

ROS1-positive Inflammatory Myofibroblastic Tumor of the Small Bowel Causing Obstruction: A Case Report

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Radiology Case. 2022 Jan; 16(1):14-21 :: DOI: 10.3941/jrcr.v16i1.3928

ABSTRACT

Inflammatory Myofibroblastic Tumors (IMTs) are rare fibroblastic/myofibroblastic neoplasms that affect predominately pediatric patients and young adults. Almost half of the patients with IMTs have a chromosomal abnormality in the Anaplastic Lymphoma Kinase 1 gene on chromosome 2p23. Although these tumors occur primarily in the lung, lesions have been reported in a variety of intra-abdominal organs like the liver, spleen, and mesentery. Small bowel IMTs are particularly rare. IMTs generally pursue a benign clinical course, however intra-abdominal and retroperitoneal tumors have typically shown higher local recurrence and even distant metastases. The most common presenting symptoms of an intra-abdominal IMT are abdominal pain and change in bowel habits. Laboratory results are nonspecific and can include anemia and minor elevation of inflammatory markers like C-reactive protein. We report an unusual case of IMT in the small bowel causing the obstruction.

CASE REPORT

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A generally healthy 23 years old woman with a family history of colon cancer presented to our emergency room (ER) with complaints of right lower quadrant abdominal pain and diarrhea.

She underwent a physical examination and abdominal ultrasound (US) that did not reveal any evidence of acute appendicitis. The blood tests have shown increased CRP of 53

mg/L (normal 0.03-5 mg/L) without leukocytosis. She was discharged with a diagnosis of gastroenteritis and was given antibiotic treatment. After 5 days, the abdominal pain became constant and worse, so she returned to the ER. Physical examination revealed a generally distended abdomen, no apparent palpable masses, and no signs of peritonitis. The blood tests showed an increased CRP of 42.8 mg/L, again without leukocytosis or any other abnormality. A transvaginal US was performed and revealed a well-defined solid mass measuring 44 * 39 mm to the left of the uterus. The solid mass was

heterogeneous with the avid flow on Doppler images (Figure 1). An abdominal computed tomography (CT) scan with parenteral and intravenous contrast materials was performed and confirmed the presence of a mass in the ileum causing small bowel obstruction (Figure 2). There were no other acute findings in the abdominal or pelvic organs.

Based on the CT findings, the patient underwent urgent small bowel resection. On laparotomy, a large tumor with prominent vascularity was found to arise from the distal ileum. There was no evidence of metastasis. The mass was resected, along with involved sections of the small bowel, and a primary small bowel anastomosis was performed. There were no postoperative complications.

DISCUSSION

Etiology & Demographics:

The first description of IMT was in 1937 as a lung tumor predominantly appearing in pediatric patients and young adults [1].

The World Health Organization (WHO) classified the IMT as a fibroblastic/myofibroblastic neoplasm of intermediate biologic potential because of its potential for invasion of surrounding structures and development of local recurrence and distant metastases [2,3]. There are several different names for IMT, including: inflammatory pseudotumor, plasma cell granuloma, fibrous histiocytoma, solitary mast cell tumor, and fibroxanthoma [4].

The factors responsible for the development of IMT are still not clearly established. IMT may represent an immunologic response to an infectious or noninfectious agent, or it may be a true tumor. *Campylobacter jejuni*, Epstein-Barr virus, and *Escherichia coli* have been associated with IMT. Also, trauma, steroid use, abdominal surgery, and genetic factors have been reported, but the pathogenesis of IMT remains unclear [5,6].

On pathological examination: The tumor in this case was non-encapsulated and infiltrative (Figure 3), showing alternating hypocellular areas with myxoid background and hypercellular fascicular areas with a collagenous background. The tumor cells were uniformly spindled, showing scant to moderate pale eosinophilic cytoplasm with a round to elongated bland nuclei and conspicuous nucleoli. Prominent lymphoplasmacytic infiltrate with minor polymorphonuclear cells component was also identified. The mitotic rate was low (4/10 HPF), and no tumor necrosis was identified (Figure 4).

On immunohistochemistry, the tumor cells were negative for ALK, Keratins, c-kit, DOG1, STAT6, beta-catenin, S100, and Desmin, and showed immunoreactivity solely for Smooth-Muscle Actin, Vimentin, and ROS1 (Figure 5).

Molecular pathology studies were performed by a targeted next-generation sequencing (NGS) based assay to detect gene fusions from formalin-fixed paraffin-embedded (FFPE) tissues. A FN1-ROS1 fusion (chr2:216256355,chr6:117650609) was identified using the FusionPlex Sarcoma NGS Panel (Archer Dx, Boulder, CO.), based on a modified amplicon approach,

referred to as Anchored Multiplex PCR. FN1-ROS1 fusions were recently reported in a few cases of ALK-negative IMTs.

Clinical & Imaging findings:

Presenting symptoms depend on the primary involved site. As mentioned before, the lung is the most commonly affected site. However, extra-pulmonary IMTs may include the mesentery-omentum, upper respiratory tract, genitourinary tract, retroperitoneum, neck, spleen, brain, pancreas, liver, and the intestines [1,6].

Patients with intra-abdominal IMTs most commonly present with intermittent abdominal pain due to the solid mass and abdominal distention, weight loss, malaise, anorexia, and vomiting [4,7,8]. Rarely, the presentation may be complicated by an intussusception, acute abdomen mimicking acute appendicitis, or intestinal obstruction, as was the case in our patient.

Laboratory abnormalities are present in a minority of the patients and include anemia, increased CRP, as in our patient, and sometimes thrombocytosis [6,7]. Leukocytosis is rare [5].

The radiological findings of IMTs are non-specific. The X-ray may be helpful only for IMTs with bone involvement. It can show bone destruction, clear and sharp boundaries, no calcification or ossification, expansive growth, internal ground-glass opacities, an unbroken sclerotic rim without cortical involvement [18].

On US, IMTs can appear as hypoechoic or hyperechoic masses with ill-defined or well-circumscribed edges and a variable Doppler appearance, with increased vascularity [15]. The US is usually the first imaging technique when IMTs appear in specific locations, such as testicles or neck. In other locations, its role is limited.

CT and MRI are the most used imaging tools in the evaluation of IMTs. On contrast-enhanced CT, IMTs can appear as homogeneous or heterogeneous lesions, with variable enhancement on delayed acquisitions due to presence of fibrous component. On T1-weighted and T2-weighted sequences, IMTs usually show low signal intensity, reflecting the presence of fibrotic tissue [15].

PET-CT can show varied FDG from low to high, which may be due to tumor cellularity, biological behaviors of the tumor cells, the composition and the proportion of inflammatory cells, and the extent of activation of the inflammatory cells [16]. The scintigraphic examination may be normal [17].

Treatment & Prognosis:

The treatment of choice is complete surgical excision, and long-term follow-up with physical examination, imaging like CT, and blood tests [9]. Chemotherapy with or without radiotherapy has been used for patients with incomplete tumor resection, positive margins, tumors not amenable to resection, and metastatic disease. There is no definitive data establishing the efficacy of adjuvant therapy [10] for patients following complete resection. The primary treatment for IMT can be

corticosteroids - which produce tumor regression and reduction of the inflammatory reaction in the surrounding tissues [11].

Like non-small cell lung cancer, the identification of ALK or *ROS1* rearrangements provides a potential therapeutic option for some patients with aggressive IMTs using Tyrosine kinase inhibitors targeting ALK oncoprotein, such as crizotinib.

Differential Diagnosis:

Because IMTs are arising in different body locations with non-specific imaging pictures, in most cases, it is impossible to distinguish IMT from other tumors - the diagnosis is generally made on pathological examination.

The microscopic morphology of spindle cell proliferation with lymphoplasmacytic infiltration raises the suspicion for IMT. However, other gastrointestinal stromal tumors may show comparable histological findings and should be excluded using other immunohistochemistry assays.

Unlike IMTs, Gastrointestinal stromal tumors (GISTs) are usually immunoreactive for c-kit and, *DOG1* and smooth-muscle tumors should be diffusely positive for Desmin and Caldesmon. Peripheral nerve sheath tumors, melanomas, and clear-cell sarcomas can be excluded by negative immunoreaction for S100. The negativity of the tumor cells for STAT6 and beta-catenin excludes solitary fibrous tumors and fibromatosis, respectively.

Positive immunohistochemistry for ALK shows a good concordance with the presence of ALK gene rearrangement, and it is a crucial marker for the accurate diagnosis of IMT. However, approximately 50% of IMT cases, including ours, are ALK-negative and harbor other gene rearrangements, mainly of *ROS1*, *ETV6*, and/or *NTRK3*.

ROS1 expression by immunohistochemistry is useful for the diagnosis of ALK-negative IMTs, as it correlates with *ROS1* gene rearrangements [13,14].

TEACHING POINT

Inflammatory Myofibroblastic Tumor is a solid tumor that can rarely present in a young adult as acute abdominal pain with bowel obstruction. A precise diagnosis should be based on histological findings, and complete surgical resection is necessary. Clinical and laboratory follow-up is mandatory due to the increased risk of local recurrence.

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FIGURES

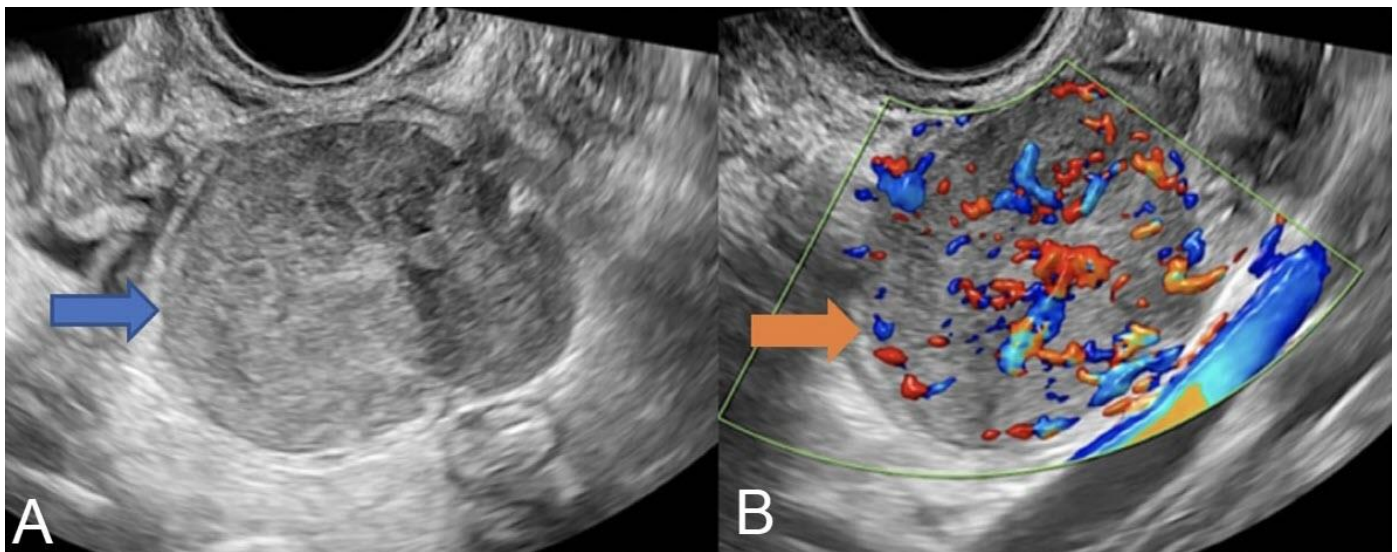


Figure 1: 23-year-old female with Inflammatory Myofibroblastic Tumor and small intestine obstruction.

FINDINGS: Well-defined solid mass (blue arrow) measuring 44 * 39 mm to the left of the uterus (A). The solid mass was heterogeneous (orange arrow) with avid flow on Doppler images (B).

TECHNIQUE: Real time trans-vaginal ultrasound of tumor using 20 mHz linear probe.

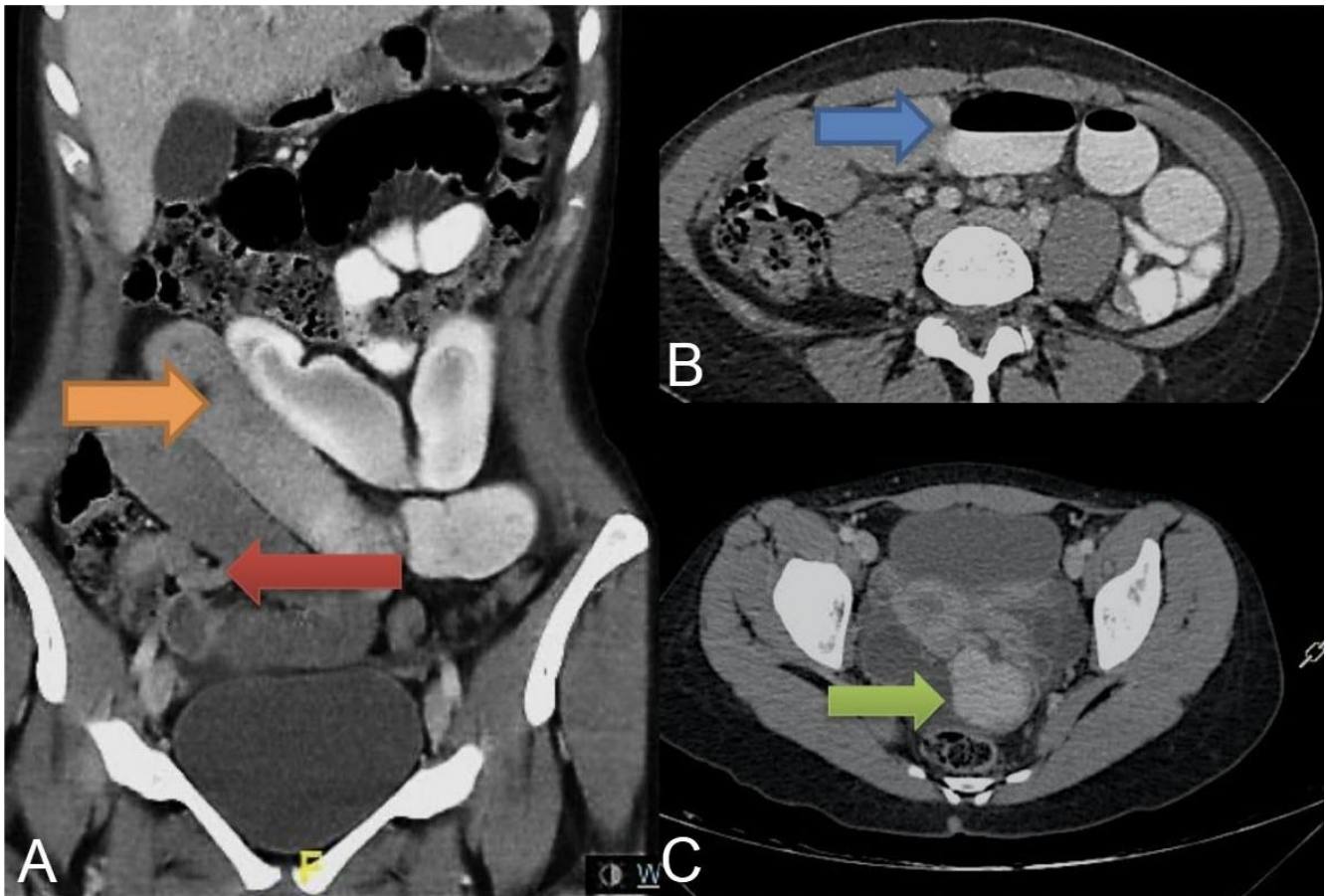


Figure 2: 23-year-old female with Inflammatory Myofibroblastic Tumor and small bowel obstruction.

FINDINGS: Complete small bowel obstruction caused by tumor that measuring 42 * 41 mm. (A) Coronal Computer Tomography scan shows the small bowel with marked distention (orange arrow) and on (B) axial slices filled with fluid and air (blue arrow). (A) Totally collapsed bowel loops are seen after the transition zone (red arrow). (C) On axial slices well defined intraluminal encased solid mass (green arrow).

TECHNIQUE: Abdominopelvic Computer Tomography with administration of intravenous contrast material (100 ml Omnipaque 350) and oral contrast material (1500 ml diluted Telebrix), acquired on the portal phase with a 64 slice Computer Tomography scanner, at 3 mm slice thickness, 120 kVp and 205 mAs. The images were acquired on the axial plane and coronal and sagittal reconstructions were created.



Figure 3 (left): 23-year-old female with Inflammatory Myofibroblastic Tumor and small bowel obstruction.

FINDINGS: Polypoid intestinal tumor measuring 45 * 40 mm, covered by intact and flattened mucosa with shallow ulcerations.

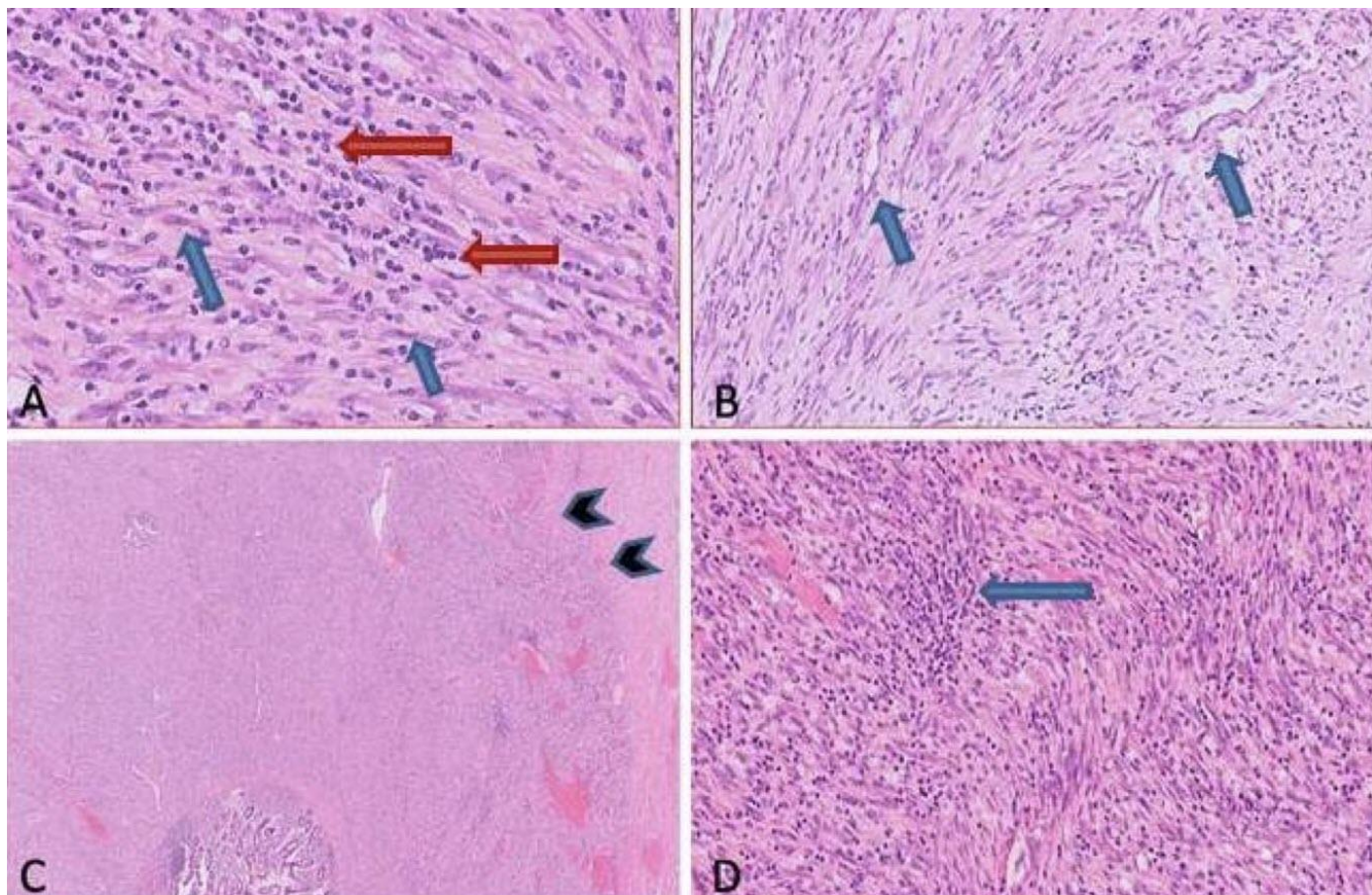


Figure 4: 23-year-old female with Inflammatory Myofibroblastic Tumor and small bowel obstruction.

FINDINGS: A: (Hematoxylin and Eosin, 40x) The tumor shows bland spindle-cells (blue arrows) with admixed lymphocytes (red arrow). B: (Hematoxylin and Eosin, 20x) The tumor may show delicate vasculature (blue arrow) and myxoid stroma. C: (Hematoxylin and Eosin, 1x) The tumor show irregular infiltration of the muscular layer (arrow heads). Note the intact mucosal layer (bottom left). D: (Hematoxylin and Eosin, 20x) The tumor shows fascicular architecture. Notice the background chronic inflammatory infiltrate (blue arrow).

TECHNIQUE: Formalin-fixed-paraffin-embedded Hematoxylin and Eosin stained sections.

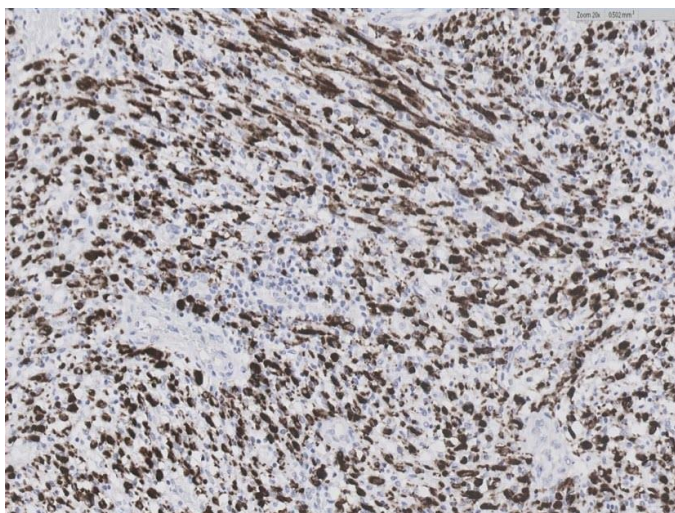


Figure 5 (left): 23-year-old female with Inflammatory Myofibroblastic Tumor and small bowel obstruction.

FINDINGS: The Inflammatory Myofibroblastic Tumor cells show positive intense cytoplasmic staining (brown).

TECHNIQUE: ROS1 (D4D6) monoclonal antibody, 1:250.

Etiology	Clearly unknown
Incidence	0.04–1% of all tumors of the lungs
Gender Ratio	1:1
Age Predilection	Children and young adults
Risk Factors	Infection like <i>Campylobacter jejuni</i> , Epstein-Barr virus, and <i>Escherichia coli</i> . Also, trauma, steroid use, abdominal surgery, and genetic factors have been reported.
Treatment	Generally, surgery. Chemotherapy with or without radiotherapy has been used for patients with incomplete tumor resection or positive margins.
Prognosis	Generally, the clinical course is benign, however intra-abdominal and retroperitoneal tumors have typically shown higher local recurrence and even distant metastases.
Findings on imaging	Not specific, the diagnosis made by microscopic morphology only, with immunohistochemistry for Anaplastic Lymphoma Kinase.

Table 1: Summary table of Inflammatory Myofibroblastic Tumor.

	Inflammatory Myofibroblastic Tumor	Gastrointestinal Stromal Tumor	Colonic Leiomyomas	Gastrointestinal schwannoma
X-ray	Useful only in bone location and can show bone destruction, clear and sharp boundaries, no calcification or ossification, expansive growth, internal ground-glass opacities, an unbroken sclerotic rim, and no cortical involvement	When large, secondary signs of the tumour may be visualised by radiograph, e.g. soft tissue density displacing bowel loops	Generally normal	Generally normal
Ultrasound	Hypoechoic or hyperechoic well-defined solid mass with avid flow on Doppler images	A well-defined solid mass lesion with central cystic foci. No calcification. Solid areas show vascularity.	Round or oval circumscribed hypoechoic solid mass, often with associated posterior shadowing due to calcifications	Oval to round mass with regular or irregular marginal border and lobulation of the surface. Vary echogenicity and homogeneity with internal echogenic or cystic foci and the presence of exophytic development.
CT	Soft tissue mass	Soft tissue mass with central areas of lower density when necrosis is present	Soft-tissue sessile mass	Typically seen as a well-defined, rounded, mural mass
MRI	Usually show low signal intensity reflecting the presence of fibrotic tissue	Usually low signal intensity on T1W and high on T2W images	Low signal intensity on T1W and T2W images	Low or intermediate signal on T1W and high on T2W images
Pattern of contrast enhancement	Homogeneous or heterogeneous lesions, with variable enhancement on delayed acquisitions due to the presence of fibrosis	Typically peripheral	Homogeneous attenuation	Homogeneous attenuation
Scintigraphy	May be normal	May be detected on Tc-99m MDP Bone Scintigraphy or 99mTc-RBC scintigraphy if bleed	May be normal	May be normal
PET	Low to high FDG uptake	Increased F-18 FDG uptake	Increased F-18 FDG uptake	Increased F-18 FDG uptake

Table 2: Differential diagnosis table for Inflammatory Myofibroblastic Tumor.

ABBREVIATIONS

ALK = Anaplastic Lymphoma Kinase
CRP = C-reactive protein
CT = Computer Tomography
ER = Emergency Room
FFPE = Formalin Fixed Paraffin Embedded
GIST = Gastrointestinal Stromal Tumor
H&E = Hematoxylin and Eosin
IMTs = Inflammatory Myofibroblastic Tumors
MRI = Magnetic resonance imaging
NGS = Next Generation Sequencing
US = Ultrasound
WHO = World Health Organization

KEYWORDS

Inflammatory Myofibroblastic Tumor, Small bowel obstruction, Inflammatory pseudotumor, extra-pulmonary Inflammatory Myofibroblastic Tumors, Bowel solitary mast cell tumor

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