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CASE REPORT

Epithelioid inflammatory myofibroblastic sarcoma arising in the pleural cavity

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Abstract A 57-year-old Japanese man presented with massive right pleural effusion, and a huge tumor arising in the pleural cavity was detected by chest computed tomography. A thoracoscopic tumor biopsy revealed that the tumor protruded extensively into the pleural cavity, and its gross appearance was cystic and glossy. Microscopically, the tumor cells were rounded and epithelioid in shape. Prominent and abundant myxoid stroma was also present together with an inflammatory infiltrate, and the tumor was anaplastic lymphoma kinase (*ALK*)-immunopositive. Fluorescence in situ hybridization revealed that the *Ran-binding protein 2-ALK* fusion gene was present. Taken together, these findings supported the diagnosis of epithelioid inflammatory myofibroblastic sarcoma (EIMS), which is a variant of an inflammatory myofibrobrastic tumor. This is the first reported case of an EIMS arising in the pleural cavity.

Keywords Epithelioid inflammatory myofibroblastic sarcoma · Inflammatory myofibrobrastic tumor · Pleural cavity · Ran-binding protein 2—anaplastic lymphoma kinase

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Introduction

Inflammatory myofibrobrastic tumor (IMT) is a rare neoplasm composed of myofibroblastic spindle cells with inflammatory cell infiltrate, predominantly occurring in the lung or abdominal cavity of children and young adults. Recently, a variant of IMT with malignant characteristics and consisting mainly of round-to-epithelioid cells has been proposed to be a subclass of epithelioid inflammatory myofibroblastic sarcoma (EIMS) [1].

Herein, we report the first case of an EIMS arising in the pleural cavity, confirmed by immunohistochemistry and fluorescence in situ hybridization (FISH), in an older adult patient.

Case report

A 57-year-old Japanese man with a complaint of dyspnea on exertion was found to have massive right pleural effusion on an annual routine chest radiograph. As an automobile repair worker, he had been exposed to asbestos over a 3-year period. He was referred to our hospital, and chest drainage was carried out to reduce his dyspnea. Chest computed tomography (CT) after pleural effusion drainage revealed a huge intrathoracic tumor with heterogeneous density (Fig. 1a) and without other intrapulmonary nodules. F18-fluorodeoxyglucose (FDG) positron emission tomography revealed abnormally increased FDG uptake in the mass (standardized uptake value, max 10.7), but no other abnormally increased FDG uptake was detected, including in the abdomen (Fig. 1b). Based on these findings, the tumor was thought to have arisen in the pleura or chest wall. Pleural effusion cytology revealed only inflammatory cells with no evidence of malignancy. Serum tumor marker levels, including carcinoembryonic antigen

and cytokeratin fragment 19–9, were all within normal limits.

We performed thoracoscopic tumor biopsy and talc poudrage for an accurate diagnosis and management of pleural effusion, because curative resection was not expected due to an insufficient pulmonary reserve. When examined during the operation, the tumor appeared cystic and glossy, and protruded extensively into the pleural cavity. A tumor tissue biopsy was obtained for pathological examination. Follow-up chest CT showed that the tumor enlarged rapidly during the following 2 months, coming to occupy much of the right pleural cavity (Fig. 1c). Based on the pathological and genetic findings, thoracic oncology group at our institution has just started administering anaplastic lymphoma kinase (*ALK*) inhibitor as an alternative treatment to surgery for this aggressive tumor.

Pathological and genetic findings

Microscopically, the tumor consisted of two different histological types, one of which was of high cell density (Fig. 2a) and the other with low cell density and myxoid stroma (Fig. 2b). Both of these areas contained inflammatory cells, mainly lymphocytes and histiocytes, and were rich in capillaries. Tumor cells were rounded and epithelioid in shape, not spindle, with round nuclei with small nucleoli. Immunohistochemical analysis revealed that the tumor cells were positive for vimentin, desmin, CAM 5.2 (focal), and AE 1/AE 3 (focal), and were negative for Calretinin, CD30, CD31, CD33, alpha-smooth muscle actin, HHF35, myogenin, S100, HMB45, CD20, CD79a, CD3, CD5, leukocyte common antigen, and CD68KP-1. In addition, the tumor cells were positive for *ALK*, exhibiting a cytoplasmic pattern with perinuclear accentuation (Fig. 2c). FISH analysis was carried out on the formalin-fixed paraffin-embedded tissue slice (4 μm in thick) in this tumor, using bacterial artificial chromosomes, RP11-348G16 for *Ran-binding protein 2* (*RANBP2*), and RP11-984I21 and RP11-62B19 for *ALK*. It produced a merged signal in the tumor cells, indicating that the partner of the gene rearrangement of *ALK* was *RANBP2* (*RANBP2-ALK* fusion, Fig. 2d). Based on these pathological and molecular findings, the tumor was diagnosed as EIMS.

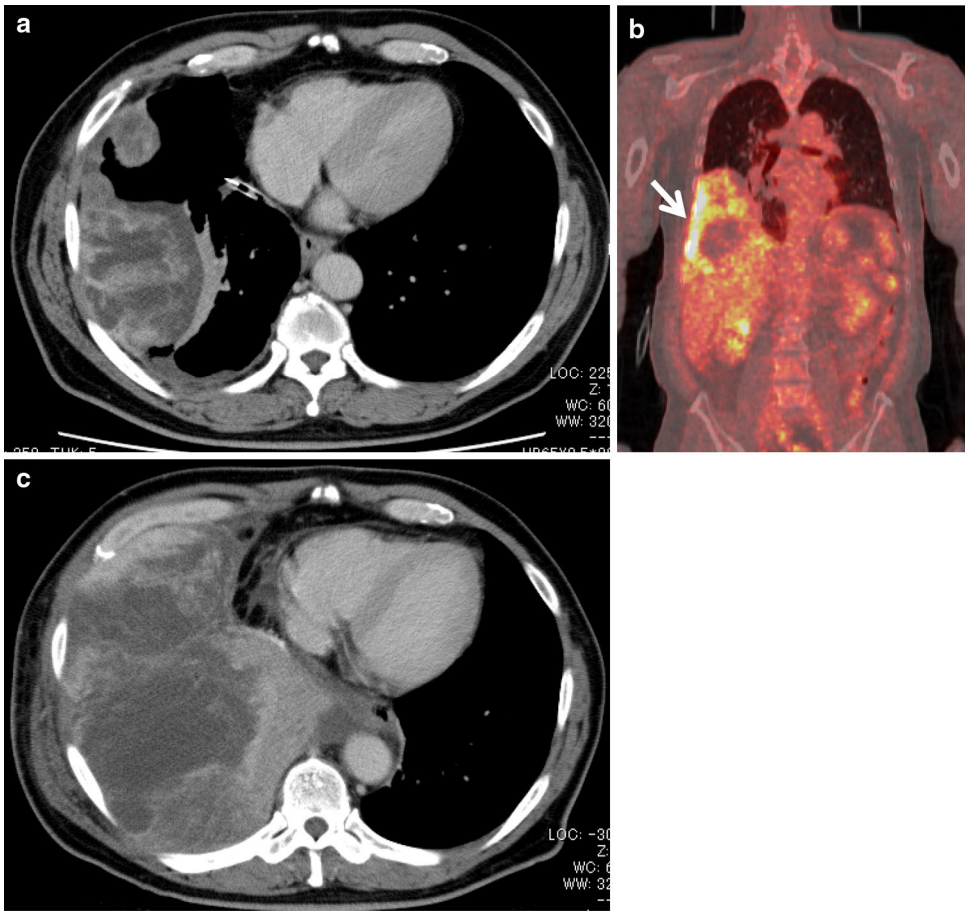

Fig. 1 **a** Chest computed tomography (CT) after pleural effusion drainage revealing a huge intrathoracic tumor of heterogeneous density. **b** F18-fluorodeoxyglucose (FDG) positron emission tomography revealing abnormally increased FDG uptake (standardized uptake value, max 10.7) in the mass (*arrow*). No other abnormally increased FDG uptake was detected, including in the abdomen. **c** A follow-up chest CT revealing that the tumor had enlarged rapidly over 2 months, coming to occupy much of the right pleural cavity

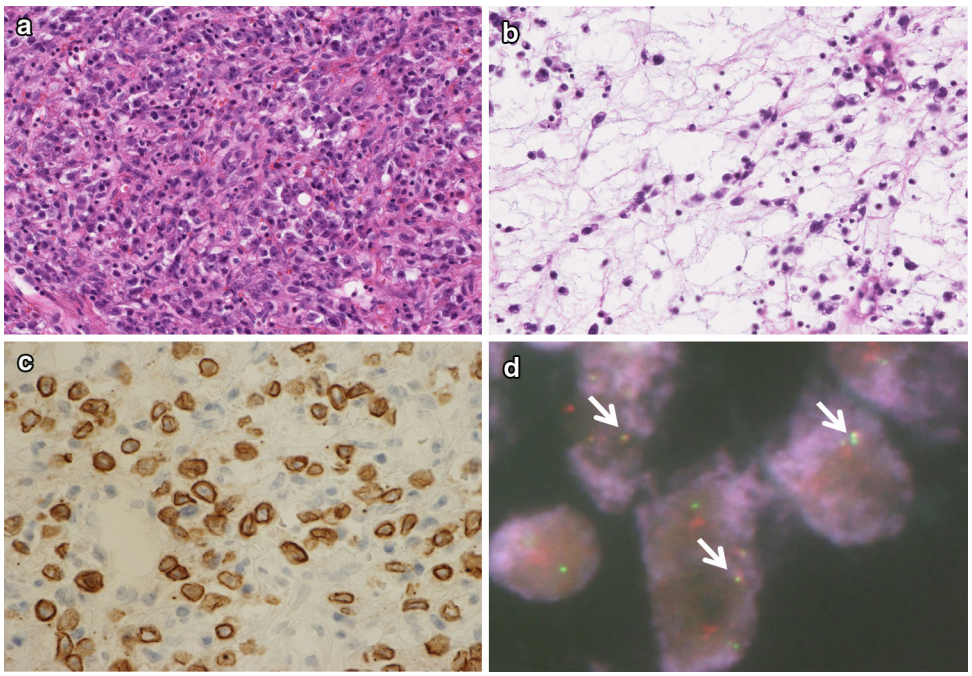

Fig. 2 **a** Microscopic findings of the dense cellular region of the tumor. Tumor cells were epithelioid in shape, not spindle, with round nuclei with small nucleoli. The tumor contained inflammatory cells, mainly lymphocytes and histiocytes, and was rich in capillaries. **b** Microscopic findings of the sparse cellular region of the tumor. The tumors contained abundant myxoid stroma and inflammatory cells. **c** The tumor was positive for anaplastic lymphoma kinase *(ALK)*, exhibiting a cytoplasmic pattern with perinuclear accentuation. d Fluorescence in situ hybridization analysis. Spectrum Green–labeled *ALK* locus-spanning and Spectrum Red–labeled ran-binding protein 2 (*RANBP2*) locus-spannig probes resulted in merged signals (*arrows*), indicative of *RANBP2-ALK* fusion

Discussion

The designation of EIMS has recently been proposed as a variant of IMT, reflecting its malignant clinical behavior [1]. This report described the morphological, immunohistochemical, and molecular genetic characterization of EIMS. The common features shared by EIMS are as follows: (1) round-to-epithelioid tumor cells, (2) abundant myxoid stroma with inflammatory infiltrate, (3) immunopositivity for *ALK*, and (4) *RANBP2-ALK* fusion gene. All of these features were identified in the present case and, therefore, we gave the diagnosis of EIMS. The only immunohistochemical difference between our case and those previously reported was a lack of CD30 expression [1].

The expression of *RANBP2-ALK* fusion, which is considered specific to EIMS, has only been reported in 8 previous IMTs (Table 1) [1–5]. It was noteworthy that there were only male patients and all tumors arose in the abdominal organs (e.g., the peritoneum, mesentery, and omentum). Although it is unclear whether the present case originated from the pleura or chest wall, this is the first case report of an intrathoracic IMT with a *RANBP2-ALK* fusion gene diagnosed as an EIMS. A conclusive explanation for this anatomical site predilection has yet to be found. There were two patterns of immunohistochemical staining for *ALK*: a nuclear membrane staining pattern in seven cases and a cytoplasmic pattern in the remaining one, as seen in the present case. Although surgical resection was performed as an initial treatment in all cases, the tumors exhibited an aggressive clinical course.

As the treatment of choice for IMT/EIMS, surgical resection is recommended when possible [1, 6, 7]. In the present case, curative resection was unrealistic, because the tumor grew very rapidly over a 2-month period (based on chest CT) and the patient had insufficient pulmonary reserve. The effectiveness of alternative treatment modalities such as radiotherapy, chemotherapy, and steroids is uncertain [6, 7]. Recently, it was reported that administration of the *ALK* inhibitor crizotinib in a case of IMT with a *RANBP2-ALK* fusion resulted in a sustained partial response [5]. Thoracic oncology group at our institution has just started administering *ALK* inhibitor, which may provide therapeutic effect for this aggressive tumor.

Conclusion

We report the first case of an EIMS arising in the pleural cavity. *ALK* inhibitor may be the best alternative treatment to surgery for this aggressive tumor.

Table 1 Comparison of 9 IMTs with *RANBP2-ALK* fusion

Author (years)	Age	Gender	Tumor site	ALK stain	Initial treatment	Clinical outcome	*RANBP2-ALK* detection techniques
Ma [4] (2003)	7 years	M	Intra-abdominal	NM	S + CT	Recurrence	RT-PCR
	7 months	M	Omentum Mesentery	NM	S	Recurrence	FISH RT-PCR
Patel [2] (2007)	2 months	M	Retro-peritoneum	CP	S	Free of disease	FISH
Chen [3] (2008)	34 years	M	Liver	NM	S	Died of disease	RT-PCR
Butrynski [5] (2010)	44 years	M	Omentum peritoneum	NM	S + CT + imatinib*	Recurrence	FISH RT-PCR
Marino-Enriquez [1] (2011)	41 years	M	Omentum	NM	S + CT + ALK inhibitor	Recurrence	RT-PCR
	6 years	M	Omentum mesentery	NM	S	Not evaluated (Short follow-up)	RT-PCR
	39 years	M	Mesentery	NM	S		RT-PCR
Present case (2012)	57 years	M	Pleura or chest wall	CP	ALK inhibitor	Not evaluated (Recent case)	FISH

* ALK inhibitor was administered after recurrence

IMT inflammatory myofibrobrastic tumor, *RANBP2-ALK* Ran-binding protein 2 anaplastic lymphoma kinase, *M* male, *NM* nuclear membrane staining, *CP* cytoplasmic staining, *S* surgery, *CT* chemotherapy, *RT-PCR* reverse transcription polymerase chain reaction, *FISH* fluorescence in situ hybridization

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