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Epithelioid inflammatory myofibroblastic sarcoma of the lung ALK+/ NTRK+/ PD-L1+

Key words: epithelioid inflammatory myofibroblastic sarcoma, ALK1, NTRK, PD-L1, lung, inflammatory myofibroblastic tumour

Introduction

Epithelioid inflammatory myofibroblastic sarcoma (EIMS) is a soft tissue neoplasm that represents an aggressive and exceptionally rare subgroup of inflammatory myofibroblastic tumor (IMT). EIMS, as well as IMT, harbor anaplastic lymphoma kinase (ALK) gene fusions; however, recent publications have described different ALK fusion genes involved in EIMS, with particular reference to Ran-binding protein 2 (RANBP2)-ALK fusion. Unlike other neoplasms such as non-small cell lung carcinomas, very little is known about neurotrophic tyrosine receptor kinase (NTRK) and/or PD1/PD-L1 immune checkpoints alterations in such tumors and their value as targets for tailored molecular therapies [1, 2].

Image report

The photos above represent the histological case of a patient in his 20s with a unilateral lung mass and consensual pleural thickening, radiologically strongly indicative of neoplasia.

The histological examination, after surgical resection, shows a proliferation of spindle myofibroblastic cells, in the context of lymphoplasmacytic inflammatory infiltrates and a small amount of eosinophilic granulocytes. The morphologically more aggressive part of the neoplasm (with the presence of mitosis, necrosis, and pleura infiltration), shows epithelioid cytology (Fig. 1A). The immunohistochemistry results are as follows 1) cytokeratins AE1/AE3–; 2) cytokeratins CAM5.2–; 3) cytokeratin 7–; 4) epithelial membrane antigen (EMA)+; 5) Vimentin+; CD31–; CD34–; 6) smooth muscle actin–; 7) specific muscle actin–; 8) desmin–; 9) caldesmon+; 10) pS100–; 11) CD117–; 12) Ki67 10–20%; 13) ALK1+ (Fig. 1B); 14) ALK(clone D5F3)+. PD-L1 expressed in 2–5% in spindle cell areas of IMT and 30–40% in epithelioid areas of EIMS (Fig. 1C); 15) NTRK nuclear expression in scattered cells (Fig. 1D).

The immunomorphological findings are consistent with a pleuro-pulmonary IMT with large neoplastic areas of aggressive evolution into EIMS.

Discussion

To the best of our knowledge, about 60 cases of EIMS have been described and this case represents the fifth primitive pulmonary one [1, 3]. Its topographic location, epithelioid microscopic morphology, immunophenotypic ALK expression, and aggressive features

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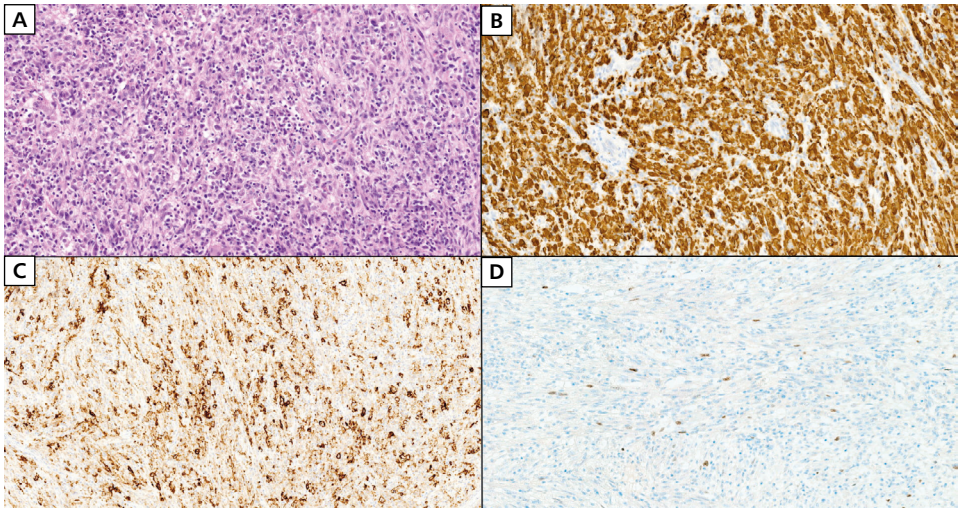

Figure 1. Microphotographs of epithelioid myofibroblastic inflammatory sarcoma (EIMS); A. View of the tumor composed of neoplastic epithelioid cells in an inflammatory background consisting of lymphocytes, plasma cells, and rare eosinophilic granulocytes (Hematoxilin and Eosin, 20×); **B.** Strong and widespread immunohistochemical expression of ALK1 in tumor cells (20×); **C.** High immunohistochemical expression of PD-L1 in neoplastic areas with epithelioid cytology (10×); **D.** Nuclear immunohistochemical staining in scattered neoplastic elements for NTRK (20×)

appear overall consistent with those already reported in the literature.

The one described case was a localized disease, and even microscopically, the surgical margins (both pulmonary and pleural) were free from neoplastic infiltration (staging: R0). In such cases, scarce literature data suggest surgery as the treatment of choice [1]. Therefore, the clinical-oncological decision was made to wait and see, with close follow-up.

In the case of a recurrence, which is reported in about one-quarter of these surgically treated tumors [1], the question will arise whether to treat with new surgery or with oncological therapy. In this context, since chemotherapy appears to have no effect on the progression of EIMS [1], two microscopical findings in our case appear noteworthy: 1) the clear overexpression of PD-L1 in areas with epithelioid morphology (EIMS) compared to those with spindle cells (IMT), and 2) the nuclear expression of NTRK.

These findings, which have been described in rare case reports, have already been the subject of studies about a) the possible interaction between PD-L1 expression and some rare tumor subtypes with rich inflammatory stroma [4]; b) the correlation between ALK molecular pathways and the PD-1/-PD-L1 immune checkpoints [2]; c) the involvement of pathways related to rearrangements of tyrosine kinase receptors [1].

Moreover, such evidence suggests that in addition to therapy with ALK inhibitors (such as crizotinib or the newer brigatinib and lorlatinib), both immunomodulatory drugs and tyrosine kinase inhibitors (TKIs) can be used. However, to date, very little is known about the real efficacy of immune checkpoint inhibitors on IMTs/EIMS (rare reports describe cases treated with nivolumab or sintilimab [1]), while the use of ALK-inhibitors and TKIs is much more established even in the neo-adjuvant phase [5]: hence histologically observed NTRK-positivity may constitute an additional clinically relevant finding as a possible target for specific therapies, e.g. with the use of entrectinib (an NTRK-inhibitor), in this category of tumors.

Conflict of interest

Authors declare no conflict of interest.

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