Case Report

# A recurrent inflammatory myofibroblastic tumor patient with two novel *ALK* fusions: a case report

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**Background:** Inflammatory myofibroblastic tumor (IMT) is a rare disease that mainly involves the lung and the abdomen. The gold standard of the IMT treatment is radical surgery, while chemotherapy and radiotherapy are represented usually for unresectable lesions. Anaplastic lymphoma kinase (*ALK*) rearrangements are present in approximately 50% of IMT patients, and several clinical trials of *ALK* tyrosine kinase inhibitors (TKIs) in the treatment of *ALK*-positive IMT patients are underway.

**Case Description:** We reported a case of IMT in the right pelvic cavity. Initially, the patient underwent resection of multiple lesions. Unfortunately, the patient's tumor recurred half a year later, and enhanced computerized tomography (CT) of the whole abdomen revealed multiple low-density masses. Then the patient underwent resection of the recurrent tumors. Immunohistochemical staining exhibited the expression of *ALK* in the tumor cells, and next-generation sequencing (NGS) technology revealed two novel ALK fusions, *ALK*-ribosome binding protein 1 (*RRBP1*) and hydroxyacid oxidase 1 (*HAO1*)-*ALK* fusions. These fusions were able to be transcribed and captured by RNA level. And the two fusions have not been reported in the IMTs.

**Conclusions:** This case expanded the range of *ALK* fusion types and provided a promising molecular-targeted treatment strategy. In addition, the two novel *ALK* fusions may be the recurrent oncogenic mechanism in clinically aggressive IMT.

**Keywords:** Inflammatory myofibroblastic tumor (IMT); *ALK-RRBP1; HAO1-ALK*; RNA-seq; case report

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## Introduction

Inflammatory myofibroblastic tumor (IMT) is a mesenchymal tumor composed of differentiated myofibroblastic spindle cells, often accompanied by numerous plasma cells or lymphocyte infiltration. It is a sporadic disease, tending to occur in soft tissues and internal organs. The most common site is the lung, followed by the mesentery and omentum. Most patients with IMT are children, adolescents, or young adults.

IMT frequently harbors chromosomal rearrangements, including anaplastic lymphoma kinase (*ALK*) rearrangements. *ALK* fusions are present in almost 50% of IMT, which fuse the 3' kinase-containing portion of *ALK* to the 5' portion of a fusion partner gene, leading to increased expression of *ALK* protein and activation the kinase domain through multimerization (1). As reported, more than ten different *ALK* fusion partners have been identified, including tropomyosin 3 (*TPM3*), tropomyosin 4 (*TPM4*), clathrin heavy chain (*CLTC*), calcium sensing receptor (*CARS*), 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase (*ATIC*), ran-binding protein 2 (*RANBP2*), SEC31 homolog A, COPII coat complex component (*SEC31L1*), PPFIA binding protein 1

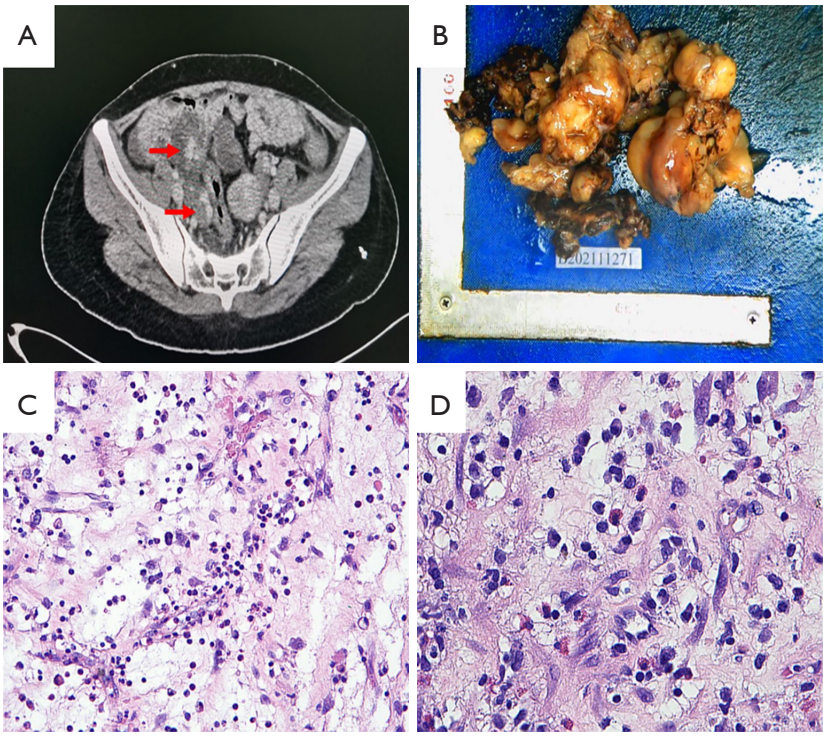


**Figure 1** CT of the abdomen and postoperative tissue. (A) The whole abdomen CT demonstrated multiple low-density masses and nodules in the pelvic mesenteric and posterior right uterus. (B) Postoperative tissue on June 18, 2021. (C,D) HE stained image (C, ×20; D, ×40). CT, computerized tomography; HE, hematoxylin and eosin.

(*PPFIBP1*), dynactin subunit 1 (*DCTN1*), echinoderm microtubule associated protein like 4 (*EML4*), protein kinase CAMP-dependent type I regulatory subunit alpha (*PRKAR1A*), lamin A/C (*LMNA*), trafficking from endoplasmic reticulum (ER) to golgi regulator (*TFG*), and fibronectin 1 (*FN1*) (2,3). Due to the abnormal gene fusion, *ALK* rendered oncogenic triggers such as in anaplastic large cell lymphoma, lung cancer, and IMT (4). Furthermore, previous researches have indicated that *RANBP2-ALK* fusion is one of the key drivers of IMT which experiences early disease recurrence and poor prognosis (5,6). Here, we report a recurrent IMT patient harboring two *ALK* fusions [*ALK*-ribosome binding protein 1 (*RRBP1*) and hydroxyacid oxidase 1 (*HAO1*)-*ALK*]. *ALK-RRBP1* was a rare fusion reported before. However, to our knowledge, the *HAO1-ALK* was a novel fusion. We present the following case in accordance with the CARE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-368/rc).

## Case presentation

A 43-year-old female was admitted to hospital with abdominal pain in October 2020. The abdominal computerized tomography (CT) showed a mass in the right pelvic cavity. Subsequently, the patient underwent resection of right pelvic mass combined with right salpingectomy and appendectomy, and the initial tumor cells were stained by immunohistochemistry (IHC): Vim (+), S100 (–), Des (+), SMA (+), ALK-V(D5F3) cytoplasm (+), CD34 (–), MDM2 cytoplasm (+), CDK4 cytoplasm (+), P16 (+), Ki-67 positive rate was about 8%, taking the changes into consideration, the pathological diagnosis was IMT. Half a year later, the patient had abdominal pain again. The levels of tumor markers were as follows CA125: 15.64 U/mL, CA199: 2.36 U/mL, AFP: 1.74 ng/mL. Enhanced CT of the whole abdomen revealed multiple low-density masses and nodules in the pelvic mesenteric and posterior right uterus (*Figure 1A*). Afterward, an irregular lesion of 11.1 cm × 5.7 cm × 7.8 cm was found in the right attachment area. In June 2021, the patient underwent resection of the recurrent tumors. At the same time, tumor masses at the bladder peritoneal reflex and near the sacral ligament were all resected for pathological measurement (*Figure 1B*). And IMT was diagnosed

 

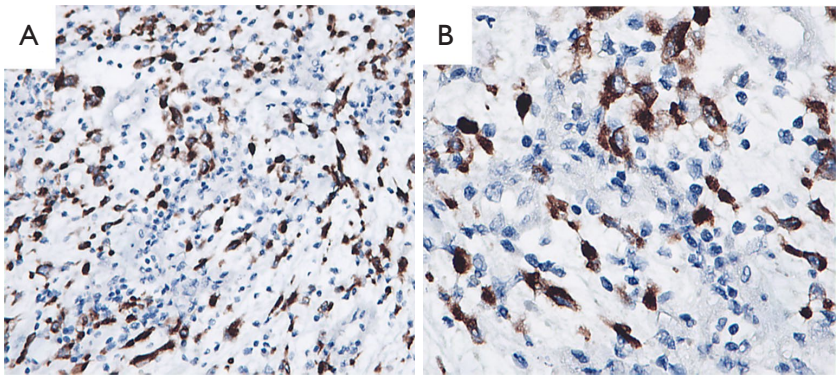


**Figure 2** Immunohistochemical staining showed diffuse expression of *ALK*, the specimen was stained by IHC with the anti-*ALK* (5A4) primary antibody. (A) Original magnification ×100. (B) Original magnification ×200. *ALK*, anaplastic lymphoma kinase; IHC, immunohistochemistry.

based on the pathological evaluation of the postoperative tissue samples (*Figure 1C*,*1D*). Because *ALK* fusions are present in most IMT, and *ALK* fusions are currently identified by IHC or reverse transcription-polymerase chain reaction (RT-PCR) in most laboratories. Indeed, immunohistochemical staining showed diffuse expression of *ALK* in the cytoplasm of tumor cells (*Figure 2A*,*2B*). Subsequently, to verify the occurrence of the *ALK* fusion and consider the possibility of precision treatment, the surgical tissues were subjected to comprehensive genomic testing via next-generation sequencing (NGS) test for 128 cancer-relevant genes by DNA and RNA sequencing. Sequencing reads were examined on Integrative Genomic Viewer (IGV) software. Compared to an inherent limitation of DNA-based sequencing, RNA sequencing assay provides a more direct approach to fusion detection as the introns are removed by splicing. The results confirmed the patient had two *ALK* fusions (shown in *Figure 3*), one was *ALK-RRBP1* (*Figure 3A*,*3C*), and the other was *HAO1-ALK* (*Figure 3B*,*3D*). Interestingly, these fusions were transcribed and captured by RNA sequencing. At present, the two fusions have not been reported in the IMTs. The National Comprehensive Cancer Network (NCCN) guideline for soft tissue sarcoma suggested that patients with IMT carrying *ALK* fusion take *ALK* inhibitors as the first treatment. Therefore, the patient with these driver mutations is likely to benefit from target therapy.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

## Discussion

IMT has intermediate biological potential, so it may relapse but rarely metastasize. Local recurrence was reported in 19% of patients in a series of IMT (3). IMT can arise in any part of the body, but it usually occurs in the lung or abdominal cavity. Previous studies have suggested that extrapulmonary IMT may have a higher risk of recurrence than pulmonary IMT (3,6,7). Consistent with these reports, the patient was extrapulmonary IMT, located outside the lung, and progressed soon following the primary tumor resection.

IMT patients express *ALK* chimeric protein aberrantly due to *ALK* fusion to many gene partners. In our patient, two *ALK* fusion partners (*RRBP1*, *HAO1*) were detected simultaneously by RNA-seq. RRBP1 is an ER membrane protein in the secretion and transportation of nascent proteins in mammalian cells (8). *RRBP1* overexpression has been confirmed to be associated with poor prognosis and an independent predictor of overall survival (OS) and disease-free survival (DFS) in other cancers, for example, epithelial ovarian cancer (9). It is due to that *RRBP1* overexpression can promote tumor cell proliferation (8). In our case, the 3' end of *ALK* exon 19 fused to the 5' end of *RRBP1* exon 10. However, the previously studies reported that *ALK* translocations had a known promoter that induced the

 

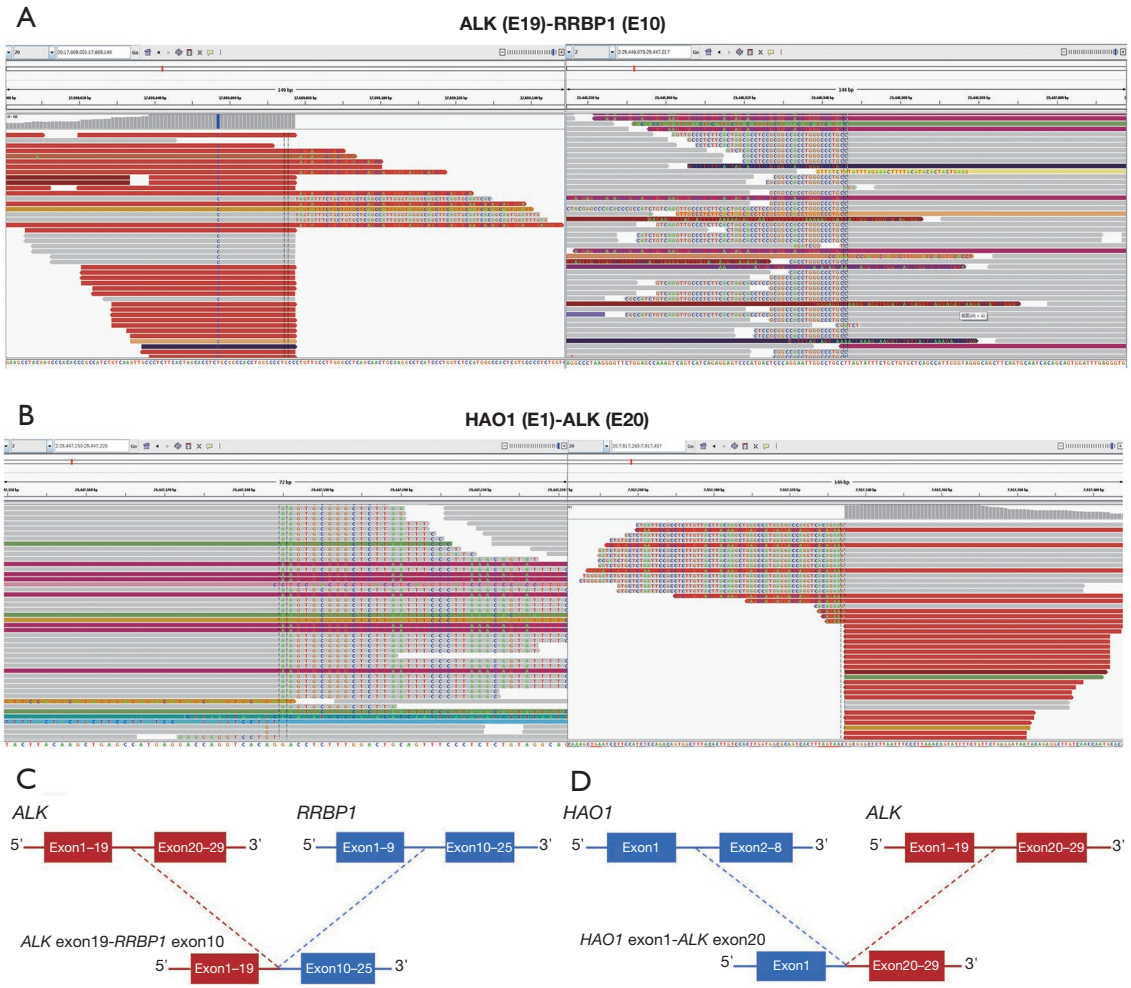


**Figure 3** Identification of the *ALK* fusions at the RNA level. (A,B) Sequencing reads of *ALK* and *RRBP1/HAO1* were visualized using the IGV. (C,D) The structure schematic map of the *ALK-RRBP1* and *HAO1-ALK* fusion locus. *ALK*, anaplastic lymphoma kinase; *RRBP1*, ribosome binding protein 1; *HAO1*, hydroxyacid oxidase 1; IGV, Integrative Genomic Viewer.

expression of the chimeric protein, and the mechanism of the reversed *RRBP1* leads to kinase activation of *ALK* remains unknown (8,9). One study has reported three epithelioid inflammatory myofibroblastic sarcomas (EIMS) patients with *RRBP1-ALK* fusion exhibiting poor prognosis. One case died after diagnosis 2 months and the other two cases relapsed with disseminated intraabdominal metastases within 10 months after the primary tumor surgery (10). Our case was spindle-cell IMT which was different from EIMS morphologically and clinically. *HAO1* is a novel partner of *ALK*, located on chromosome 20. *HAO1* encodes liver-specific glycolate oxidase protein, which catalyzes the conversion of glycolate to glyoxylate in the peroxisome (11). In our case, the 3' end of *HAO1* exon 1 fused to the 5' end of *ALK* exon 20. Up to now, this fusion pattern has not been reported.

In a phase II single-arm clinical trial, 20 IMT patients were treated with crizotinib, and 12 patients were *ALK*-positive among them. The results showed that 100% of *ALK*-positive patients and 85.7% of *ALK*-negative patients were under control. The median reaction time for *ALK*-positive patients was 9 months, and for *ALK*-negative patients was 7.6 months (12). A case reported an IMT metastatic patient with *ALK*-positive was treated with crizotinib for 8 months and developed disease progression. Afterward, the patient changed to ceritinib treatment to achieve a partial remission (13). In addition, a clinical trial of brigatinib in the treatment of *ALK*-positive IMT

 

children and adults is underway (NCT04925609). An IMT case with proline rich coiled-coil 2B (*PRRC2B*)-*ALK* fusion achieved the durable clinical response to sequential use of *ALK* tyrosine kinase inhibitors (TKIs) (crizotinib, alectinib, ceritinib, and lorlatinib). And it highlighted the importance of NGS in identifying actionable mutations and resistance mechanisms that could guide the use of molecular targeted therapies for the effective management of IMT patients with *ALK* gene arrangement (14). An IMT patient with *RRBP1-ALK* fusion progressed after crizotinib treatment for 6 months. But the patient achieved the best response after 2 months from alectinib; no severe side effects were observed. And during the treatment with alectinib, a resistance mutation of *ALK* L1196Q was found, the patient then changed to ceritinib therapy to achieve a partial remission (15). This case might support the strategy that *ALK*-TKIs could provide a feasible treatment option for the patient in this study in the future.

In summary, with the confirmed RNA expression of *ALK*, without any other oncogenic mutation detected, we speculate that the novel *HAO1-ALK* fusion served as a driver mutation of the patient's disease. And *ALK-RRBP1* or *HAO1-ALK* may be the recurrent oncogenic mechanism in clinically aggressive IMT. Additionally, our case report expanded the range of *ALK* fusion types and provided a promising targeted treatment strategy.

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## Footnote

*Reporting Checklist*: The authors have completed the CARE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-368/rc

*Conflicts of Interest*: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-368/coif). The authors have no conflicts of interest to declare.

*Ethical Statement*: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.



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