A case of advanced infantile myofibromatosis harboring a novel MYH10-RET fusion

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ABBREVIATIONS:

CGP Comprehensive genomic profiling

IM Infantile myofibromatosis

IMT Inflammatory myofibroblastic tumor

MRI Magnetic resonance imaging

MTZ Methotrexane

TMB Tumor mutational burden

VBL Vinblastine

INTRODUCTION

Infantile myofibromatosis (IM), predominantly observed in infants and young children, features variable prognosis, as evidenced by some tumors spontaneously regressing, others successfully surgically managed, and those multi-focal or with visceral involvement requiring systemic therapy[1-3]. For patients with unresectable, persistent, and disseminated IM, comprehensive genomic profiling (CGP) may identify targetable genomic alterations. In this case of a child with a single focus unresectable IM, CGP identified a novel *MYH10-RET* fusion, suggesting possible utility of RET targeted therapies.

RESULTS

The index patient is a newborn female with a large mass in the left sacrum and inability to move lower extremities. Magnetic resonance imaging (MRI) revealed a single large multi-lobulated retroperitoneal mass encasing the lumbosacral spine, with a portion of the mass within the lumbosacral spinal canal and multiple neural foramina bilaterally. This mass encased multiple vessels and narrowed the iliac veins bilaterally and the inferior vena cava. Surgical resection was deemed unfeasible.

Biopsy revealed a moderately cellular lesion composed of spindle cells with a fascicular architecture and some areas displaying prominent hemangiopericytomatous vascular pattern with adipose tissue infiltration. Patchy extramedullary hematopoiesis and focal intervascular extension by the tumor were noted. CD34, HHF35, desmin and myogenin were negative, whereas smooth muscle actin was focally and weakly positive. Based on these features and FISH negativity for the t(12;15)(p13;q25) *ETV6-NTRK3* translocation, the diagnosis was a low-grade spindle cell tumor consistent with IM.

Initial treatment with vincristine, actinomycin-D, and cyclophosphamide was poorly tolerated, leading to necrotizing enterocolitis, liver dysfunction and veno-occlusive disease. Subsequent weekly vinblastine and methotrexate (VBL/MTZ) were well-tolerated - after 26 weeks, tumor shrunk by ~40%, and neurologic function of extremities and urinary continence improved. Currently at 42 weeks on VBL/MTZ, she is continuing to respond.

CGP of the tumor revealed a single alteration, a *MYH10-RET* fusion (Figure 1).

DISCUSSION

This is the first report describing a *RET* fusion in IM. In lung and thyroid carcinomas, *RET* fusions are established oncogenic drivers, sensitive to RET inhibitors[4,5]. *MYH10-RET*, although novel, has the same domain structure as the well-characterized *KIF5B-RET*, indicating that this fusion is an oncogenic driver.

This finding also suggests broadening of diagnostic possibilities. Previously, familial IM has been associated with mutations of *PDGFRB*[6,7]. Kinase fusions, particularly involving *ALK*, but also *ROS1*, *PDGFRB*, and *RET*, are observed in a related entity, inflammatory myofibroblastic tumor (IMT). The differential diagnosis for this lesion does include IMT, and morphologic and immunohistochemical features of both entities do overlap. Since *RET* alterations have never previously been observed in IM but have been observed in IMT, it is possible that this lesion might be characterized as an IMT under other circumstances[8].

Importantly, IMTs harboring various kinase fusions, including *ALK* and *ROS1,* were sensitive to small molecule kinase inhibitors[9,10].

For this child, identification of the *MYH10-RET* fusion indicates possible benefit from RET inhibitors. Further CGP myofibromatosis and IMT should reveal whether *RET* fusions are a recurrent feature of aggressive myofibromatosis or whether the index case is genomically unique and may be better characterized as an IMT.

Industry support and conflicts of interest

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Legends

Figure 1. Identification of a *MYH10-RET* fusion in the soft tissue myofibromatosis. A rearrangement between the *MYH10* and *RET* loci resulted in a MYH10-RET fusion protein that is predicted to include the MYH10 myosin motor, IQ domain and a portion of the coiled-coil domain, as well as the entire kinase domain of RET.

Supplemental Figure S1. Identification of a *MYH10-RET* fusion in the soft tissue myofibromatosis. DNA sequencing (top panel) identified a rearrangement between the *RET* locus on 10q11 (blue bars) and the *MYH10* locus on 17p13.1 (pink bars). Break points are in intron 33 of *MYH10* and intron 11 of *RET*. RNA sequencing (bottom panel) identified an in-frame fusion joining exons 1-33 (residues 1-1598, NM_005964) of *MYH10* with exons 12-19 (residues 713-1072, NM_020630) of *RET*.

Supplemental File S1.

Methods

Comprehensive genomic profiling