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CASE REPORT

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Anaplastic large cell lymphoma with *ALK::ATIC* fusion mimicking a histiocytic sarcoma debuting as an anterior thoracic soft tissue tumor with exceptional clinicopathological, morphological and molecular features

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INTRODUCTION

Hematopathology is currently undergoing a revolution in diagnostic and treatment guidelines due to more routine implementation of technologies such as next-generation sequencing (NGS) tests for diagnosis and the FDA approval of a variety of new therapeutic options for the management of lymphoid neoplasms. Recently, several key molecular events have been described that have important clinicopathologic and therapeutic implications in mature non-Hodgkin T-cell lymphomas which have historically been poorly understood, such as anaplastic large cell lymphoma with ALK rearrangements (ALK ALCL).[1] Recent studies have shown that ALK-positive ALCL (ALK + ALCL) exhibit constitutive activation of signaling pathways that dysregulate essential canonical events in T-cell activation, affect epigenetic regulation, lead to immune evasion, and dysregulate metabolic pathways.[1] This type of lymphoma has a wide variety of clinicopathologic features described and many times when clinical data, histology and immunophenotypic profile are inconclusive other rare exclusion diagnoses should be considered because the may mimic this type of lymphoma and to rule them out it is necessary to have access to more advanced molecular studies, making ALK ALCL an extremely challenging diagnosis.[1–3] NPM1 was the first fusion partner described in ALK + ALCL in the 1990s, and to date a large number of fusion partners have been reported, some of them with very low frequency rates described.[1,3]

CASE REPORT

A 56-year-old woman with no relevant previous medical history debuted with a palpable painless mass in the anterior thorax wall at the level of the second and third right parasternal intercostal spaces, which progressively increased in size over the next 5 months, and was accompanied by a localized skin rash, mild dyspnea and chest pain when changing position, without accompanying B symptoms and Eastern Cooperative Oncology Group (ECOG) performance scale of 1. A simple computerized axial tomography (CT) was performed, which revealed a soft tissue mass measuring 75 × 62 mm and a density of 34 Hounsfield units (HU) that had caused lysis of the costal arches and grown expansively towards the anterior mediastinum. Systemic and mediastinal lymph-node involvement was ruled out only by this imaging method (Figure 1). The patient did not attend follow-up visits until 1 month later and reported a weight loss of 4 kg and an increase of palpable tumor volume. The

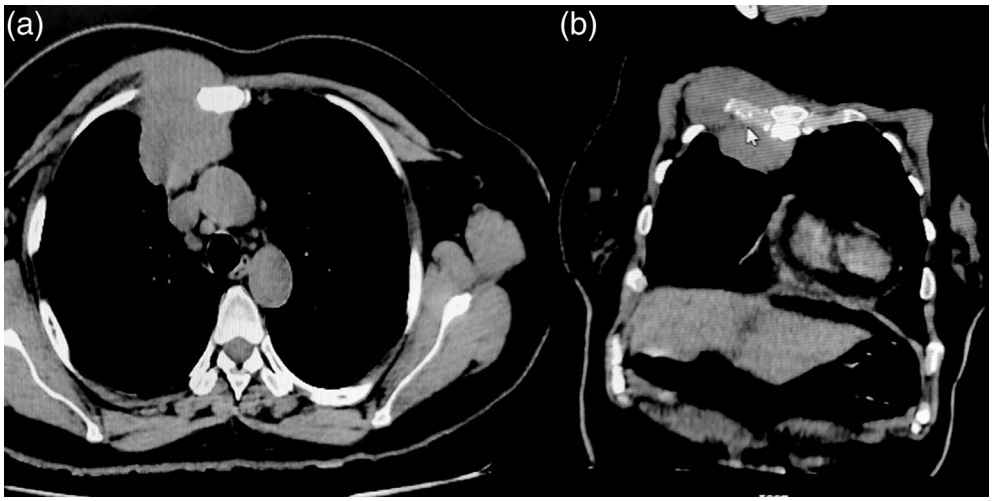

FIGURE 1 Initial noncontrast computed tomography (CT) scan. (a) The axial view revealed a tumor arising from the intercostal soft tissues with expansion to the anterior mediastinum. (b) The coronal view revealed foci of osseous lysis of the right first costal arch (white arrow). Simple CT scan (a) axial projection and (b) coronal projection.

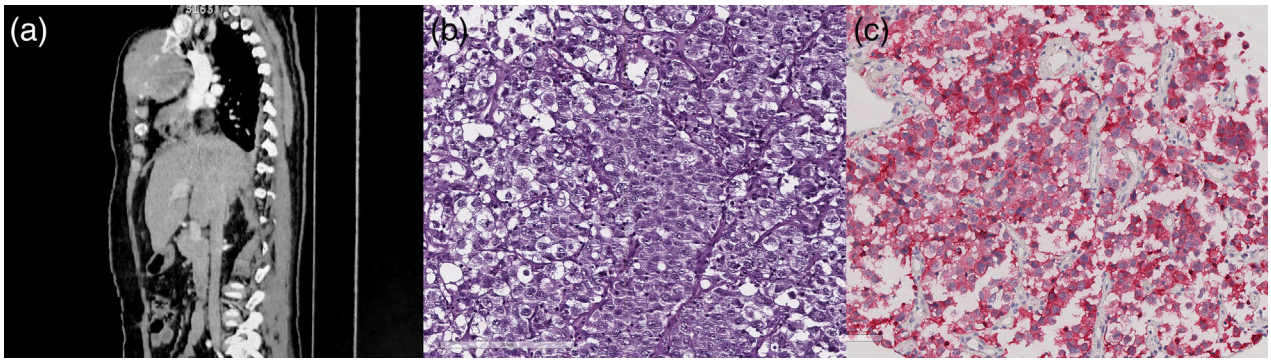

FIGURE 2 (a) Contrast-enhanced computed tomography (CT) scan after 1 month revealed a tumor arising from the intercostal soft tissues with an increase in size with respect to the previous study and compression of major vascular structures. (b) Histologically, the tumor was solid, poorly differentiated with mixed morphology (compound and lymphohistiocytic) with (c) strong and diffuse positivity for CD-163. (a) Contrast-enhanced CT scan, sagittal projection in arterial phase. (b) Hematoxylin and eosin, original magnification 20×. (c) Immunohistochemistry, original magnification 20×.

patient was unable to undergo a more advanced imaging study due to economic reasons. A contrast-enhanced CT scan was performed which revealed an 85 × 87 mm heterogeneous mass expanding into the anterior and middle mediastinum with densities of 53 HU in arterial phase and 90 HU in venous phase, associated with scarce right pleural and pericardial effusion (Figure 2a). A core needle biopsy was performed (Figure 2b). Morphologically, a poorly differentiated, solid neoplasm with epithelioid, lymphohistiocytic and compound appearance, also extensive necrosis was observed; it showed negativity for immunohistochemical markers S100, HMB45, SOX-10, OSCAR (7, 8, 18 and 19), SALL-4, PanTRK, NUT, TFE-3, CD34, INSM1, CD56, CD45, CD23, CD20 and positivity for vimentin, CD99, CD163, CD68, lysozyme and CD4 (Figure 2c). In addition, a study for rearrangements in EWSR1(22q12) was performed by fluorescence in situ hybridization (FISH: Break-apart) which was negative. Given the histological and immunohistochemical evidence, added to the absence of peripheral lymphadenopathies and limited clinical information, the initial diagnosis was histiocytic sarcoma (HS). With the initial diagnosis, a surgical approach was ruled out, and management with systemic chemotherapy was considered; however, the patient stopped attending the follow-up and after a month she went to the emergency service with rapid clinical deterioration, tumor growth of 30%, severe dyspnea and increased pleural and pericardial effusion. Upon re-evaluation of the case and the biopsy, support was obtained from the pathology department to perform NGS tests for DNA and RNA in paraffinized tissue with the Oncomine precision assay (OPA) for solid tumors in the Ion Torrent Genexus (ThermoFisher Scientific TM) equipment, by which the *ALK::ATIC* fusion was found; CD30 and ALK immunohistochemical stains (Figure 3) were added and found to be positive. Finally, the diagnosis was an ALK + extra nodal type ALCL with an unusual presentation, aggressive clinical behavior, and a very rare genomic fusion. Given the natural course of the disease and not receiving specific treatment due to socioeconomic factors. Due to the rapid tumor growth, the window of treatment opportunity was rapidly closing and the patient died of acute myocardial infarction associated with compression effect of the tumor to the large vessels and acute pulmonary edema.

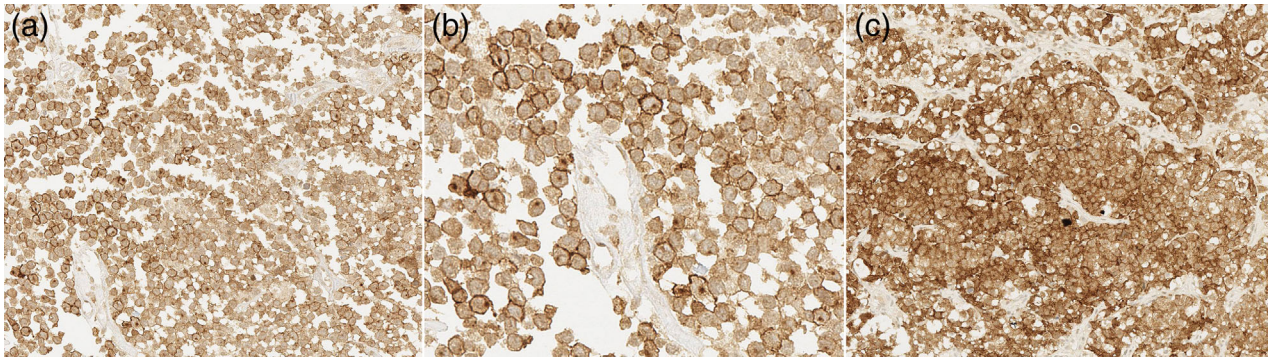

FIGURE 3 (a, b) Strong and diffuse positivity for CD-30 (Ber-H2 clone) with cytoplasmic and Golgi pattern. Strong and diffuse positivity for ALK (D5F3 clone) with cytoplasmic pattern; Immunohistochemistry, (a) original magnification 20× and (b) 40×; (c) Immunohistochemistry, original magnification 20×.

DISCUSSION

ALK + ALCL is defined as a distinct type of T lymphoma characterized by a proliferation of large cells that may present in sheets or a discohesive pattern, with abundant cytoplasm and pleomorphic nuclei which consistently express CD30 and translocation-derived (2p23) ALK expression, being one of the rarest subtypes of non-Hodgkin lymphoma (NHL).[1] It occurs predominantly in males, accounting for 10%–15% of pediatric NHL and only 3% of adult NHL, presenting in stage III or IV with systemic involvement.[1] Nodal involvement is seen in up to 90% of cases and extra nodal involvement in up to 60% (soft tissue only in 15%); however, isolated extranodal involvement is extremely rare. In our case we had no evidence of systemic lymphadenopathies, but imaging studies were limited so it was not possible to rule it out completely.[1] When there is extranodal involvement the tumor cells show an infiltrative, diffuse growth pattern with marked necrosis.[1] There are five histological patterns described by the WHO: common, lymphohistiocytic, small cell, Hodgkin-like, and compound.[1,2] Interestingly, certain patterns have an association with their molecular background; in our case we observed a mixed pattern with compound and lymphohistiocytic morphologies which in contrast to the clinical and immunohistochemical features initially oriented towards the diagnosis of an HS since it shows a similar immunophenotypic profile as ALK + ALCL and led to a misdiagnosis.[1,2] ALK shows a wide variety of fusion partners (more than 25 described) with NPM1 being the most common; the ATIC partner found in our case has been described in less than 1% of ALCL.[1,3] The aggressive behavior of this neoplasm is consistent with its molecular background, which could explain the unusual histology, clinical presentation and biological behavior. It is therefore important in the context of challenging cases with small biopsies not to overlook the diagnostic pearls and fine details despite having ruled out the most frequent morphological mimickers. It is of utmost importance not to forget the performance of markers such as CD30 or ALK in similar diagnostic scenarios, making a significant difference in the prognostic and therapeutic implications given that the lines of treatment between a HS and an ALK + ALCL are radically different.[1,4,5]

AUTHOR CONTRIBUTIONS

J.A.G.M, N.V.C, J.P.F.G, and O.B.Q contributed equally to the drafting, writing, editing, and critical revision of the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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