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# Case report: Crizotinib is effective in a patient with *ROS1*-rearranged pulmonary inflammatory myofibroblastic tumor

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ABSTRACT

*Objectives:* Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal tumor and is prevalent among children and adolescents. In recent years, following the emergence of high-throughput sequencing techniques, rearrangements in genes, such as *ALK*, *ROS1*, *NTRK*, *RET*, and *PDGFRβ*, have been detected in a considerable proportion of IMT patients. However, the practice of targeted therapy for those patients remains extremely limited. In this study, we report about a 14-year-old boy diagnosed with pulmonary IMT with a mass measuring 12 × 8 cm in the right lower lobe.

*Materials and methods:* Immunohistochemistry (IHC) assay and comprehensive next-generation sequencing (NGS) were performed on the biopsied tumor tissue.

*Results:* The IHC assay revealed an ALK-negative tumor, while NGS detected a*TFG-ROS1* rearrangement. The patient achieved continuous remission after treatment with crizotinib (250 mg, bid).

*Conclusion:* This case broadens the experience regarding targeted therapy for*ROS1*-rearranged IMT and supports the use of broad molecular profiling testing for optimizing therapeutic options.

## 1. Introduction

Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal tumor that belongs to a subtype of soft tissue sarcoma, with a global prevalence of approximately 0.04%–0.7% [1]. IMT may occur at any age; however, it is more common among children and adolescents. The lungs are the most common site of IMT onset, although it may also occur at multiple sites such as the retroperitoneum, abdomen, and pelvic cavity. Surgery is the most important therapeutic approach for IMT because the tumor is insensitive to radiotherapy and chemotherapy; thus, the therapeutic options for patients with unresectable IMT are very limited [1]. Approximately 50% of IMT cases are anaplastic lymphoma kinase (ALK)-positive tumors that can be effectively treated using ALK inhibitors [2,3]. In recent years, a considerable proportion of ALK-negative IMT patients have been found to harbor rearrangements in various genes, including *ROS1*, *NTRK*, *PDGFRβ*, and *RET*. Effective targeted drugs are available for patients harboring those rearrangements [4,5]. However, very few studies have reported the efficacy of targeted therapy in this group of IMT patients. Here, we report a pediatric case of pulmonary IMT in the right lower lobe.

## 2. Case presentation

A 14-year-old boy was admitted to a local hospital in September 2017 because of significant cough and chest tightness. A chest computed tomography (CT) scan showed an 80-mm-sized mass in the right lower lobe that was likely to be a malignant tumor. Because of the rarity of this disease, the patient did not receive a confirmed diagnosis despite being transferred to several hospitals with multiple biopsies for pathological diagnosis; moreover, the tumor continued to grow.

The patient was subsequently admitted to our hospital in January 2018. A new chest CT scan revealed a large soft tissue mass in the right lower lobe. The mass had increased to 120 × 80 mm in size and had compressed the left atrium. To clarify the pathological type of the tumor, thoracoscopic exploration was performed. The tumor was evaluated to be unresectable because it had invaded the left atrium and major vessels. The final pathological result determined that the tumor was IMT (Fig. 1A), and immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) results indicated that the tumor was ALK negative.

Next-generation sequencing (NGS)-based broad molecular profiling

*Abbreviations:* IMT, inflammatory myofibroblastic tumor; ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; NGS, next-generation sequencing; NSCLC, non-small-cell lung carcinoma; CT, computed tomography; FISH, fluorescence in situ hybridization

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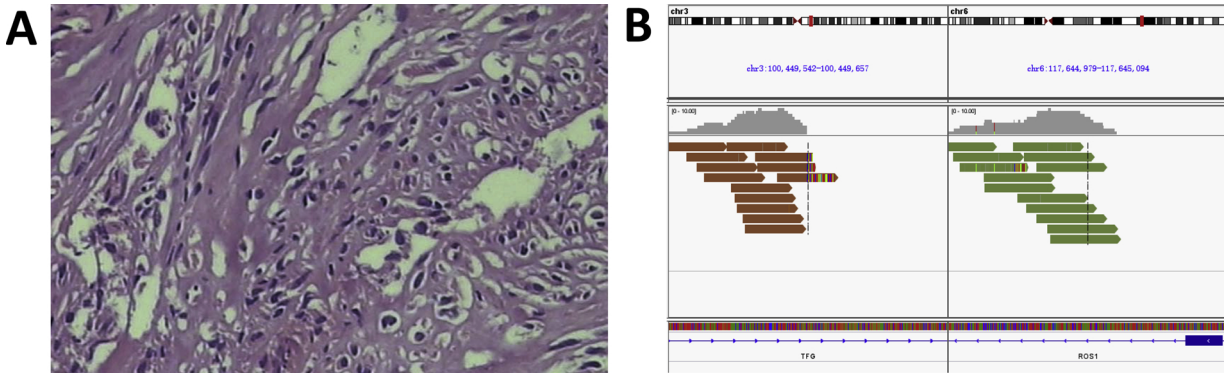


**Fig. 1.** Histopathologic and NGS results of the reported pulmonary IMT case. (A) Hematoxylin-eosin staining for biopsy specimens of the tumor. (B) NGS indicates a somatic genomic rearrangement between *TGF* and *ROS1* as demonstrated by Integrative Genomics Viewer.
NGS: next generation sequencing; IMT: inflammatory myofibroblastic tumor.

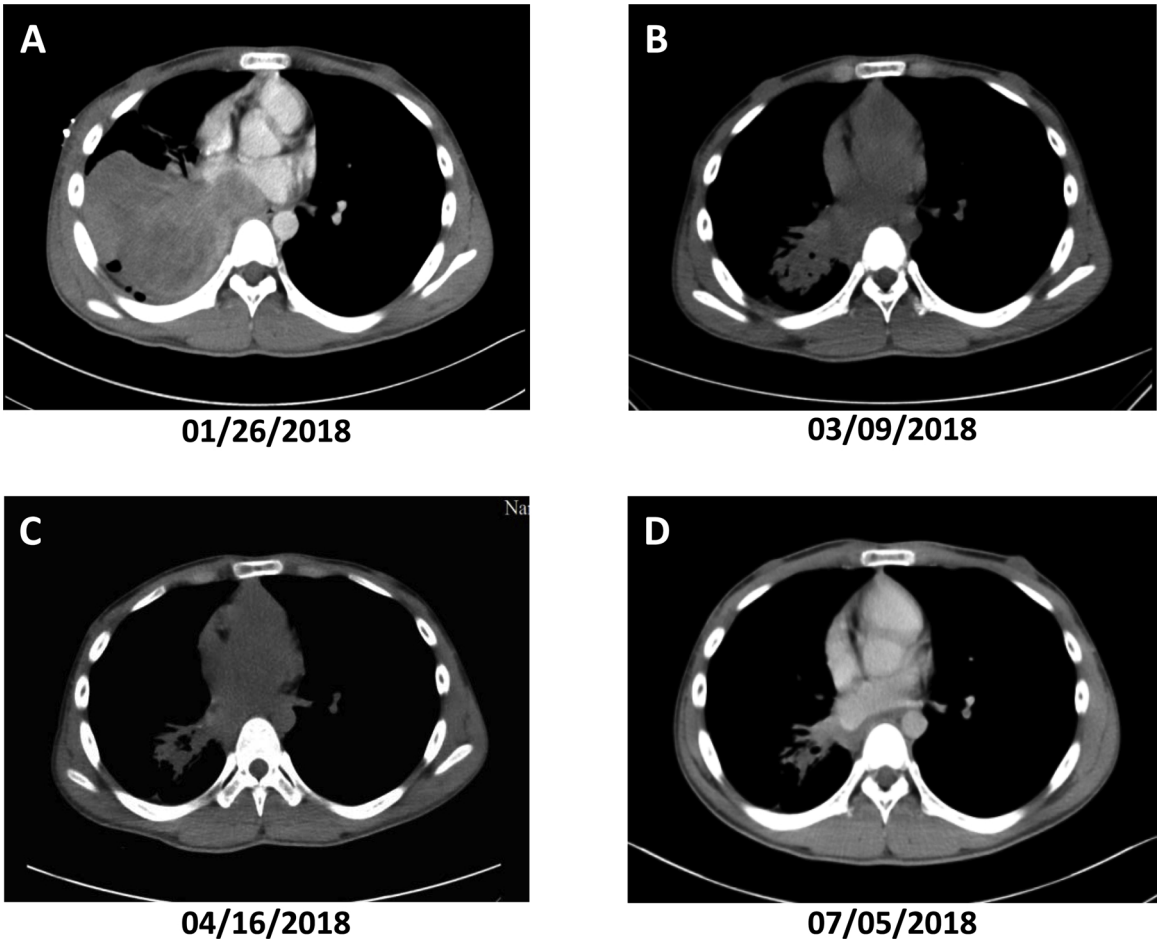


**Fig. 2.** Treatment efficacy with crizotinib for a 14-year-old male with pulmonary IMT based on CT scans. (A) Before crizotinib treatment. (B) One month after crizotinib treatment. (C) 2.5 months after crizotinib treatment. (D) 5 months after crizotinib treatment.
IMT: inflammatory myofibroblastic tumor; CT: computed tomography.

of the tumor tissue was performed at OrigiMed (Shanghai, China). A *TFG-ROS1* rearrangement involving exons 1–4 of *TFG* and exons 35–43 of *ROS1* was detected (Fig. 1B). The rearrangement contains the full kinase domain of *ROS1* and is predicted to result in *ROS1* activation. The patient was orally administrated crizotinib (250 mg, twice daily) from February 10, 2018, and he completely recovered from the symptoms of cough and chest tightness after 1 month of treatment. One month later, follow-up CT scan showed a significant reduction in the tumor size (50 × 42 mm). The patient continued treatment, and 2.5 months after initiating crizotinib treatment, the tumor size reduced to 47 × 35 mm, as evident on CT scan. The scan also revealed a clearer separation between the tumor and left atrium (Fig. 2). The tumor continued shrinking to 2.5 × 1.3 cm in size 5 months after treatment initiation. Subsequently, the patient continued taking crizotinib and was assessing to determine the optimal time of radical surgery. There was no significant adverse drug reaction throughout the treatment course. Ethics approval was received for this study.

**Table 1**
Cases of targeted treatment for specific genetic variants of IMT tumor patients reported in the literature.

| Study | Fusion gene | Age, years | Sex | Primary lesion | Detection method | Drug | Efficacy evaluation |
|---|---|---|---|---|---|---|---|
| Daniel, Sugganth et al, J Clin Oncol, 2017. [8] | *ROS1-TFG* | 59 | M | abdomen | NGS | crizotinib | PD |
| Lovly, C. M. et al, Cancer Discov, 2014. [4] | *ROS1-TFG* | 6 | M | left lung | NGS | crizotinib | PR |
| Vassal, G. et al, J Clin Oncol, 2016. [9] | *ROS1* | unknown | unknown | unknown | IHC and NGS | crizotinib | PR |
| Butrynski, James E et al, N Engl J Med, 2010. | *RANBP2-ALK* | 44 | M | abdomen, pelvis | IHC and FISH | crizotinib | PR |
| Nagumo, Y. et al, Int J Surg Case Rep, 2018. | *ALK* rearrangement | 17 | M | bladder | FISH | crizotinib | PR |
| Rao, N. *et al,* J Natl Compr Canc Netw, 2018 | *NUMA1-ALK* | 21 | F | mediastinum | NGS | crizotinib | PR |
| Shash et al, J Pediatr Hematol Oncol, 2016 | *TPM3-ALK* | 8 | F | left lower lung | FISH | crizotinib | PR (fatal Pulmonary Toxicity) |
| Lorenzi, L. et al, Int J Surg Pathol, 2014 | *CLTC-ALK* | 24 | M | abdomen | FISH | crizotinib | SD |

## 3. Discussion

IMT is a rare disease. It was previously believed that surgery was the main therapeutic approach for IMT, while pharmacotherapeutic approaches for patients with tumors that could not be resected were extremely limited with low efficacy. However, IMT has regained attention in recent years because of its molecular characteristics and actionable targets being reported. Here, we reported about a 14-year-old boy who was diagnosed with ALK-negative pulmonary IMT based on IHC and FISH assays. NGS-based broad genomic profiling showed that the patient harbored *TFG-ROS1* rearrangement. The patient achieved continuous remission following treatment with crizotinib. This report has enriched our therapeutic experience of IMT patients harboring *ROS1* gene rearrangement.

*ROS1* rearrangements are reported in approximately 9%–13% of IMT and all have been reported in ALK-negative cases [4–6]. A previous study involving 33 IMT patients identified 2 cases of *TFG-ROS1* rearrangement and one case of *YWHAE-ROS1* rearrangement via NGS [4]. A 6-year-old IMT patient with *TFG-ROS1* rearrangement had a significant reduction in tumor size after treatment with crizotinib. Another study involving 30 IMT patients identified 4 cases of *TFG-ROS1* rearrangement via NGS, of which one was a 59-year-old patient with metastatic gastric IMT who was treated with crizotinib but showed a poor response [6]. A phase II trial on the treatment of advanced tumors among children and adolescents with *ROS1*, *MET*, or *ALK* rearrangements using crizotinib reported about a patient with *ROS1* rearrangement (partner gene unknown) who achieved PR with a progression-free survival of 16.7 months [7]. *ROS1*-arranged IMT has also been reported to occur in the esophagus and pelvic cavity; however, its subsequent therapy and prognosis are unknown [5]. Crizotinib has been approved for treating *ROS1*-positive metastatic non-small-cell lung carcinoma (NSCLC). A study regarding the treatment of 50 metastatic NSCLC patients with *ROS1* rearrangement using crizotinib showed that the objective response rate was 72% and the rearranged type was not associated with response to crizotinib [8].

Gene rearrangements, such as *ALK*, *ROS1*, and *PDGFRβ*, have been found in 85% of IMT patients, all of which are actionable targets of FDA-approved drugs [4], In addition, rearrangements in *NTRK* [5], *RET* [5], *JAK1* [6], *MUTYH* [6], and MDM2/CDK4 amplification [9] have recently been detected in IMT. *ALK* rearrangement is the most common genetic alteration of IMT and has previously been mainly detected via IHC or FISH assays. A recently published phase II clinical trial [10] on crizotinib treatment of IMT with or without positive ALK showed that 50% (6/12) of ALK-positive patients achieved an objective response; however, only 14% (1/7) of ALK-negative patients had a response, prompting us to perform a broader range of molecular testing for ALK-negative patients, so as to identify comprehensive genomic status and select possible targeted therapies. In the future, targeted therapy may be used for most unresectable IMT patients according to the specific detected molecular targets, and this would greatly improve the outcomes of these patients. Currently reported cases of targeted therapies against IMT patients are summarized in Table 1.

## 4. Conclusion

In summary, we report a case of *ROS1*-rearranged pulmonary IMT. The patient had a significant reduction in tumor size and achieved a persistent response with crizotinib. This study provided a new therapeutic strategy for IMT patients with *ROS1* rearrangement. It should be considered that conventional detection methods, such as IHC and FISH, may fail to detect a range of actionable gene rearrangements, such as *ROS1*, *RET*, *NTRK*, and *PDGFRβ*, in IMTs. A broader molecular testing, such as NGS, is necessary to explore the comprehensive genetic characteristics and potential drug targets for patients with IMT, especially for those identified as ALK negative in clinical practice.

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