Int J Clin Exp Pathol 2017;10(3):3727-3734
www.ijcep.com /ISSN:1936-2625/IJCEP0018851

*Original Article*

# D2-40 expression in ALK-positive anaplastic large cell lymphoma resembles CD30 expression: a potential diagnostic pitfall

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Received October 30, 2015; Accepted April 26, 2016; Epub March 1, 2017; Published March 15, 2017

**Abstract:** D2-40 is a useful marker for identifying lymphatic vessels in normal tissues and tumors. D2-40 is also expressed in malignant mesothelioma and seminomas and plays an important role in differential diagnosis. However, expression of D2-40 is very rare in lymphoma. We aimed to retrospectively review two cases of anaplastic lymphoma kinase (ALK) + anaplastic large cell lymphoma (ALCL) that express D2-40 at our hospital. One was a 34-year-old man with a chemotherapy-sensitive tumor in the anterior upper mediastinum. He has been alive for 29 months and has no other health concerns. Another was a 64-year-old man who presented with a lump in his right armpit and had been treated for adenoid cystic carcinoma of the nasal cavity six years ago. He was allergic to hormones and could not tolerate the side effects of chemotherapy; he discontinued therapy and died four months after being diagnosed with ALCL. Histologically, two cases showed "hallmark cells" and these cells expressed D2-40 on their membrane and in the perinuclear (Golgi) region. These cells were also positive for CD30, ALK, EMA, LCA, and CD45RO but negative for cytokeratin, CD117, and HMB45.

**Keywords:** D2-40, anaplastic large cell lymphoma, ALK

## Introduction

Anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphoma (ALCL) is a T cell lymphoma consisting of lymphoid cells that are unusually large with abundant cytoplasm and pleomorphic, often with horseshoe-shaped nuclei. This lymphoma is characterized by a translocation in the ALK gene and expression of ALK and CD30 protein [1]. D2-40 is a monoclonal antibody against an oncofetal antigen, the M2A antigen, a 40-kDa transmembrane sialoglycoprotein with an O-linked, but not N-linked, simple mucin-type carbohydrate structure [2, 3]. It has been implicated in the development of lymphatic vessels, in promoting platelet aggregation and in cancer cell invasion, metastasis, and malignant progression [4-7]. D2-40 positivity can be seen in normal cells, including lymphatic endothelium, glomerular epithelium, mesothelium, type I alveolar cells, myoepithelial cells in breast tissue, interstitial cells of Cajal bodies, peripheral/basal cells of normal sebaceous glands, adrenal cortex, follicular dendritic cells and the brain [8-15]. Some tumors also stain with the D2-40 such as Kaposi's sarcoma, lymphangioma, hemangioblastoma, follicular dendritic cell tumors, malignant mesothelioma, pure seminoma, and the seminomatous components of mixed germ cell tumors, gastrointestinal stromal tumors (GIST), histiocytic sarcomas, monophasic synovial sarcomas, inflammatory myofibroblastic tumors (IMT), malignant peripheral nerve sheath tumors, and leiomyosarcomas [8, 12-23]. Lymphomas rarely express the D2-40 [24].

To date, two cases of ALCL have been reported that were positive for D2-40 [25, 26]. Marián Švajdler detailed a case of $ALK^+$ ALCL with cervical lymphadenopathy and an anterior mediastinal mass in a 9-year-old boy. In this case, ALCL cells displayed a membranous and perinuclear (Golgi) pattern of D2-40 staining [25]. Yu also reported a case of ALCL with a focal non-specific cytoplasmic D2-40 staining pattern [26]. Here, we describe another two case of $ALK^+$ ALCL that are positive for D2-40 with membranous and perinuclear (Golgi) staining pattern.

**Table 1.** Results of the immunohistochemical study

| Antibody | Clone | Antigen retrieval | Tumor cell reaction | |
|---|---|---|---|---|
| | | | Case 1 | Case 2 |
| ALK | Polyclonal | Citric Acid | 4+ | 3+ |
| Actin | 1A4 | None | 0 | 0 |
| CD1a | O10 | EDTA | 0 | ND |
| CD117 | 2E4 | EDTA | 0 | 0 |
| CD20 | L26 | Citric Acid | 0 | 0 |
| CD21 | 2G9 | Citric Acid | 0 | 0 |
| CD3 | SP7 | Citric Acid | 0 | 0 |
| CD30 | Ber-H2 | EDTA | 4+ | 3+ |
| CD34 | QBEnd/10 | Citric Acid | 0 | ND |
| CD45RO | UCHL-1 | None | 3+ | 3+ |
| CD5 | 4C7 | Citric Acid | 0 | 0 |
| CD68 | KP1 | Citric Acid | 0 | 0 |
| Cytokeratin | AE1/AE3 | Pancreatin | 0 | 0 |
| D2-40 | D2-40 | Heat | 4+ | 2+ |
| EMA | E29 | Citric Acid | 4+ | 3+ |
| Factor VIII | Polyclonal | Heat | 0 | 0 |
| Melanoma | HMB45 | Citric Acid | 0 | 0 |
| LCA | PD7/26+2B11 | None | 3+ | 3+ |
| MyoD1 | 5.8A | Pepsin | 0 | 0 |
| Pax-5 | SP34 | Citric Acid | 0 | 0 |
| PLAP | SP15 | None | 0 | 0 |
| S-100 | 4C4.9 | None | 2+ | 0 |
| Vimentin | SP20 | Citric Acid | 3+ | 3+ |

0, no staining; 1+, <25% tumor cells reactive; 2+, 26%-50% tumor cells reactive; 3+, 56%-75% tumor cells reactive; 4+, >76% tumor cells reactive.

## Materials and methods

### *Clinicopathological studies*

The two cases were selected based on their positivity for LCA, CD30, ALK, and D2-40 from our hospital from 2010 to 2015. All specimens were fixed in 10% neutral buffered formalin, dehydrated in graded alcohols, embedded in paraffin, and cut into 4-μm-thick sections for hematoxylin and eosin staining and visualization using light microscopy.

### *Immunohistochemical studies*

Immunohistochemical staining was performed on formalin-fixed, paraffin-embedded tissue sections using the EnVision method. The primary antibodies used included ALK, CD117, CD1a, CD3, CD20 (L26), CD21, CD45RO, CD68, cytokeratin, D2-40, FVIII, epithelial membrane antigen (EMA), leukocyte common antigen (LCA), melanoma, MyoD1, Pax-5, placental alkaline phosphatase (PLAP), S-100, actin, and vimentin. All the antibodies were purchased from Maxin-Bio Co. (Fuzhou, China). The clonal codes and dilution of the antibodies are shown in (**Table 1**).

### *In situ hybridization studies*

In situ hybridization for EBV-encoded RNA was performed on formalin-fixed, paraffin-embedded tissue sections, and the probes used were purchased from Triplex International Biosciences CO., LTD. (Fujian, China).

## Results

### *Clinical data*

*Case 1:* A 34-year-old Chinese man presented with pain in his left shoulder for two months and cough and expectoration for one week; the subject had no significant past medical history. A CT scan was performed and showed a tumor located in the top of his left lung. The non-small cell lung cancer was made. The man came to our hospital for further therapy where both bronchoscopic and puncturation biopsies were conducted; no tumor cells were detected. Therefore, exploratory surgery was then performed. A highly vascularized tumor in the anterior, upper mediastinum was discovered that had infiltrated the left top lobe of the lung. A portion of the tumor was removed for evaluation. After surgery, the two courses of chemotherapy consisting of cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP) were administered. However, multiple swollen lymph nodes were detected in his left armpit. Then the patient was treated with CHOP plus the etoposide VP-16 (CHOPE) and swollen lymph nodes in the armpit disappeared. He has now been alive for 29 months.

*Case 2:* A 64-year-old Chinese man presented with a lump located in the right armpit for 20 days. The tumor was red in color and had an unclear boundary. The left armpit was normal. He had been diagnosed with adenoid cystic carcinoma of the nasal cavity six years ago. He was allergic to hormones. The tumor was excised to determine whether it had originated from the adenoid cystic carcinoma. After surgery, a course of CHOPE chemotherapy was

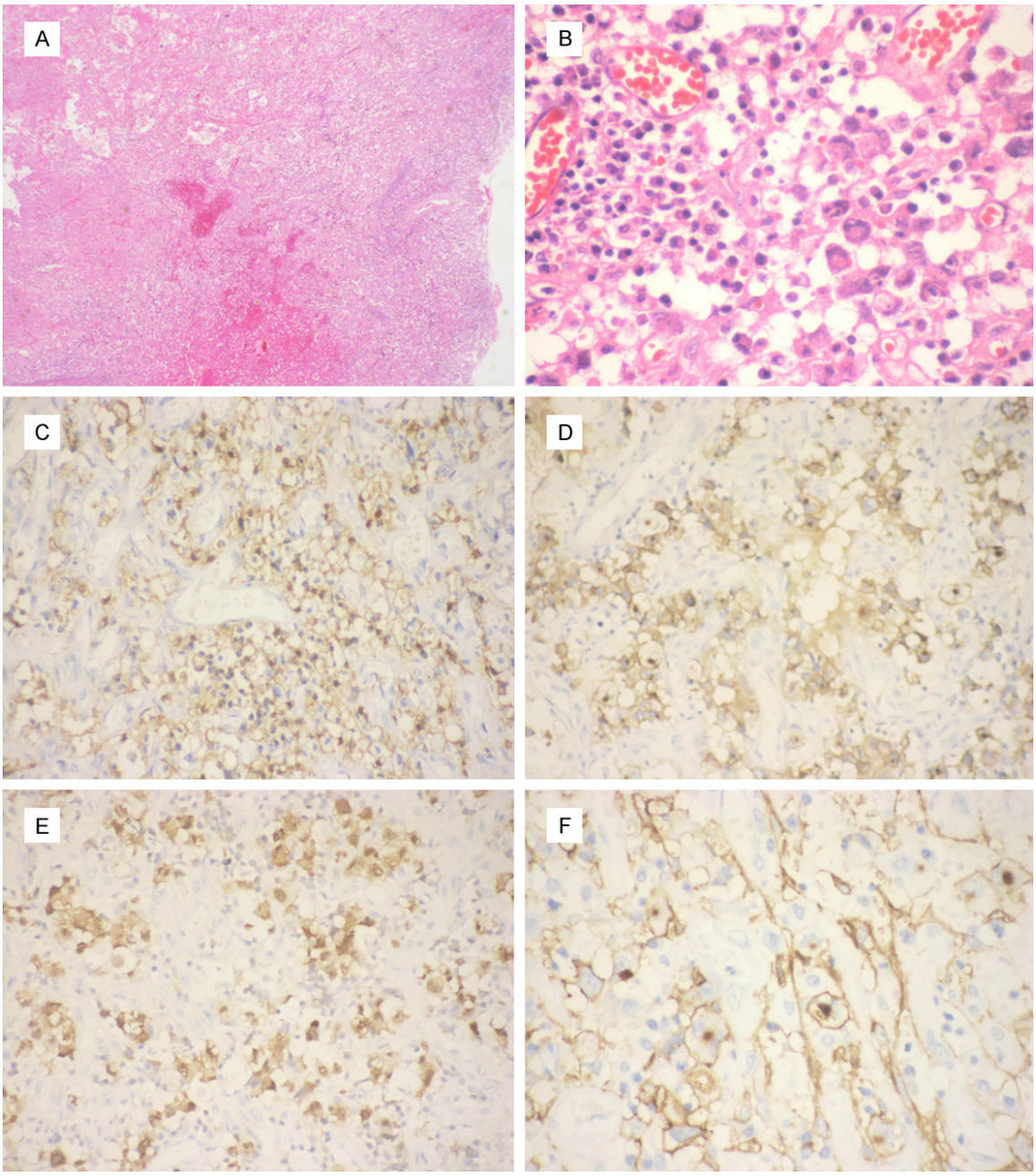


**Figure 1.** Case 1. A. Micrograph showing the abundant blood vessels of tumor at low magnification. B. Micrograph showing the "horseshoe-shaped" nuclei of the tumor cells. The nuclear chromatin was condensed with no protrudent nucleoli and the tumor cells had abundant eosinophilic cytoplasm with focal eosinophilic staining in Golgi region. C. The tumor cells expressing LCA on their surface. D. The tumor cells expressed CD30 on their membrane and in the Golgi region. E. Tumor cells were positive for ALK in the cytoplasm and nuclei. F. The tumor cells stained with the D2-40, mimicking the CD30 expression pattern.

administered. However, during treatment, the nasal cavity adenoid cystic carcinoma recurred. After two courses of CHOPE chemotherapy, he refused additional therapy and died three months later. This patient survived only four months after being diagnosed with ALCL.

*Histopathological, immunohistochemical, and in situ hybridization findings*

The tumor from case 1 was highly vascularized (**Figures 1A**, **2B**) and contained histiocytes and atypical tumor cells that were round or irregular

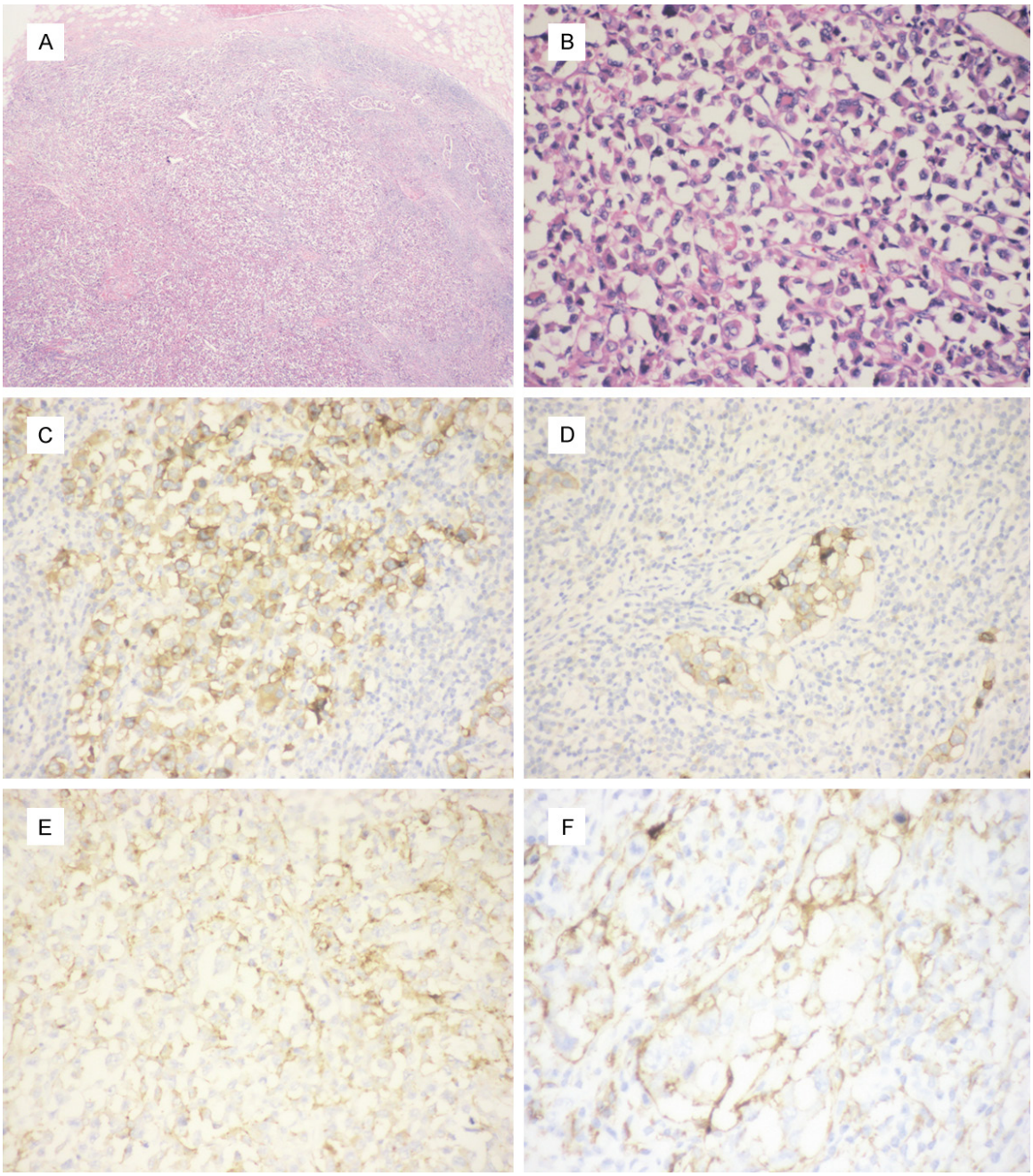


**Figure 2.** Case 2. A. Micrograph showing part of a lymph node destroyed by the tumor cells with the lymph vessels filled with tumor cells. B. The tumor cells displayed an aciniform growth pattern, pleomorphic cells were common, and tumor cells had abundant eosinophilic cytoplasm. C. Tumor cells expressed CD30 on their membrane and in their Golgi region. D. Tumor cells inside the lymph vessels also expressed CD30 but the lymph vessel was negative for CD30. E. Tumor cells stained with the D2-40 mAb, mimicking the CD30 pattern of expression; some lymph vessels expressed the D2-40. F. The tumor cells inside the lymph vessels also expressed the D2-40 and the lymph vessel was positive for D2-40 staining.

with eccentric or horseshoe-shaped nuclei (**Figure 2B**). The nuclear chromatin was condensed with no protrudent nucleoli (**Figure 2B**); the tumor cells contained abundant eosinophilic cytoplasm with focal eosinophilic staining in the Golgi region (**Figure 2B**). There were pleomorphic giant cells present and hemophagocytosis could be seen in some histiocytes. The tumor also contained neutrophils and plasma cells and a few eosinophils. The tumor cells

expressed Vim, LCA (**Figure 2C**), and CD45RO on the cell surface, CD30 (**Figure 2D**), D2-40 (**Figure 2F**) and EMA on the membrane and the Golgi region, and ALK in the cytoplasm and nuclei (**Figure 2E**). These cells also expressed S-100 in the cytoplasm and nuclei. The tumor was negative for all other markers evaluated. The immunohistochemical features are listed in **Table 1**.

Case 2 had a tumor with lymph node involvement (**Figure 2A**). The tumor cells were round to oval or irregular with abundant eosinophilic cytoplasm, with one or two nuclei with condensed to vesicular chromatin and prominent nucleoli (**Figure 2B**). When two nuclei were present, some formed a herringbone pattern. Pleomorphic cells were common and tumor cells grew in an aciniform (**Figure 2B**). Tumor cells were positive for surface expression of Vim, LCA, CD45RO, and EMA; CD30 (**Figure 2C**, **2D**) was expressed on the membrane and the perinuclear (Golgi) region; and ALK was detected in the cytoplasm. While these cells were negative for CK, MoyD1, actin, CD117, HMB45, they were positive of the D2-40 on the membrane and in the perinuclear (Golgi) region as assessed by CD30 staining (**Figure 2E**). However, the tumor cells in the lymphatic vessels stained with D2-40 mainly in the membrane (**Figure 2F**). The immunohistochemical features are listed in **Table 1**.

Additionally, the tumor cells from these two cases were both negative for EBV-encoded RNA as determined using in situ hybridization.

## Discussion

ALCL is a T cell lymphoma that can be divided in to three types: $ALK^+$ systemic ALCL, $ALK^-$ systemic ALCL, and primary cutaneous ALCL. The two cases detailed in this report were both positive for CD30 and LCA; ALK was expressed in the cytoplasm and nuclei in case 1 and in the cytoplasm in case 2. Therefore, these data confirm that both patients had $ALK^+$ systemic ALCL. $ALK^+$ ALCL remains difficult to diagnose definitively, although, it has been well described. It should be distinguished from metastatic carcinoma based on the sinusoidal growth pattern and carcinoma can be excluded by the presence of $CD30^+$ and $ALK^+$ tumor cells. ALCL cells are pleomorphic and have polynucleation, some may exhibit the "horseshoe" nucleus, and they also express S-100. Collectively, these features may lead to ALCL being confused with melanoma. However, unlike melanoma cells, ALCL tumor cells are negative for HMB45 but positive for LCA and CD45RO. Further, ALCL may be mistaken for rhabdomyosarcoma because the tumor cells have an abundant, acidophilic cytoplasm and asymmetrical nucleus but rhabdomyosarcomas express desmin, myoD1, or myogenin and negative for CD30, ALK, and other lymphoma markers. Histiocytic sarcoma also displays a sinusoidal growth pattern with pleomorphic cells; however, the tumor cells from the two cases in this report failed to show any evidence of hemophagocytosis and were negative for CD68 and lysozyme. The most important differential diagnosis is seminoma, especially with the mediastinal tumors. $ALK^+$ ALCL and seminoma have a similar etiology in the mediastinum. The morphology of these two tumors may show a similar alteration and tumor cells stain with the D2-40. However, $ALK^+$ ALCL tumor cells, unlike seminomas, express ALK, CD30, and a number of T cell markers and are negative for CD117 and PLAP.

D2-40 is useful for detecting lymphatic vessels, but it can be expressed on some tumors including follicular dendritic cell tumors, malignant mesothelioma, and seminomas [20, 22, 24]. As we known, there have only been four reported cases of ALCL, including the two cases reported here, that express the D2-40 antigen [25, 26]. Marián Švajdler Jr. reported a case of $ALK^+$ ALCL with cervical lymphadenopathy and an anterior mediastinal mass in a 9-year-old boy; in this case, the ALCL cells expressed a membranous and perinuclear (Golgi) pattern of D2-40 staining [25]. Yu also reported a case of ALCL that had a focal nonspecific cytoplasmic D2-40 staining [26]. However, clear clinical and pathologic features were not provided for either of the previously reported cases. In our two cases, case 1 was a 34-year-old man with a tumor located in the anterior and upper mediastinum. Case 2 was a 64-year-old man who presented with a lump in his right armpit with a history of adenoid cystic carcinoma of the nasal cavity that recurred due to chemotherapy for the treatment of ALCL. Both of these cases were ALK positive. Whether these four cases of $D2\text{-}40^+$ $ALK^+$ ALCL should be further divided into different groups requires further study.

Although most normal tissues or cells and tumors express the D2-40, the D2-40 staining pattern differs between different cell types. FDC tumor cells are mainly membranous, with some cells showing cytoplasmic immunoreactivity; Kaposi sarcoma involving the lymph nodes displays a strong membrane expression; and GISTs, monophasic synovial sarcomas, malignant peripheral nerve sheath tumors, and leiomyosarcomas have cytoplasmic immunoreactivity for D2-40 [20]. In malignant mesothelioma, epithelioid areas display a predominantly membranous staining whereas the sarcomatoid component exhibits cytoplasmic staining. Also, there have been a few cases with a dot-like staining [24]. Seminomas display a diffuse membrane staining with the D2-40, however immunoreactivity in embryonal carcinomas is always focal and confined to the apical or luminal surfaces of the tumor cells [22, 27]. In our two cases, the $ALK^+$ ALCL cells displayed membranous and perinuclear (Golgi) patterns of D2-40 staining, similar to the CD30 staining pattern. Interestingly, in case 2, the tumor cells in the lymphatic vessels expressed M2A only in the perinuclear (Golgi) area. This was in contrast to the findings reported by Dumoff et al. in squamous cell carcinoma of the uterine cervix [28]. They found that tumor emboli within lymphatic spaces were negative for podoplanin immunostaining in the vast majority of tumors, even in cases when the main tumor mass was D2-40 positive [28]. Because D2-40 expression in the tumor emboli within lymphatic spaces in other tumors has been rarely reported, we are uncertain if this conflicting finding is related to the tumor classification.

The significance of D2-40 staining varies depending on the tissue or cell type examined. It could suggest that the tumor is derived from the lymphatic vessels or has partially differentiated into cells of the lymphatic endothelial lineage [18, 19]. It has been demonstrated that D2-40 may be related to the invasion and metastasis of squamous cell carcinomas of the uterine cervix [28]. Dumoff et al. examined the D2-40 mAb staining pattern in invasive squamous cell carcinomas of the uterine cervix and found that lymphatic invasion and nodal metastasis were significantly more common in tumors displaying low D2-40 immunoreactivity [29]. In a later study, they also demonstrated that, in advanced-stage cervix carcinomas treated by radiation, when traditional prognostic indicators are not available and treatment decisions are based on biopsy material and clinical staging parameters, examination of D2-40 expression in pretreatment biopsy material may be useful for predicting lymphatic metastasis and patient outcome [28]. The significance of D2-40 expression in $ALK^+$ ALCL is not unclear, especially for the membranous and perinuclear (Golgi) expression. It is also unclear if this pattern of D2-40 expression ALCL indicates that these cases should be further divided into different sub-groups; this requires further study.

The mechanism underlying the D2-40 on the membrane and in the perinuclear (Golgi) region staining pattern in ALCL. We presume that this is not artifact, but a cross reactivity of D2-40 to the unknown antigenic determinant in the membrane and cytoplasm.

These two patients had a different prognosis. In case 1, the patient reacted well to the CHOPE chemotherapy and is still alive 29 months after diagnosis. In contrast, the patient in case 2 had a poor prognosis and died 4 months after diagnosis. This could be due to many factors. He did have a history of adenoid cystic carcinoma that recurred during treatment for ALCL. Additionally, this patient was sensitive to hormone treatment and could not tolerate the side effects of chemotherapy.

## Disclosure of conflict of interest

None.

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