Partial Response to Ceritinib in a Patient With Abdominal Inflammatory Myofibroblastic Tumor Carrying a *TFG-ROS1* Fusion

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ABSTRACT

Inflammatory myofibroblastic tumor (IMT), a rare sarcoma, is primarily treated via resection of the mass. However, there is no standard treatment for recurrence or unresectable tumors. Almost 50% of IMTs carry *ALK* gene rearrangement that can be treated using *ALK* inhibitors, but therapeutic options for *ALK*-negative tumors are limited. This report describes a woman aged 22 years with unresectable *ALK*-negative IMT. Next-generation sequencing revealed a *TFG-ROS1* fusion, and she had a partial response to the *ROS1* inhibitor ceritinib. This report provides the first published demonstration of a patient with IMT with *ROS1* fusion successfully treated using ceritinib. Our study suggests that targeting *ROS1* fusions using the small molecule inhibitor shows promise as an effective therapy in patients with IMT carrying this genetic alteration, but this requires further investigation in large clinical trials.

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Inflammatory myofibroblastic tumor (IMT) is a rare soft tissue neoplasm containing myofibroblastic spindle cells with inflammatory cells.¹ It usually arises in the lung, abdomen, or pelvis and affects primarily children and young adults.² Symptoms of disease are often restricted to the involved organ, and 15% to 30% of patients present with fever, malaise, microcytic anemia, weight loss, thrombocytosis, elevated erythrocyte sedimentation rate, or polyclonal hypergammaglobulinemia.³

Surgery is the primary management for patients with localized IMT; however, there is no standard treatment for patients with advanced and/or unresectable IMT. At the molecular level, gene fusion is a feature of IMT and also a common molecular feature of soft tissue sarcoma. Almost half of IMT cases carry *ALK* gene rearrangement that can be treated using *ALK* inhibitors,^{4–6} but therapeutic options for *ALK*-negative tumors are limited. *ALK*-negative IMTs may be more aggressive, with a higher frequency of metastasis compared with *ALK*-positive IMTs.⁷ Recent studies have described novel fusions involving *ROS1*, *NTRK*, *RET*, and *PDGFRβ* genes in a subset of *ALK*-negative cases.^{8–10} Little is known on the genomic level about potential oncogenic drivers in this subset of IMTs. Given the rarity of IMT, few prospective studies focusing on its targeted therapy are available. This report presents a case of *TFG-ROS1*-positive IMT that developed in the abdominal cavity and shrank remarkably after treatment with ceritinib.

Case Description

On September 3, 2018, a woman aged 22 years with no relevant past medical history presented to a local hospital with multiple masses in the left abdominal cavity and retroperitoneum seen on CT scan, and polypoid hyperplasia in the large intestine seen on colonoscopy. PET scan showed enhanced FDG-avid uptake in the retroperitoneum, suggesting a malignant tumor in the abdomen. The patient was subsequently referred to our hospital, where she underwent gastrojejunostomy on October 8, 2018. Postoperative pathologic diagnosis was

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intermediate spindle cell tumor of omental nodules. Under a light microscope, the tumor was found to be composed of proliferating fusiform fibroblasts/myofibroblasts and collagen fibers; fibroblasts were displayed with the shapes of striate, star, and bundle; and the mesenchyme contained abundant lymphocytes and plasmocytes. Immunohistochemical (IHC) staining of *CD34*, *SMA*, Ki67, β -catenin, CR, IgG4, *CD38*, CK, EMA, calretinin, and desmin were positive, whereas *ALK*, *DOG1*, *CD117*, S100, *CD30*, HMB45, Melan-A, *STAT6*, IgG, Era, progesterone receptor, and caldesmon were negative. Based on her IHC results and the tumor characteristics seen on light microscopy, the patient was finally diagnosed with abdominal IMT.

On November 7, 2018, the patient was treated with cisplatin (40 mg/d intravenously) and methotrexate (25 mg/d intravenously) as adjuvant chemotherapy for 1 cycle. Meanwhile, next-generation sequencing (NGS) of the tumor tissue was performed at Origimed. A *TFG-ROS1* fusion involving exons 1–4 of *TFG* and exons 35–43 of *ROS1* was identified (Figure 1). The fusion retained the intact kinase domain of *ROS1*. During reexamination in December 2018, PET/CT scan (Figure 2A, B) showed enhanced hypermetabolic lesions in the retroperitoneum and mesenteric roots and the left lower abdomen. The patient withdrew from chemotherapy because of severe adverse effects and started ceritinib (450 mg/d) monotherapy on December 8, 2018. After 2.5 months of ceritinib treatment, PET/CT scan showed remarkable shrinkage and even disappearance of masses in the retroperitoneum and mesenteric roots and the left lower abdomen (Figure 2C, D). Clinical efficacy was evaluated as partial response. The patient developed vomiting and diarrhea after ceritinib treatment. These adverse effects disappeared after a ceritinib dose reduction to 300 mg/d beginning in June 2019. In August 2019, she restarted ceritinib at 450 mg/d, and no adverse effects occurred.

Discussion

According to WHO classification, IMT is currently a distinctive neoplasm composed of myofibroblasts accompanied by an inflammatory infiltrate of lymphocytes,

plasma cells, and/or eosinophils.¹¹ Surgery is considered the main therapeutic approach for IMT, because other treatment approaches for patients with advanced and/or unresectable IMT are extremely limited. Importantly, IMT has drawn increasing attention because of its molecular characteristics and actionable targets reported in recent years. This report describes a woman aged 22 years who was diagnosed with *ALK*-negative abdominal IMT based on IHC results and tumor characteristics seen on light microscopy, and in whom NGS testing identified a *TFG-ROS1* fusion. The patient achieved partial response after treatment with ceritinib. This report provides a new potential therapeutic option for some patients with *ROS1* gene rearrangement of this tumor type.

ROS1 is a receptor tyrosine kinase involved in the regulation of several cellular processes, including proliferation, differentiation, apoptosis, and cell migration.¹² Substantial evidence supports *ROS1* as a key player in many solid tumors, including non-small cell lung cancer (NSCLC), cholangiocarcinoma, gastric adenocarcinoma, and colorectal cancer.¹³ *ROS1* rearrangements create fusion proteins that result in constitutive activation of the tyrosine kinase and acceleration of cellular proliferation.^{14,15} *ROS1* gene fusions were recently identified in a subset of *ALK*-negative IMT,^{8,16} suggesting a new diagnostic marker for this group of neoplasms. Thus far, only 2 *ROS1* fusion partners, *TFG* and *YWHAE*, have been identified in IMTs, with *TFG* the most common partner.^{8,16,17} In our patient's case, because complete tumor resection was not possible, tumor biopsies were subjected to NGS testing and a *TFG-ROS1* fusion was identified. The chromosomal rearrangement was identified between regions 3p12 and 6q22, causing fusion between exon 4 of *TFG* and exon 35 of *ROS1*. This result is consistent with previous reports on *TFG-ROS1* fusion, the breakpoints of which are located between exon 4 of *TFG* and exon 34 or 35 of *ROS1*, leading to constitutive activation of *ROS1* that contains its intact kinase domain.^{8,18}

The discovery of *ROS1* fusions in patients with IMT has facilitated the clinical development of *ROS1* inhibitors, including crizotinib and ceritinib. Crizotinib is a small molecule tyrosine kinase inhibitor (TKI) that was found to actively inhibit *ALK*, *MET*, and *ROS1*. Crizotinib was originally developed as an anti-*MET* molecule,¹⁹ but subsequently showed significant activity in *ALK*-driven tumors and was FDA-approved for *ALK*-positive advanced NSCLC.²⁰ Crizotinib has also shown remarkable efficacy against *ROS1*-positive lung cancer and was the first TKI approved for *ROS1*-positive advanced NSCLC.²¹ A patient aged 14 years with pulmonary IMT with a *TFG-ROS1* fusion achieved continuous remission²² and a boy aged 8 years with treatment-refractory *ALK*-negative IMT harboring a *TFG-ROS1* fusion experienced a dramatic response after treatment with crizotinib.⁸ However, another study found that a patient

Figure 1. Genomic fusion of exons 1–4 of *TGF* to exons 35–43 of *ROS1*.

Figure 2. PET/CT imaging showing enhanced hypermetabolic lesions in the (A) retroperitoneum and mesenteric roots and (B) left lower abdomen before ceritinib treatment, and remarkable shrinkage and even disappearance of masses in the (C) retroperitoneum and mesenteric roots and (D) left lower abdomen after 2.5 months of ceritinib treatment.

aged 59 years with metastatic gastric IMT carrying a *TFG-ROS1* fusion and treated with crizotinib showed a poor response.²³

Ceritinib, a selective oral TKI of *ALK*, is similar in action to crizotinib without *MET*-inhibiting ability. It was FDA-approved for treatment of crizotinib-resistant *ALK*-positive NSCLC. In enzymatic assays, ceritinib showed 20 times greater potency than crizotinib

against *ALK*.²⁴ In addition, ceritinib has shown comparable activity to crizotinib against *ROS1*.^{25,26} In an open-label multicenter phase II study, ceritinib showed potent clinical activity in patients with NSCLC harboring *ROS1* rearrangement, with a 62% objective response rate and 9.3 and 19.3 months of median progression-free survival among all patients and those who were crizotinib-naïve, respectively.²⁷ Ceritinib has

also shown clinical activity in patients with IMT. A male patient aged 32 years with an *ALK*-rearranged IMT showed partial response to ceritinib after failure of crizotinib,²⁸ and another patient with a highly aggressive *ALK*-rearranged IMT arising in the pleural cavity showed a drastic response to 2 *ALK* inhibitors: ASP3026 and ceritinib.⁵ In our study, the patient began ceritinib therapy and achieved partial response with an excellent tolerance after 2.5 months. This is the first report of a patient with *ROS1*-rearranged IMT being treated successfully with ceritinib.

Conclusions

Because no standard treatment exists for patients with advanced and/or unresectable IMT, we hope that the identification of actionable genetic alterations will redefine management strategies for this disease. We

identified a *TFG-ROS1* fusion in a patient with IMT, who showed remarkable tumor shrinkage and achieved partial response after treatment with ceritinib. Our study provides the first report of a patient with *ROS1*-rearranged IMT being treated successfully with ceritinib. However, the response seen in this patient, although promising, requires further investigation in large clinical trials.

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