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Original Article

Sarcomatoid variant of ALK$^-$ anaplastic large cell lymphoma involving multiple lymph nodes and both lungs with production of proinflammatory cytokines: report of a case and review of literature

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Abstract: Sarcomatoid variant of anaplastic large cell lymphoma (ALCL) is one of the rarest histologic variants of ALCL that consists of large, bizarre, often spindle-shaped, neoplastic cells resembling a soft tissue sarcoma. We report here such a case of ALCL with both pulmonary and multiple nodal involvement in a 47-year-old woman who initially presented with fever, cough, sputum, itching skin, and weight loss. The initial transbronchial lung biopsy showed discohesive pleomorphic malignant cells in a strong inflammatory milieu reminiscent of inflammatory malignant fibrous histiocytoma (MFH). Subsequent cervical lymph node biopsy revealed a spindle cell sarcoma predominantly composed of plump spindle and oval neoplastic cells in interweaving fascicles, with sparse inflammatory infiltrates, resembling pleomorphic-storiform type of MFH. However, these tumor cells in the lung and node lesions revealed essentially similar immunohistochemical features that were positive for CD30, EMA, TIA-1, granzyme B, and fascin, but negative for anaplastic lymphoma kinase (ALK), and T- or B-lineage-specific marker. The spindled cells stains diffuse strong positive for smooth muscle actin (SMA), along with vimentin. Further studies showed that the tumor produced large quantities of the proinflammatory cytokines interleukin-2 (IL-2), IL-6, and IL-8, which we believe may contribute to the pathogenesis of sarcomatoid transformation of this tumor, and was associated with the patient's inflammatory symptoms. To the best of our knowledge, this is the first reported case of sarcomatoid variant of ALK-negative ALCL with null cell phenotype and in situ production of proinflammatory cytokines presenting as multiple nodes and pulmonary involvement.

Keywords: CD30, anaplastic large-cell lymphoma, anaplastic lymphoma kinase, ALK, cytokines, inflammation, sarcomatoid variant, lymph node, lung

Introduction

Anaplastic large cell lymphoma (ALCL) is a T-cell or null-cell lineage non-Hodgkin lymphoma (NHL) consisting of lymphoid cells that are usually large with abundant cytoplasm and pleomorphic, often horseshoe-shaped nuclei, and consistently and strongly expresses CD30, also known as Ki-1 antigen [1-3]. About 25% to 60% of ALCL lymphomas has been shown to carry the t (2;5) (p23; >q35) translocation that results in the formation of a novel chimeric protein, nucleophosmin-anaplastic lymphoma kinase (NPM-ALK), which is believed to be involved in neoplastic transformation [3]. On the basis of their expression of the ALK protein, ALCL can be subdivided into two subgroups with distinct clinical and prognostic features between positive and negative cases [3]. ALK-negative ALCL is a provisional entity in the WHO 2008 Classification that represents 2-3% of NHL and 12% of T-cell NHL [4]. This tumor tends to occur in older individuals, extranodal involvement is less common. It is often in III-IV stage, associated with B symptoms, and has an aggressive course with poor overall prognosis [5].

ALCL may exhibit a wide spectrum of histologic appearances, but overlap exists between these histologic features. The common or classic type accounts for approximately 70% of ALCL and is characterized by sheets of large pleomorphic

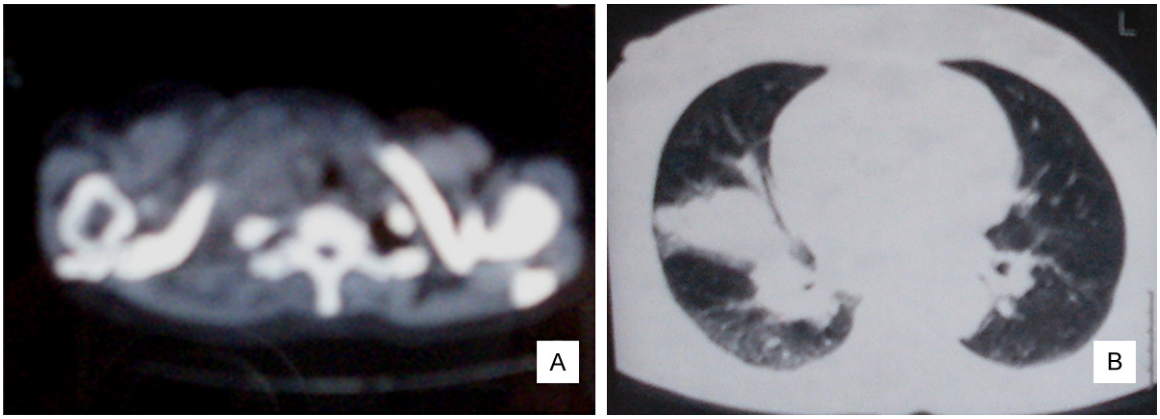

Figure 1. Radiographs of the neck and lung. A. T2-weighted magnetic resonance image of the neck showing multiple tumoral mass invading the surrounding structures. B. Transverse CT photograph showing multiple bilateral lesions with a large tumoral mass surrounded by peripheral ground-glass opacities of right lung and, to lesser extent, of left lung.

tumor cells and the presence of hallmark cells, multi-nucleated cells, Reed-Sternberg-like cells, and doughnut cells that often preferentially involve the lymph node sinuses and paracortex [3, 6, 7]. In addition to this classic variant, several less common morphologic variants of ALCL have been described, these include the small cell, monomorphic, lymphohistiocytic, neutrophil-rich, clear cell, signet ring cell, giant cell-rich, Hodgkin-like, and sarcomatoid variants [3, 6, 7]. In some patients, different subtypes coexisted in a single biopsy or were found in successive biopsies from a single patient [8]. Despite their drastically altered morphology, all the variants are characterized by a variable proportion of large hallmark cells with eccentric horse-shoe or kidney-shaped nuclei, often with eosinophilic region near the nucleus. The sarcomatoid variant is one of the rarest and most misleading presentations of this fascinating T-cell or null-cell lineage non-Hodgkin lymphoma that may simulate a soft tissue sarcoma, with only 11 such cases being reported in the literature [9-19].

Cytokine and cytokine receptor can be aberrantly produced by many tumors, including malignant lymphomas [20, 21], where they serve as autocrine or paracrine growth factors to control various biological responses, including development, differentiation, cell proliferation and survival of normal and malignant cells [22-24]. The elevated serum concentration of these cytokines, caused by excessive release of these cytokines into the circulation, could be responsible for most of the clinical signs and symptoms such as weight lost, anorexia, fever, and malaise, described by many patients with lymphomas when first seeking medical attention. Thus, the cytokine production by tumor cells has close relevance to their local and/or systemic effects in the patients with lymphomas. Numerous cytokines, including interleukin-2 (IL-2), IL-6, IL-8, and TNF-α, have been identified in a variety of lymphoid neoplasms [23, 24], including some of ALCL, but none in sarcomatoid ALCL.

Herein, we review the relevant literature and report for the first time a case of ALK-negative sarcomatoid ALCL with production of proinflammatory cytokine IL-2, IL-6, and IL-8 in an adult woman who initially presented with inflammatory or B symptoms, associated pulmonary disease, and subsequently developed multiple lymphadenopathies

Case report

A 47-year-old woman presented to another hospital with a 4-month history of cough, sputum, itching, and a 3-month history of additional progressive enlarged bilateral cervical and axillary lymph nodes. The clinical presentation, including fever, malaise, and leukocytosis, suggested an infection, but exhaustive microbiologic work-up did not yield any microorganisms, also antibiotic therapy did not improve symptom resolution. Thereafter, her clinical condition continued to deteriorate and she was markedly debilitated by her persistent intermittent fever,

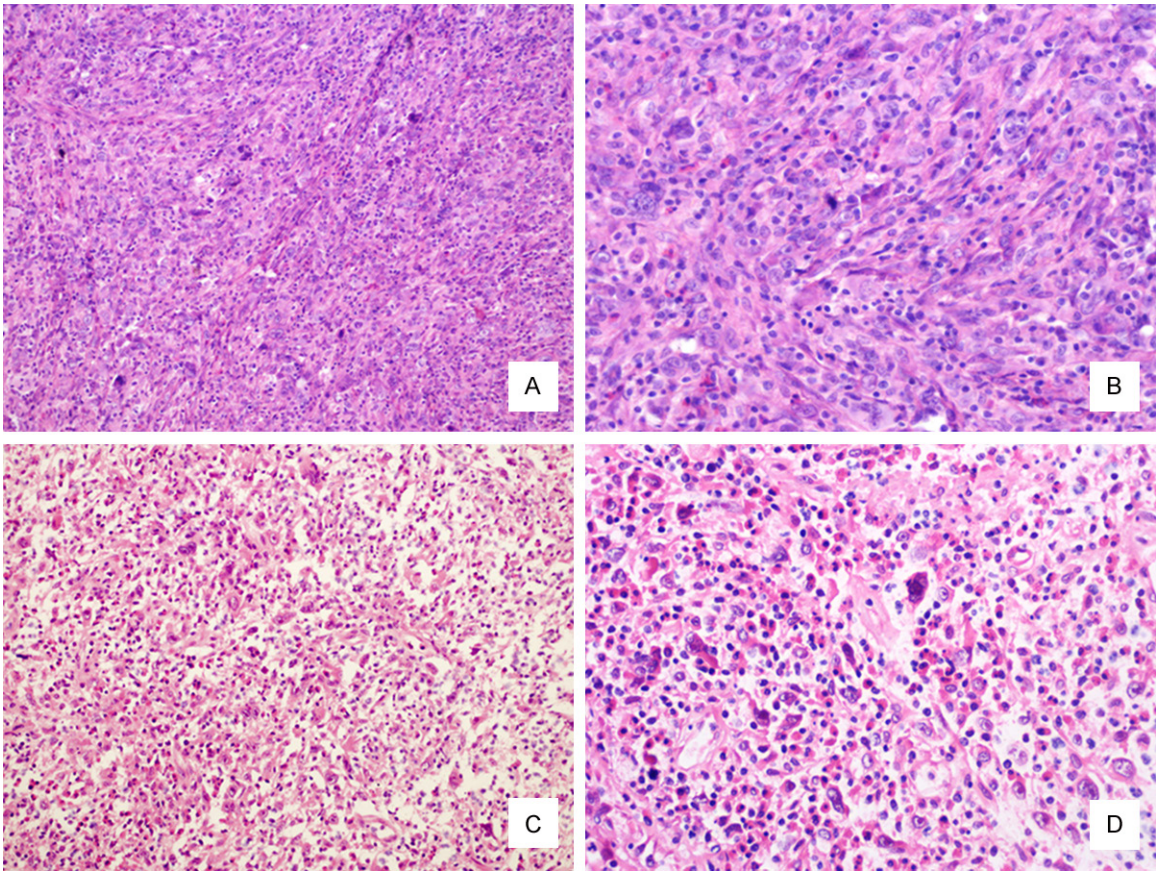

Figure 2. Histology of sarcomatoid variant of ALCL. A. Lymph node biopsy shows highly cellular fascicles of spindle-shaped cells and scattered hallmark cells with numerous small lymphocytes and eosinophils. B. The neoplasm showing atypical large hallmark cells with pleomorphic, indented or embryoid-appearing nuclei, prominent nucleoli, and abundant cytoplasm, mixed with spindle cells arranged in fascicles. C. The lung biopsy shows a Hodgkin-like lesion composed of spindle-shaped cells, highly pleomorphic cells and scattered hallmark cells with numerous small lymphocytes and eosinophils. D. Tumor cells growing in a patternless fashion. Hematoxylin-eosin stain, original magnifications, A, C, ×200; B, D, ×400.

marked fatigue, night sweats, and anorexia, accompanied by further weight loss of 3 kg and generalized malaise. Magnetic resonance imaging (MRI) showed a neck tumoral mass invading the surrounding structures (**Figure 1A**). Chest computed tomography (CT) revealed mediastinal and bilateral hilar lymphadenopathy and multiple bilateral lung masses with a large mass (5.4 cm×3.5 cm×5 cm) in the right lung compressing the main bronchus, resulting in a partial right middle lobe atelectasis and a mediastinal shift toward the left (**Figure 1B**). A right pleural effusion was also presented. A transbronchial lung biopsy prompted diagnosis of a Hodgkin lymphoma (HL). Bone marrow aspiration was normal. The patient was referred to our hospital for further evaluation and treatment. Physical examination revealed multiple firm masses in her bilateral cervical, supraclavicular, and axillary lymph nodes, measuring 4 cm×4 cm in maximal size. No neurological or vascular problems were evident in the left upper extremity. Abdominal ultrasound showed multiple enlarged lymph nodes, near the left kidney and para-aortic regions. Four days after admission, a further open cervical lymph node biopsy was performed.

Materials and methods

The tissue samples of bronchoscopic and node biopsies were fixed in 10% buffered formalin and embedded in paraffin. Four-micrometer-thick tissue sections were routinely stained with hematoxylin and eosin for histological evaluation. Immunohistochemical staining was performed with the DAKO Envision Peroxidase detection system and using 3.3-diaminobenzidine (DAB) (Dako, Carpinteria, CA, USA) as substrate, according to standard protocols. Primary

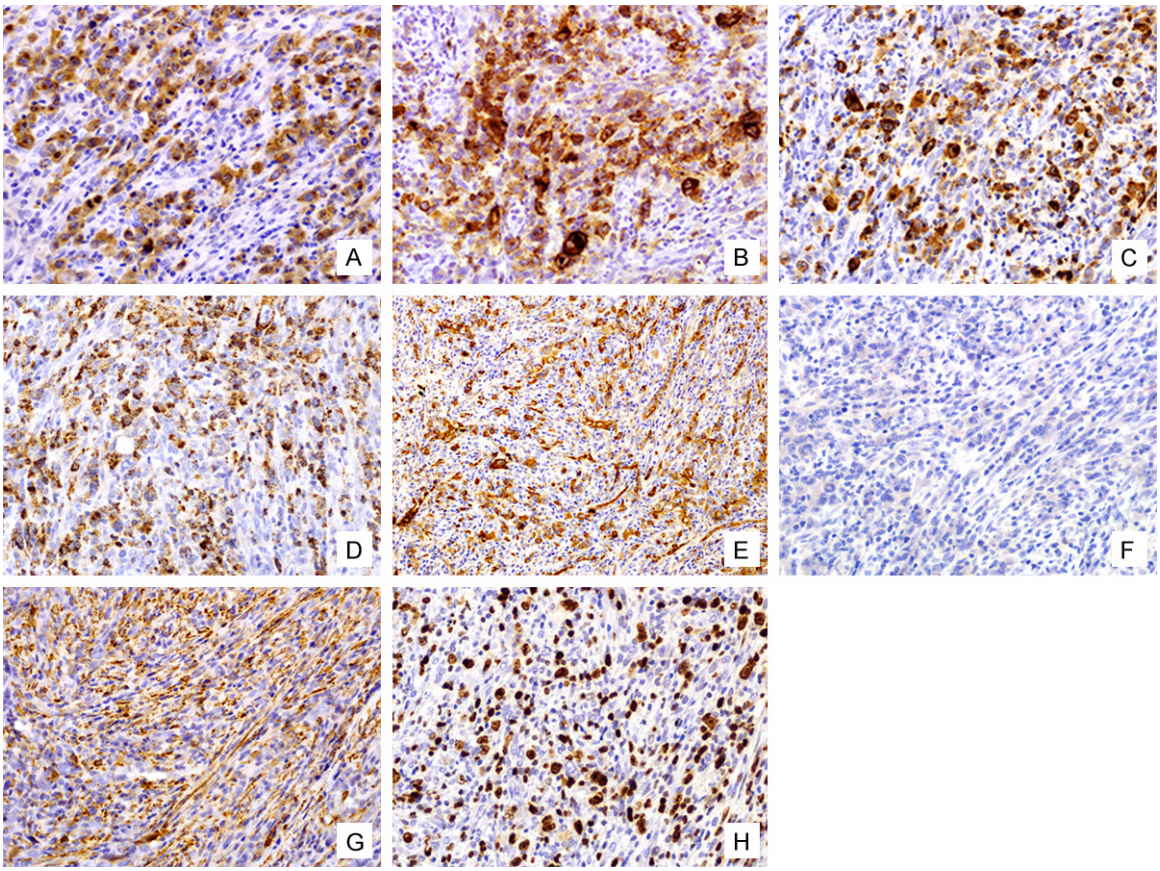

Figure 3. Immunhistochemical profiles of sarcomatoid variant of ALCL. A. The large anaplastic cells and hallmark cells are immunoreactive for CD30 in a characteristic membrane and Golgi-associated staining pattern. B. The large anaplastic cells and typical hallmark cells show positive membranous and paranuclear immunoreactivity for EMA. C. The tumor cells are strongly positive for granzyme B in dot-like aggregates in the cytoplasm, whereas the bystander cells are negative. D. The tumor cells display granular cytoplasmic positivity for TIA-1 with paranuclear accumulation in the Golgi region. E. The large anaplastic cells and hallmark cells are immunoreactive for fascin. F. Tumor cells show negative immunoreactivity for ALK-1. G. SMA staining showing positivity of the spindled-cells cells and internal control of the blood vessels, but not the large anaplastic cells. H. Ki-67 nuclear staining is shown in 51% of the tumor cells. Dako Envision/diaminobenzidine, original magnification, each ×400, with an exceptional E, ×200.

antibodies used in this case included alpha-smooth muscle actin (α-SMA) (1A4, prediluted), BOB.1 (1:100), CD1a (010, 1:100), CD3 (SP7, prediluted), CD4 (SP35, 1:100), CD5 (4C7, 1:100), CD8 (SP16, 1:100), CD15 (Garb-3, 1:100), CD20 (L26, 1:200), CD21 (2G9, prediluted), CD30 (Ber-H2, 1:50), CD35 (Ber-MAC-DRC, prediluted), leukocyte common antigen CD45 (PD7/26+2B11, prediluted), CD45RO (OPD4, 1:200), CD68 (PG-M1, 1:50), CD79α (JCB117, prediluted), CD163 (10D6, 1:100), CK7 (OV-TL12/30, prediluted), Cytokeratin (AE1/AE3, 1:50), EMA (E29, 1:50), G-CSF (H-133: sc-7896, 1:50, Santa Cruz, CA), fascin (55k-2, 1:100), granzyme B (GrB-7, 1:40), HMB45 (HMB-45, 1:50), Ki-67 (MIB-1, 1:150), IL-2 (H-133: sc-7896, 1:50, Santa Cruz, CA), IL-6 (sc-130326, 1:50, Santa Cruz, CA), IL-8 (1:50, Santa Cruz, CA), NPM-ALK fusion protein (ALK-1, 1:50), OCT-2 (Oct-207, 1:100), S100 protein (polyclonal, 1:200), synaptophysin (SY38, 1:100), TIA-1 (2G910F5, 1:50), TTF-1 (SPT24, prediluted), and Vimentin (V9, 1:200). Unless otherwise stated, all antibodies were mouse monoclonal and from Dako Cytomation (Dako North America, Inc., Carpinteria, CA, USA). Appropriate positive, including using ALK-positive ALCL case, and negative controls were run in parallel.

Results

Histologically, the resected cervical node displayed a highly cellular sarcomatoid lesion

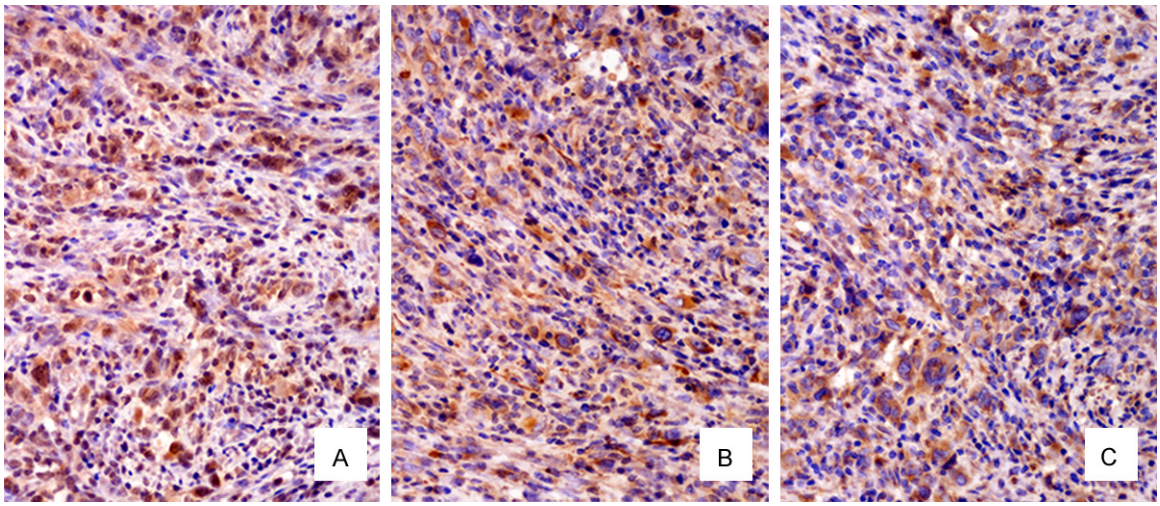

Figure 4. Immunhistochemical detection of cytokine expression in sarcomatoid variant of ALCL. A. Tumor cells show a cytoplasmic expression of IL-2. B. Tumor cells are positive for IL-6. C. Tumor cells are positive for IL-8. Dako Envision /diaminobenzidine, original magnification, each ×400.

composed of large bizarre cells and spindle to stellate shaped cells grown in fascicular with a focally whorled pattern with additional infiltrations of small lymphocytes, while the lymph node architecture was completely effaced by the tumor (**Figure 2A**). The large anaplastic cells possessed coarse vesicular nuclei with irregular nuclear contours, prominent nucleoli and eosinophilic cytoplasm (**Figure 2B**). A retrospective review of transbronchial lung biopsy revealed a sarcoma composed of small numbers of discohesive bizarre malignant cells with a stronger inflammatory milieu, mainly lymphocytes and granulocytes (**Figure 2C**), more closely resembling that of an inflammatory malignant fibrous histiocytoma (MFH) or HL. The tumor cells contained moderate amount of pink cytoplasm, pleomorphic, cerebriform, donut shaped or horseshoe-shaped nuclei with prominent nucleoli (**Figure 2D**). These atypical anaplastic large cell infiltrate involved the peribronchial and interstitial areas of the lung, and completely destroyed the normal pulmonary architecture.

By immunohistochemical staining, the large cells within tumor were strongly positive for CD30 (**Figure 3A**), EMA (**Figure 3B**), Granzyme B (**Figure 3C**), TIA-1 (**Figure 3D**), and fascin (**Figure 3E**), but negative for ALK-1 (**Figure 3F**). The interspersed spindled cells in the tumor were diffusely and strongly positive for α-SMA (**Figure 3G**), along with vimentin, but negative reaction to lymphoid makers and all other antibodies. The background cells were variably positive for BOB.1, CD1a, CD3, CD4, CD15, CD45, CD45RO, CD5, CD8, CD20, CD79α, CD21, CD35, CD68, CD163, OCT-2, and PAX-5. Stain for Cytokeratin, CK7, HMB45, S100 protein, synaptophysin, and TTF-1 were totally negative. The MIB-1 proliferative index of this tumor was 51% (**Figure 3H**). The immunoprofile of the pulmonary lesion were virtually identical to that of the node biopsy described above (not shown). These findings were diagnostic of ALCL of null-cell lineage, sarcomatoid variant.

Because the patient showed severe inflammatory symptoms, several inflammatory cytokines that might be produced in situ by tumor cells were evaluated by immunohistiochemistry. As shown in **Figure 4**, the malignant cells were consistent positivity for IL-2 (**Figure 4A**), IL-6 (**Figure 4B**), and IL-8 (**Figure 4C**), with no detectable G-CSF. Among these, the tumor showed a much higher concentration of IL-6 as determined by a higher intensity of staining.

With a diagnosis of ALCL, the patient underwent three cycles of CHOP chemotherapy regimen. The patient achieves complete remission and remains free of disease 10 months after diagnosis.

Discussion

Sarcomatoid variant of ALCL is an extremely rare histologic variant of ALCL that consists of large, bizarre, often spindle-shaped, neoplastic cells, resembling a soft tissue sarcoma [9]. So

Table 1. Summary of sarcomatoid variant of anaplastic large cell lymphoma of T-cell/null-cell lineage

Source	*Age (y)/Sex*	*Nodal Sites*	*Extranodal Sites*	*Initial Diagnosis*	*Lineage*	*IHC Profile*	Follow-up
Chan JK, et al. [9]	45/M	Inguinal, paraaortic, and cervical	Soft tissue of leg	High-grade sarcoma	T-cell	LCA, CD30, EMA, UCHL-1	DOD-infection
Dusenbery D, et al. [10]	42/F	Inguinal, paratrcheal, mediastinal, thoracic, para-aortic, rightgroin lymph nodes	Breast, subxiphoid area, right groin, psoas muscle, liver, pancreas, thyroid, lung, right thigh	Poorly differentated malignant neoplasm (carcinoma×sarcoma)	T-cell	Ki-1, Vimentin, EMA, UCHL-1	DOD
Bueso-Ramos CE, et al. [11]	79/M	Para-aortic	Soft tissues of elbow	Malignant fibrous histiocytoma	T-cell	LCA, UCHL-1, CD43, CD30	FOD
Suzuki R, et al. [12]	6/F	Axillary and supraclavicular		Inflammatory myofibroblastic tumors	Null cell	ALK (cytoplasmic), CD30, CD4, EMA, TIA-1, and granzyme B	FOD
Pereira EM, et al. [13]	92/F	Right axilla	Left breast	Primary breast neoplasm	T-cell	ALK1-negative, Vimentin, LCA, Ki-1, EMA, UCHL-1	DOD-infection
Ogose A, et al. [14]	51/M		Superficial mass in left groin	Malignant fibrous histiocytoma	T-cell	ALK1-negative, Vimentin, Ki-1, EMA, UCHL-1	FOD
Wang J, et al. [15]	60/M		Right pre-auricular skin mass	Large cell lymphoma	T-cell	ALK1-negative, CD30, CD45, CD2, CD43, Actin	Undergoing chemotherapy
Bassett K., et al. [16]	68/F		Right and left lower back skin mass	Spindle-shaped cell sarcoma	T-cell	ALK1-negative, CD3, CD4, CD30, CD8	FOD
Allory Y, et al. [17]	78/F		Bladder	Inflammatory myofibroblastic tumors	T-cell	ALK-1, CD30, EMA, TIA-1, and granzyme B, CD2, CD3, CD5	Unknown
Kashiwabara K, et al. [18]	44/M	Hilar, mediastinal, paraaortic, left supraclavicular and inguinal	Gastric and pulmonary involvement		T-cell	Ki-1/Ber-H2 (CD30), UCHL-1 (CD45RO), EMA	Remission
Vij M, et al. [19]	14/M	Left iliac bone, retroperitoneal mass, multiple intra-abdominal lymphnodes	Supraclavicular swelling involving right steronoclavicular joint.	Soft tissue sarcoma	T-cell	ALK-1, LCA, CD3, CD30	Unknown
Present case	47/F	Bilateral cervical, supraclavicular axillary, mediastinal, hilar, paraaortic	Bilateral lung	Malignant fibrous histiocytoma	Null cell	ALK1-negative, CD30, CD45, EMA, TIA-1, granzyme B	Remission

*IHC indicates immunohistochemical; LCA, leukocyte common antigen; EMA, epithelial membrane antigen; CK, cytokeratin; DOD, dead of disease; FOD, free of disease.

far, less than 11 such cases have been reported after extensive review of the literature in the literature [9-19], and only 5 cases are well documented [9, 11-14]. The clinical and pathological features of previously documented cases and the present cases are summarized in **Table 1**. The patient's ages ranged from 6 to 92 years, with a median age of 52 years, but most are adult aged between 42 and 92 years of age. Men and women are equally affected. These tumors presents with lymph node involvement in about 66% (8/12) of cases, while extranodal spread in 91% (11/12) of cases. Among them, 3 cases are ALK-positive and 5 cases are ALK-negative, whereas the remaining 4 cases have not been tested for ALK. However, no case testing for ALK with both nodal and pulmonary involvement has been described previously, and the expression of cytokines was not evaluated in any of these cases. The present report describes an extremely rare case of ALK-negative sarcomatoid ALCL involving multiple lymph nodes and both lungs in an adult woman who presented with severe inflammatory symptoms. A transbronchial lung biopsy and subsequent lymph node biopsy displayed a mixture of scattered large atypical cells or with interweaving fascicles of plump spindle-shaped cells in strong inflammatory background, mimicking a soft tissue sarcoma, particularly MFH. Nerveless, the immunoreactivity for CD30, EMA, TIA-1, Granzyme B, and fascin, but absence of ALK expression, in combination with its sarcomatoid morphologic and clinical features, support the diagnosis of an ALK-negative form of systemic sarcomatoid ALCL. More importantly, the tumor in this case also produced large quantities of IL-2, IL-6, IL-8, and G-CSF, which we believe could contribute to the sarcomatoid morphology of this tumor and associate with the patient's systemic inflammatory symptoms through their local and systemic effects. Thus, we believe our case represent first example of sarcomatoid variant of ALCL expressing cytokines.

Clinically, our patient, as seen in the majority of cases with systemic ALCL, initially presented with a relatively uniform clinical picture related to her tumors, the B symptoms, including fever of unknown origin, cough, night sweats, weight loss, and high white blood cell counts, combined with pulmonary involvement and subsequent enlargement of peripheral lymph nodes. Primary pulmonary ALCL are very uncommon, whereas secondary infiltration of the lung by hematologic malignancies is a frequent finding [25]. Several case reports and clinical studies show similar presentation in ALCL patients, in which the clinical manifestations naturally prompte extensive but mostly negative microbiology and serology tests for a cause of presumed infection and/or sepsis [26-28]. Other tests can suggest that malignancy is present, but cannot be differentiated clinically and radiologically from other common mass lesions. A biopsy, with the help of ancillary studies, such as immunohistochemical stains, is usually necessary to make a definitive diagnosis.

Histologically, the nodal lesion in our case showed sarcomatoid histologic features composed of pleomorphic spindle-shaped cells, similar to those previously described sarcomatoid variant of ALCL [9, 11], while the pulmonary lesion showed scattered large, discohesive bizarre malignant cells set amidst a stronger inflammatory milieu, a morphological appearance resembling inflammatory MFH or HL. In fact, coexistence of different morphological patterns involving at least two separate sites in a single patient with ALCL is extremely uncommon [8]. Despite morphologic diversity, the hallmark cell is characteristic of this variant having an eccentrically placed nucleus with horseshoe, wreath, or embryoid appearing morphology and a paranuclear hof. Also, these malignant cells in both nodal and pulmonary lesions revealed essentially similar immunohistochemical features, they were positive for CD30 in a membranous and Golgi staining pattern, EMA, TIA-1, granzyme B, fascin, but no reactivity for ALK-1, CD15, and T- or B-lineage-specific marker, ruling out other subtypes of CD30-positive T- or B-cell lymphoma with anaplastic features, and classical HL, thus being consistent with a ALK-negative ALCL of null-cell lineage. Most ALCL tumors express some T-cell markers such as CD3, CD7 and CD43, but all B-cell markers are negative. In the null cell type, virtually all T-cell markers are negative, but most cases harbor T-cell receptor rearrangements, suggesting T-cell lineage [4]. CD45 can be negative and CD15 is almost always negative, which is helpful in distinguishing this entity from HL. Fascin, an actin-bundling protein involved in the formation of dendritic processes of maturing Langerhans cells, were found to be positive in these large cells in our case. Previously, fascin has been found to be a sensitive marker for

classical Reed-Sternberg cells, and can be used to distinguish HL from ALCL and other NHL. Recently, it was shown that ALCL also expresses this protein [29, 30]. SMA has been reported in several cases of sarcomatoid variant of ALCL [12, 17], but whether individual SMA positive cell is a neoplastic or a reactive process is controversial. It was of great interest that the spindled cells in our case reacted for α-SMA, along with vimentin, but not lymphoid makers, indicative of myofibroblasts, thus at least a subset of such cells, if not all, represents a reactive, rather than a neoplastic, process, the true neoplasia cells as previously reported [12, 17].

Sarcomatoid variant of ALCL is frequently misdiagnosed as high-grade sarcoma [9], such as MFH [14], inflammatory myofibroblastic tumor [12], melanoma, anaplastic or sarcomatoid carcinoma [3, 9, 13], due to its sarcomatoid features [4]. As the morphological variants of ALCL cannot reliably be identified without ALK expression, ALK-negative ALCL comprises exclusively cases with sarcomatoid morphology. The negativity for ALK in sarcomatoid variant of ALCL and react positively with vimentin and EMA may be a further point of confusion since this tumor, whereas reactivity may be negative or weak with respect to leukocyte common antigen [9, 11-14]. Inflammatory myofibroblastic tumors, which showed cytoplasmic ALK and α-SMA expression, thus may mimic sarcomatoid variant of ALCL [12], but they are negative for CD30 and EMA. Malignant melanomas may show unusual, variable morphological features, usually express HMB-45, melan-A, and S100 protein, while sarcomatoid ALCL does not express these melanocytic markers, but consistently show lymphoid markers as well as paranuclear and membranous immunoreactivity for CD30 [1, 3, 9, 11]. Sarcomatoid carcinoma is an infrequent neoplasm demonstrating variable histologic appearances, including a fibromatosis-like or MFH pattern. However, the highly characteristic perivascular cuffs of large pleomorphic cells in ALCL are not observed in sarcomatoid carcinoma [3, 9]. In addition, despite the similar pattern of immunopositivity for EMA in both sarcomatoid carcinoma and ALCL, the former does not express CD30 and the latter usually does not express cytokeratins [3, 9, 11]. Inflammatory MFH, consisting of large, atypical histiocyte-like cells set amidst an inflammatory backdrop of eosinophils, neutrophils, lymphocytes, and xanthoma cells, can be difficult to distinguish from HL and NHL, particularly of the Ki-1 anaplastic large-cell type in small biopsy specimens, but it consistently lacks CD30 and other lymphoid markers [31]. Spindled cell sarcomas are considered a diagnosis of exclusion, and immunohistochemical panels should be used to differentiate them from sarcomatoid variant of ALCL primary affecting the node and lung. Strong CD30 positivity in the majority of the neoplastic cells is the most important diagnostic feature for ALCL, and it also has a cytotoxic phenotype as shown by expression of TIA-1 or granzyme B or both in the neoplastic cells.

Among the lymphomas, H-RS cells in HL secrete a variety of cytokines, while most NHL cells do not produce cytokines in excess amounts [20], with a notable exception of ALCL [20, 21]. ALCL cells in cultures can express many cytokines including IL-1, -5, -6, -8, -9, TNF-α, as well as a variety of cytokine receptors [20]. Cytokines either can be produced or exert effects on neoplastic or reactive cells to promote growth and survival and foster immune privilege. Increased expression of cytokines, such as G-CSF and IL-2 or IL-6, and release into the blood might also relate to the systemic symptoms and the aggressive course of the disease [28]. Such effects, however, may be influenced by the quantity and the type of cytokine produced, with tumors secreting IL-6 being particularly associated with pronounced systemic features [26, 27]. The production of IL-6 by ALCL was previously suggested by two case reports of patients with ALCL whose elevated serum IL-6 levels normalized following successful chemotherapy [26, 32]. However, in these patients, only the serum level of IL-6, other than production from tumor cell, has been measured. In our case, the tumor cells selectively produce IL-2, IL-6 and IL-8, which may explain the systemic inflammatory B symptoms in our patient. In addition, inflammatory mediators secreted by tumour cells are growth-stimulatory for diverse cell types. For example, they might promote the proliferation of both stromal fibroblasts or myofibroblasts and tumour cells associated with the development and progression of ALCL. In this regard, these SMA-positive spindled cells might develop by aberrantly expressed cytokines or chemokines from tumor cells, thus resulting in sarcomatoid morphology of this variant. Our case, however, in contrast to previ-

ous reports, somewhat confirms previous observation that in sarcomatoid variant, the sarcomatoid features may not be correlated with ALK expression [12, 13].

Clearly, further studies are required to fully elucidate this hypothesis.

ALK-negative ALCL has progressive clinical course and prognosis are worse in comparison to patients with ALK-positive tumors [33]. Specifically, the overall 5-year survival of patients with ALK-negative ALCL was only 49% compared with 70% for those with ALK-positive ALCL [33]. With regard to sarcomatoid variant of ALCL, due to its rarity, the prognosis is not well defined. Among the 10 cases of sarcomatoid ALCL with available follow-up data in the literature, including the present case [9, 11-14], two patients died of disease as a consequence of delayed diagnosis or infection, the remaining patients underwent multidrug chemotherapy, and achieved complete response and partial response, respectively.

In conclusion, ALK-negative sarcomatoid variant of ALCL with multiple nodal and bilateral pulmonary involvements was a rarest and most misleading condition that has never been reported previously. Because this patient initially presented with pulmonary involvement and B symptoms due to cytokines produced by tumor, therefore mimic inflammatory syndromes, which may delay the diagnosis and treatment. This case also highlights the fact that histological confirmation of an underlying malignancy, especially the ALK-negative form, can prove difficult. However, to avoid such pitfalls, sarcomatoid variant of ALCL should be considered when a nodal or extranodal sarcomatoid lesion is encountered. An immunohistochemical panel including lymphoid markers and CD30 is recommended as part of the work-up for such neoplasm.

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Disclosure of conflict of interest

None.

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