Case Report
Anaplastic lymphoma kinase-positive large B-cell lymphoma with a diagnostic pitfall of carcinoma: a case report

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Abstract: Anaplastic lymphoma kinase-positive large B-cell lymphoma (ALK+LBCL) is a rare non-Hodgkin lymphoma that exhibits a characteristic immunoblastic/plasmablastic morphology and is frequently expressing Clathrin-anaplastic lymphoma kinase fusion protein. Since being negative for T- and B-lineage markers, this tumor is easy to be misdiagnosed, especially when it has unusual morphology and immunophenotype. Here, we report an ALK+LBCL with a diagnostic pitfall of carcinoma. The patient was a 28-year-old man with enlargement of a right submandibular lymph node. Morphologically, the lymph node had an unusual nodular growth pattern, with nodules surrounded by collagen bands. The neoplastic cells expressed epithelial membrane antigen, CD138, CD38, Mum-1, but negative for T- and B-lineage markers, and showed a strong granular cytoplasmic Anaplastic Lymphoma Kinase staining pattern. Some tumor cells had the expressing of Cytokeratin.

Keywords: Anaplastic lymphoma kinase, B cell lymphoma, pathologic diagnosis

Introduction
Anaplastic lymphoma kinase-positive large B-cell lymphoma (ALK+LBCL) is a rare, distinct and aggressive subtype of diffuse large B-cell lymphoma (DLBCL), accounting for less than 1% of DLBCL [1]. Since it was first reported by Delsol and his colleagues [2] in 1997, there have been approximately 60 reported cases in literature. It occurs in all age group (range 9-90, median 35-36 years) with a male predominance (M:F ratio, 3-5:1) [1, 3, 4]. Although ALK+LBCL primarily involves lymph nodes (most commonly to be cervical nodes), extranodal involvement has been reported, such as the brain, nasopharynx, and stomach [4-6]. Most patients follow an aggressive clinical course, presenting with advanced stage (III or IV) and the prognosis is poor with a 5-year overall survival rate of 25% [4]. Histopathologically, the lymphoma shows a sinusoidal growth pattern and is composed of monomorphic large immunoblast- or plasmablast-like cells, but may occasionally show atypical morphology mimicking other types of tumors [7-11]. Immunophenotypically, neoplastic cells express plasma cell markers but negative for B-cell markers. ALK expression in immunohistochemistry is the key for the correct diagnosis of the atypical neoplasm. In the present study, we reported a case of ALK+LBCL with nodular growth pattern and fibrosis capsule forming, which is similar with carcinoma.

Clinical history
A 28-year-old man developed gradual painless enlargement of a right submandibular lymph node (the maximum diameter was 5 cm) without other symptoms, without remarkable past medical history and family history. On the physical examination, there was no other superficial lymph nodes enlargement and the blood test appeared normal. The enlarged submandibular lymph node excisional biopsy was performed and reported as ALK+LBCL. The bone marrow biopsy showed no involvement. Then the patient underwent whole-body positron emission...
ALK positive large B cell lymphoma

Figure 1. Morphologic features of the lymph node. A. A multiple nodular growing pattern was seen at low magnification (HE, magnification was seen in figure). B and C. At higher magnification, the nodules were surrounded by collagen bands. (HE, original magnification 40× and 100× respectively). D. At higher magnification, the majority neoplastic cells were medium to large sized, and immunoblastic-appearing with oval to round nuclei, dispersed chromatin, a single, prominent, central nucleolus and moderate amounts of amphophilic cytoplasm.

Figure 2. The neoplastic cells were strongly and diffusely positive for CD138 (A), EMA (B), negative for CD20 (C), CD3 (D) and Cytokeratin (E), with a cytoplasmic granular staining of anaplastic lymphoma kinase (ALK) (F). Cytokeratin had non-specific staining (Original magnification for all pictures were 20×).

tomography/computed tomography (PET-CT) for evaluation of extramedullary disease and did not show abnormality in any other regions. The patient was considered as being at Stage IA according to the Ann Arbor stage system, with a low International Prognostic Index risk. He had not received any treatment until presented with generalized cervical lymph nodes enlargement (the maximum diameter was 2.7 cm) 6 months later. The second lymph node biopsy was performed and ALK+LBCL was diagnosed. The patient was treated with 6-cycle CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisolone) and 2-cycle DICE (dexamethasone, ifosfamide, cisplatin, etoposide) as second-line treatment. The patient stopped chemotherapy for pan-cytopenia and then received radiotherapy 20 times. Unfortunately, a few months later, the patient presented with central nervous system involvement and passed away 25 months after the initial diagnosis.

Morphologic features

At lower magnification, the lymph node capsule thickened and the architecture was effaced. Lymph node had a nodular growth pattern, with nodules surrounded by colla-
ALK positive large B cell lymphoma

Discussion

In reporting this case, we would like to focus on a potential pitfall in pathology practice. Nowadays, despite the full knowledge of this entity, because of the morphologic and immunophenotypic overlap with other hematologic and nonhematologic malignancies, diagnosis of ALK+LBCL in routine pathology remains challenging. Several cases in the literatures were actually misdiagnosed as ALK-positive anaplastic large cell lymphoma (ALK+ALCL) [12], poorly differentiated or anaplastic carcinoma [4], plasmablastic lymphoma [13]. The diagnosis of the tumor requires synthesis of the morphologic features and immunohistochemical findings. The tumor usually shows a sinusoidal growth pattern and is composed of monomorphic large immunoblastic or plasmablastic cells with strong ALK protein expression [14]. In IHC, lymphoma cells express CD138, CD38 and usually cytoplasmic IgA with light chain restriction, and are negative for both B and T lineage markers (Table 1).

ALK+ALCL and ALK+LBCL share some common features, including the expression of ALK and EMA, the lack of both T and B lineage immunophenotype, tendency of sinusoidal growth pattern. However, these two entities can be discriminated, based not only on morphology but also on the marked homogeneous expression of CD30 in ALCL and CD138 in ALK+LBCL. Moreover, because of its plasmablastic appearance and positive for plasma cell markers, neg-

Immunohistochemical characteristics were as following. The neoplastic cells were positive for ALK in a granular cytoplasmic distribution with accentuation in the para-nuclear Golgi area of the cytoplasm. They were negative for B cell markers (CD20, CD79a, pax-5) and T/NK cell markers (CD2, CD3, CD4, CD8, CD5, CD7, CD56, GranzymB, TIA-1). While these cells were strong positive for the plasma cell markers (CD138, CD38, Mum-1 and EMA) and showed weak positive kappa but negative lambda, indicating a light chain restriction. In addition, the neoplastic cells were weak and partial positive for cytokeratin, which might be non-specific staining. The neoplasm was negative for CD30, CD15, MPO, and Melan-A, S-100, HHV8 (Figure 2).

In situ hybridization for Epstein-Barr virus was negative.

Polymerase chain reaction (PCR) based clone study was performed according to the BIOMED-2 protocols. IGK and IGH gene rearrangement revealed clonal results (Figure 3).

Figure 3. Polymerase chain reaction-(PCR) based clonal study was performed according to the BIOMED-2 protocols. IGK and IGH gene rearrangement revealed clonal results.
ALK positive large B cell lymphoma

Table 1. Differential diagnosis of ALK+LBCL and predominant staining patterns with several antibodies

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<th>ALK+LBCL</th>
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This table summarizes the predominant staining patterns for these entities, with the understanding that exceptional cases have been reported.

ative for both T- and B-cell markers, ALK+LBCL has to be distinguished from plasmablastic lymphoma (PBL). In pathologic features, majority of PBL are EBV positive, whereas ALK+LBCL is EBV negative and shows ALK protein expression. Clinically, PBL was predominantly described in the immunodeficiency patients and extranodal sites, rarely in immunocompetent patients and nodal presentation [15]. ALK+LBCL occurs in non immunocompromised patients and has a predominant nodal distribution, although it can occur in extranodal sites [4].

The typical cohesive and prominent sinusoidal growth pattern of nodal infiltration morphologically mimics a metastatic, poor differentiated carcinoma, especially when the fibrosis nodular formed, as in our case. Immunoreactivity can be misleading: cytokeratin expression in ALK+LBCL has already been described in sporadic patients [16]. The EMA positivity and the negativity for CD45 and B- and T-cell markers also may lead to the misdiagnosis of carcinoma. This misdiagnosis may be further supported by the fact that CD138 is positive in the majority of carcinomas [17]. It is also worth mentioning that 2-7% of non-small cell lung carcinoma patients show a cytoplasmic granular staining for ALK [18]. On the other hand, other plasma cell markers, such as CD38, positive for ALK+LBCL, but do not express in carcinomas. Given that ALK+LBCL are generally positive for CD138, CD38 and Mum-1, the combination of these markers, together with ALK positive is useful for differentiating ALK+LBCL from carcinoma.

Based on the HE staining sections, our case was initially considered as metastatic carcinoma, with the differentiated diagnosis of ALCL, metastatic melanoma and seminoma. Therefore, our initial IHC panel was focused on these tumors without considering ALK+LBCL at all. After the first panel IHC, since it was negative for cytokeratin, CD30, S-100 and CD117, we ruled out all of above tumors. However, we were surprised to find that it was positive for ALK and EMA. It was the first time we started to consider whether it was ALK+LBCL. Then we added on the plasma cell and B cell markers and got the corrected diagnosis of ALK+LBCL.

Positivity for ALK immunohistochemistry is the key to the correct diagnosis of this neoplasm. ALK alteration plays an important role in a wide range of human tumors. As for hematopoietic neoplasms, ALK mutation has been identified in subsets of ALCL, DLBCL, histiocytosis [19] and leukemia [20]. The most commonly observed ALK staining pattern was cytoplasmic and granular. Frequently associated with t(2;17) (p23;q23) and more rarely with the t(2;5) (p23;q35). Actually, since the subcellular localization of ALK fusion proteins reflects the product of the partner gene, the ALK immunohistochemistry staining pattern is suggestive of what gene is the ALK fusion partner. A coarse granular cytoplasmic staining (GCS) pattern is observed in case with clathrin (CLTC)-ALK and a nuclear and diffuse cytoplasmic staining pattern are observed in cases with NPM-ALK. Some researchers’ data suggested the possibility that the clinical and biological behaviors of ALK-associated cancers differ according to the ALK fusion partner. The non-GCS pattern was significantly associated with inferior overall survival [21].

In conclusion, we report a case of ALK+LBCL, which had the diagnostic pitfall of carcinoma. A full panel of IHC and detail review of the clinical history is helpful for differential diagnosis.
ALK positive large B cell lymphoma

Disclosure of conflict of interest

None.

Authors’ contribution

Mulan Jin was responsible for the design; Ping Wei contributed to collect and interpret data, and write the manuscript; all authors edited the final version of the manuscript.

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ALK positive large B cell lymphoma

