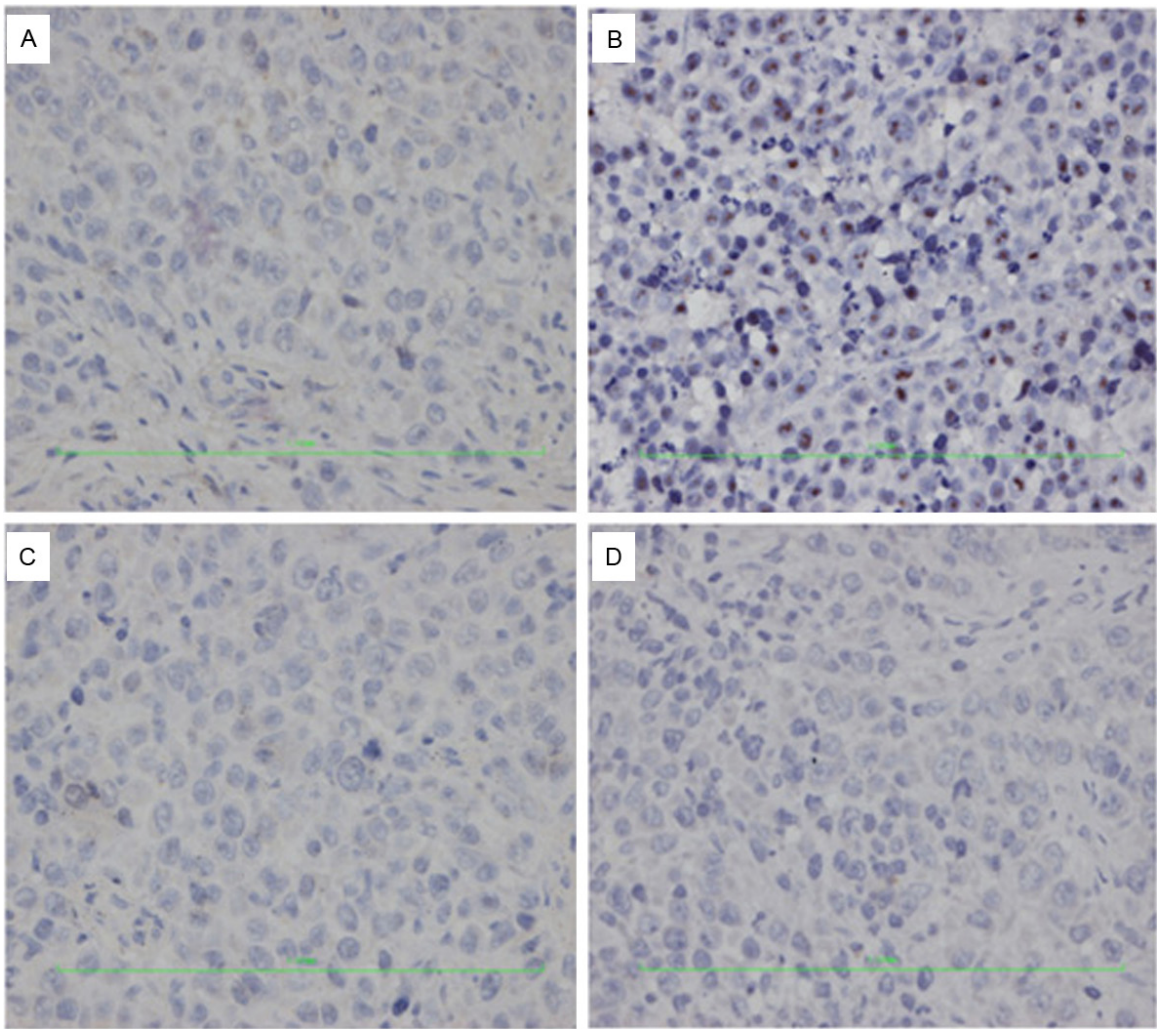

Figure 3. Immunohistochemical findings of other characteristic proteins negatively expressed in this tumor. Neoplastic cells failed to express mature B cells markers like CD79a (A), CD20 (B) (original magnification 400 ×) and T cells markers like CD5 (C), CD7 (D) (original magnification 400 ×).

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. Extranodal 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-

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 tumor cells were positive for biomarkers suggesting plasmacytic differentiation like MUM1 (**Figure 2B**), EMA, CD138 (**Figure 2C**). These observations suggest that the tumor cells 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

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 ALK can be detected in various tumors, such as ALK-positive ALCL [15], NSCLC (Non-small-cell carcinoma) [24], neuroblastoma [25], and rhabdomyosarcoma [26]. Uncontrollable expression of this gene could result in the activation of signal pathways that promote oncogenic transformation. 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]. 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

[1] Delsol G, Lamant L, Mariamé B, Pulford K, Dastugue N, Brousset P, Rigal-Huguet F, al Saati T, Cerretti DP, Morris SW, Mason DY. A new subtype of large B-cell lymphoma expressing the ALK kinase and lacking the 2; 5 translocation. Blood 1997; 89: 1483-90.

[2] Laurent C, Do C, Gascoyne RD, Lamant L, Ysebaert L, Laurent G, Delsol G, Brousset P. Anaplastic lymphoma kinase-positive diffuse large B-cell lymphoma: a rare clinicopathologic entity with poor prognosis. J Clin Oncol 2009; 27: 4211-6.

[3] Li S. Anaplastic lymphoma kinase-positive large B-cell lymphoma: a distinct clinicopathological entity. Int J Clin Exp Pathol 2009; 2: 508-18.

[4] Rudzki Z, Rucińska M, Jurczak W, Skotnicki AB, Maramorosz-Kurianowicz M, Mruk A, Piróg K, Utych G, Bodzioch P, Srebro-Stariczyk M,

Włodarska I, Stachura J. ALK-positive diffuse large B-cell lymphoma: two more cases and a brief literature review. Pol J Pathol 2005; 56: 37-45.

[5] Choung HS, Kim HJ, Kim WS, Kim K, Kim SH. Cytomorphology and molecular characterization of CLTC-ALK rearrangement in 2 cases of ALK-positive diffuse large B-cell lymphoma with extensive bone marrow involvement. Korean J Lab Med 2008; 28: 89-94.

[6] Li K, Tipps AM, Wang HY. Anaplastic lymphoma kinase-positive diffuse large B-cell lymphoma presenting as an isolated nasopharyngeal mass: a case report and review of literature. Int J Clin Exp Pathol 2010; 4: 190-6.

[7] Beltran B, Castillo J, Salas R, Quiñones P, Morales D, Hurtado F, Riva L, Winer E. ALK-positive diffuse large B-cell lymphoma: report of four cases and review of the literature. J Hematol Oncol 2009; 2: 11.

[8] Gascoyne RD, Lamant L, Martin-Subero JI, Lestou VS, Harris NL, Müller-Hermelink HK, Seymour JF, Campbell LJ, Horsman DE, Auvigne I, Espinos E, Siebert R, Delsol G. ALK-positive diffuse large B-cell lymphoma is associated with Clathrin-ALK rearrangements: report of 6 cases. Blood 2003; 102: 2568-73.

[9] De Paepe P, Baens M, van Krieken H, Verhasselt B, Stul M, Simons A, Poppe B, Laureys G, Brons P, Vandenberghe P, Speleman F, Praet M, De Wolf-Peeters C, Marynen P, Wlodarska I. ALK activation by the CLTC-ALK fusion is a recurrent event in large B-cell lymphoma. Blood 2003; 102: 2638-41.

[10] Onciu M, Behm FG, Downing JR, Shurtleff SA, Raimondi SC, Ma Z, Morris SW, Kennedy W, Jones SC, Sandlund JT. ALK-positive plasmablastic B-cell lymphoma with expression of the NPM-ALK fusion transcript: report of two cases. Blood 2003; 102: 2642-4.

[11] Adam P, Katzenberger T, Seeberger H, Gattenlöhner S, Wolf J, Steinlein C, Schmid M, Müller-Hermelink HK, Ott G. A case of diffuse large B-cell lymphoma of plasmablastic type associated with the t(2;5)(p23;q35) chromosome translocation. Am J Surg Pathol 2003; 27: 1473-6.

[12] McManus DT, Catherwood MA, Carey PD, Cuthbert RJ, Alexander HD. ALK-positive diffuse large B-cell lymphoma of the stomach associated with a clathrin-ALK rearrangement. Hum Pathol 2004; 35: 1285-8.

[13] Suzuki R. NK/T-cell lymphomas: pathobiology, prognosis and treatment paradigm. Curr Oncol Rep 2012; 14: 395-402.

[14] Kondo N, Takahashi H, Nii Y, Nagao J. Olfactory Neuroblastoma: 15 Years of Experience. Anticancer Res 2012; 32: 1697-1703.

[15] Pletneva MA, Smith LB. Anaplastic large cell lymphoma: features presenting diagnostic challenges. Arch Pathol Lab Med 2014; 138: 1290-4.

[16] Ferreri AJ, Govi S, Pileri SA, Savage KJ. Anaplastic large cell lymphoma, ALK-positive. Crit Rev Oncol Hematol 2012; 83: 293-302.

[17] Vega F, Chang CC, Medeiros LJ, Udden MM, Cho-Vega JH, Lau CC, Finch CJ, Vilchez RA, McGregor D, Jorgensen JL. Plasmablastic lymphomas and plasmablastic plasma cell myelomas have nearly identical immunophenotypic profiles. Mod Pathol 2005; 18: 806-15.

[18] Takeuchi K, Soda M, Togashi Y, Ota Y, Sekiguchi Y, Hatano S, Asaka R, Noguchi M, Mano H. Identification of a novel fusion, SQSTM1-ALK, in ALK-positive large B-cell lymphoma. Haematologica 2011; 96: 464-7.

[19] Van Roosbroeck K, Cools J, Dierickx D, Thomas J, Vandenberghe P, Stul M, Delabie J, De Wolf-Peeters C, Marynen P, Wlodarska I. ALK-positive large B-cell lymphomas with cryptic SEC31A-ALK and NPM1-ALK fusions. Haematologica 2010; 95: 509-13.

[20] Gong Q, Huntsman C, Ma D. Clathrin-independent internalization and recycling. J Cell Mol Med 2008; 12: 126-44.

[21] Rappoport JZ. Focusing on clathrin-mediated endocytosis. Biochem J 2008; 412: 415-23.

[22] Grisendi S, Mecucci C, Falini B. Nucleophosmin and cancer. Nat Rev Cancer 2006; 6: 493-505.

[23] Reichard KK, McKenna RW, Kroft SH. ALK-positive diffuse large B-cell lymphoma: report of four cases and review of the literature. Mod Pathol 2007; 20: 310-9.

[24] Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, Fujiwara S, Watanabe H, Kurashina K, Hatanaka H, Bando M, Ohno S, Ishikawa Y, Aburatani H, Niki T, Sohara Y, Sugiyama Y, Mano H. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007; 448: 561-6.

[25] Janoueix-Lerosey I, Lequin D, Brugières L, Ribeiro A, de Pontual L, Combaret V, Raynal V, Puisieux A, Schleiermacher G, Pierron G, Valteau-Couanet D,Frebourg T, Michon J, Lyonnet S, Amiel J, Delattre O. Somatic and germline activating mutations of the ALK kinase receptor in neuroblastoma. Nature 2008; 455: 967-70.

[26] van Gaal JC, Flucke UE, Roeffen MH, de Bont ES, Sleijfer S, Mavinkurve-Groothuis AM, Suurmeijer AJ, van der Graaf WT, Versleijen-Jonkers YM. Anaplastic lymphoma kinase aberrations in rhabdomyosarcoma: clinical and prognostic implications. J Clin Oncol 2012; 30: 308-15.

[27] Shaw AT, Kim DW, Nakagawa K, Seto T, Crinó L, Ahn MJ, De Pas T, Besse B, Solomon BJ, Blackhall F, Wu YL, Thomas M, O'Byrne KJ, Moro-

Sibilot D, Camidge DR, Mok T, Hirsh V, Riely GJ, Iyer S, Tassell V, Polli A, Wilner KD, Jänne PA. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013; 368: 2385-94.

[28] Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, Ou SH, Dezube BJ, Jänne PA, Costa DB, Varella-Garcia M, Kim WH, Lynch TJ, Fidias P, Stubbs H, Engelman JA, Sequist LV, Tan W, Gandhi L, Mino-Kenudson M, Wei GC, Shreeve SM, Ratain MJ, Settleman J, Christensen JG, Haber DA, Wilner K,Salgia R, Shapiro GI, Clark JW, Iafrate AJ. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010; 363: 1693-1703.

[29] Mossé YP, Lim MS, Voss SD, Wilner K, Ruffner K, Laliberte J, Rolland D, Balis FM, Maris JM, Weigel BJ, Ingle AM, Ahern C, Adamson PC, Blaney SM. Safety and activity of crizotinib for paediatric patients with refractory solid tumours or anaplastic large-cell lymphoma: a Children's Oncology Group phase 1 consortium study. Lancet Oncol 2013; 14: 472-80.

[30] Cerchietti L, Damm-Welk C, Vater I, Klapper W, Harder L, Pott C, Yang SN, Reiter A, Siebert R, Melnick A, Woessmann W. Inhibition of anaplastic lymphoma kinase (ALK) activity provides a therapeutic approach for CLTC-ALK-positive human diffuse large B cell lymphomas. PLoS One 2011; 6: e18436.

[31] Gambacorti Passerini C, Farina F, Stasia A, Redaelli S, Ceccon M, Mologni L, Messa C, Guerra L, Giudici G, Sala E, Mussolin L, Deeren D, King MH, Steurer M, Ordemann R, Cohen AM, Grube M, Bernard L, Chiriano G, Antolini L, Piazza R. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. J Natl Cancer Inst 2014; 106: djt378.

[32] Wass M, Behlendorf T, Schädlich B, Mottok A, Rosenwald A, Schmoll HJ, Jordan K. Crizotinib in refractory ALK-positive diffuse large B-cell lymphoma: a case report with a short-term response. Eur J Haematol 2014; 92: 268-70.