Inflammatory Myo-Fibroblastic Tumor: A Borderline Malignant Entity; Case Series and Literature Review

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ABSTRACT
IMTs are mesenchymal tumors of borderline malignant potential. Clinically IMTs mimic other soft tissue tumors and pseudo-tumors which can be differentiated by pathology and immunophenotyping. IMTs are mostly benign, but they can be locally aggressive, recurrent, and metastatic. IMTs with RANBP2-ALK fusion mutation behave aggressively and are now termed as ‘Epithelioid Inflammatory Myofibroblasts Sarcoma’. Surgery is the treatment of choice for primary as well as recurrent cases. Crizotinib is the chemotherapy of choice in ALK mutant IMTs. Overall prognosis is good with some exceptions of deaths caused by metastatic IMTs. We present a series of five patients of IMT at different sites, which reflect the variations in management.

KEYWORDS
Inflammatory myofibroblastic tumors; Pseudotumors; Soft tissue sarcomas; Inflammatory fibroid polyp; Calcifying fibrous tumor.

ABBREVIATIONS
CT: Computed Tomography; GIST: Gastrointestinal Stromal Tumor; MRI: Magnetic Resonance Imaging; IHC: Immunohistochemistry; PCR: Polymerase Chain Reaction; AJCC: American Joint Committee on Cancer; NSAID: Non-Steroidal Anti-Inflammatory Drug; VEGF: Vascular Endothelial Growth Factor; COX-2: Cycloxygenase 2

INTRODUCTION
Inflammatory Myo-fibroblasts Tumors (IMT) are uncommon soft tissue tumors usually seen in pediatric age group and young adults most commonly in the lungs [1]. It was later realized that IMTs can arise from almost every anatomical location; it was just that they were reported under different names. Omental and mesenteric IMTs are most common extra-pulmonary IMTs [1]. It is difficult to know the exact incidence of abdominal IMTs as they were reported with various different names in the past. The true nature of this tumor was debatable, however; IMTs are now categorized as discrete entities. It is often misdiagnosed due to the fact that it shares clinical and pathological features with other soft tissue tumors and pseudo-tumors. Its clinical behavior is varied; attempts are being made to know the biology behind such clinical variations. Recent chemotherapy trials have given new hopes for the inoperable cases [2]. This article attempts to give insights into the clinical and
pathological behavior of IMTs and therapeutic options available.

**MATERIALS AND METHODS**

Accumulated series of cases of inflammatory myofibroblastic tumors were reviewed and analyzed. Search for available literature was done from standard oncological text books, PubMed and google scholar. Available studies were collected, reviewed and interpreted.

**CASE REPORT**

*Case 1*

A three-year-old female child presented with complaints of pain abdomen, fever and mass per abdomen for four months. CT scan showed a large calcified retroperitoneal mass of size 8.5cm × 6.5cm × 5cm in the right lumbar region (Figure 1) deeply embedded in the psoas muscle. The patient underwent exploratory laparotomy. There was a hard, calcified tumor of size 8cm × 7cm in size in the right lumbar region, adherent to the psoas muscle and inferior venacava pushing the right kidney inferno-medially. The tumor was excised, but part of the tumor, which was adhered to inferior vena cava could not be resected. Histology showed it to be an IMT of the retroperitoneum with calcification (Figure 2). The cells showed positive staining for desmin, actin, and vimentin (Figure 3). Postoperative patient was kept on steroids in the form of tablet Prednisolone for three months under the guidance of the pediatricians. There was no recurrence over five years of follow-up and the residual tumor was not seen on investigative imaging.

*Case 2*

A 28-year-old male patient presented with features of gastric outlet obstruction of 15 days duration. CT scan showed a soft tissue density mass of size 3.5 cm × 3.0 cm arising from lesser curvature of stomach with well-defined margins and mild contrast enhancement (Figure 4). It was thought to be GIST. Patient had a pre-operative endoscopic biopsy, which was inconclusive as the tumor was located in the muscular layer of the stomach. He underwent an exploratory laparotomy, intraoperatively it was around, well circumscribed mass arising from the lesser curvature of the stomach and projecting into the lumen of the stomach causing gastric outlet obstruction (Figure 5). The tumor was firm in consistency, and it was not fixed to any of the surrounding structures, the mucosa and submucosa overlying were normal. There were no enlarged lymph-nodes and all other visera were normal. Wedge resection of the tumor with a provisional diagnosis of a benign lesion but as a precaution, adequate margins were taken. Histology showed it to be IMT (Figure 6). There was no recurrence seen up to five year follow up, even though the patient was not prescribed any specific post-operative medications.

*Figure 1: CT scan showing large calcified mass in right lumbar region.*

*Figure 2: Microscopic image of Inflammatory Myofibroblastic tumor.*

*Figure 3: Immunohistochemistry showing positivity for actin.*

*Bracing New Features to Explore the Innovative Approaches in Surgical Field*
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*Figure 4:* CT scan showing mass in the lesser curvature of stomach.

*Figure 5:* Intraoperative picture of tumor arising from lesser curvature of stomach.

*Figure 6:* Microscopic image of inflammatory myofibroblastic tumor.

*Figure 7:* Microscopic image of inflammatory myofibroblastic tumor.

*Figure 8:* Immunohistochemistry shows positive staining for SMA.

**Case 3**

A 23-years-old female patient presented with dull aching pain abdomen, intermittent fever and a progressively increasing mass on the left side of her abdomen over past six months. CT scan revealed heterogeneously enhancing, lobulated, hypodense, solid lesion measuring 11.8 cm × 10.3 cm × 9.2 cm in the retroperitoneum involving left hypochondrium and lumbar region.

Superiorly it was abutting splenic vein and its tributaries, greater curvature of stomach and tail of the pancreas; anteriorly compressing greater curvature of the stomach and abutting small bowel loops; medially abutting pancreas, left renal vein, peri-gastric vein and small bowel loops; and laterally abutting the lateral abdominal wall. It was associated with dysplastic left kidney with compensatory hypertrophy of right kidney. The Patient also had hepatomegaly with epigastric varices. Radiologic suspicion was of a neuroectodermal tumor. The Patient was subjected to exploratory laparotomy. Intraoperatively there was 20cm × 20cm mass in left hypochondrium and lumbar region, firm, with patchy hard areas. The Tumor was adherent to greater curvature of the stomach and tail of pancreas, besides this mass was mobile on
all sides. Mass was compressing splenic vessels with associated peri-gastric varices. Mass was separated from stomach and pancreas and was excised successfully. Histology proved it to be an IMT (Figure 7 & Figure 8). The Patient did well without further medications or recurrence in five-year follow-up.

**Case 4**

A 28-year-old male patient presented with complaints of fever, pain abdomen and vomiting for 20 days with lump in left hypochondrium. Ultrasound showed a hypoechoic, round mass in epigastrium probably arising from the pylorus of the stomach. Diagnostic laparoscopy showed a mass of size 5cm x 5cm arising from a body of stomach, well circumscribed not fixed to any of the surrounding structures. The tumor was excised, it was firm in consistency. Histology proved it to be IMT (Figure 9, 10). No postoperative medication was given. There was no recurrence in following years.

**Case 5**

A 52-years- old female patient presented with recurrent attacks of subacute intestinal obstruction for three months. CT scan showed skipped mild mural thickening in proximal and mid third of ileum with mild proximal loop dilation suggestive of nonspecific inflammatory pathology.

![Figure 11: Microscopic image of inflammatory myofibroblastic tumor of small intestine.](image1)

![Figure 12: Immunohistochemistry showing positive staining of SMA.](image2)

![Figure 13: Immunohistochemistry showing positive staining of ALK.](image3)
3cm × 3cm in mid third of ileum, remaining viscera were normal. The tumor was resected with 5 cm margins on either side. Histology showed it to be an IMT (Figure 11) with positive staining for Desmin, Smooth muscle actin (Figure 12), and variable cytoplasmic ALK1 (Figure 13). Negative for S100, CD117, CD34. The patient is under follow-up since six months, as of now there is no recurrence.

**DISCUSSION**

This series of five cases of IMTs depicts a wide range of clinical spectrum of abdominal IMTs. Among five cases, one was a three-year-old child, three cases were young adults and one was 52-years-old. M: F ratio is 2:3 in our series. Anatomical location was varied, in two cases, tumor originated from the wall of the stomach. Two cases were retroperitoneal tumors in lumbar region and one case was of an ileal tumor. Tumor size varied from 3cm to 20cm. Conspicuous feature among all these cases is that despite their large size, symptoms were only due to mass effect and three cases were associated with fever. None of the cases had lymph nodal involvement or distant metastasis and none had multifocal lesions. Surgery alone was curative in four of these cases and in one case surgery with steroids were given postoperatively. Four cases showed no recurrence in next five years, fifth case is under follow-up at the time of publication, there is no recurrence at the end of six months.

**LITERATURE REVIEW**

IMTs were known in the past under different names such as plasma cell granuloma, plasma cell pseudotumor, inflammatory myo-fibro-histiocytic proliferation, omental/mesenteric myxoid hamartoma, inflammatory fibrosarcoma, many times referred as pseudo-tumors [1]. Pseudotumor is a broad terminology used in varying instances such as cutaneous mycobacterial spindle cell pseudotumor [3], Epstein-Barr virus related clonal proliferation of follicular dendritic cells in liver or spleen [4], reactive inflammatory pseudo-tumors of lymph nodes [5], pseudo-sarcomatous myo-fibroblastic proliferations of the lower genitourinary tract [1]. Hence, it is better to use the term ‘Inflammatory Myo-fibroblastic Tumor’ instead of inflammatory pseudotumor. In WHO histological classification of soft tissue sarcomas IMTs are grouped under Fibroblastic / Myo-fibroblastic tumors of intermediate malignant potential (rarely metastasizing) [6].

Age of presentation can be from early childhood to old age; however, these tumors show a predilection for children and young adults. They are slightly more common in females. Presenting symptoms are related to mass effect depending on the location of the tumors. Tumors arising from hollow viscus are detected earlier due to the fact that they cause obstruction producing early symptoms. However, as our series suggests, tumors arising from omentum, peritoneum or solid organs may remain unnoticed for a longer period and grow substantially before producing symptoms due to involvement of adjacent organs. Some patients do have systemic symptoms such as fever, malaise, night sweats, or weight loss due to interleukin production [1]. Laboratory abnormalities such as anemia, thrombocytosis, polyclonal hypergammaglobulinemia, and elevated erythrocyte sedimentation rate may also be seen in some case [7].

On ultrasonography, mesenteric IMT appears as a well-defined or infiltrating, solid, mixed-echogenic mass within the mesentery. Vascularization may be seen with Doppler ultrasound [8]. In CT scan calcifications are uncommon. Involvement of adjacent bowel segments is exceptional. The mass is typically heterogeneous in attenuation and large lesions may have central areas of hypo-attenuation suggestive of necrosis. Enhancement after iodine injection is variable, from non-enhancing to peripheral or heterogeneously enhancing and may be related to the age of fibrosis. In MRI scans the lesions have a homogeneous signal intensity on T1 weighted sequences without contrast. T1 weighted images after Gadolinium injection is very similar to the CT aspect at portal venous phase. On T2 weighted sequences, the lesion presents two components: an irregular central fibrotic component with low signal intensity and a peripheral inflammatory component with relatively high signal intensity. Peripheral enhancement in both techniques is highly representative of the inflammatory component [8]. However, radiological findings are nonspecific and definitive diagnosis is always histology based.

IMTs are often confused with other soft tissue tumors and pseudo-tumors. IMTs arising from the stomach are clinically indistinguishable from GISTs. IHC confirms the diagnosis. GIST consistently stains for CD117, DOG1 and is ALK negative. GISTs occur predominantly in middle and older age group and rarely under the age of 40 years. In children GISTs...
Ties. Abdominal tuberculosis is uncommon but the differences in pathology and a unique pattern of nuclear IFPs which are considered sarcomas or epithelioid sarcomas were described as discrete entities. However, studies have shown that inflammatory fibro-sarcomas and IMTs share clinical and pathological features, and hence it is believed now that both entities are one and the same and IMT is the preferred terminology [7]. Abdominal Calcifying Fibrous Tumors (CFT) mimic IMTs very much both clinically and pathologically but calcifying fibrous tumors do not express SMA, actin, desmin, and ALK-1 [10]. This differentiation is important because CFTs are benign tumor [6]. Interestingly, Tomassen T. et al [11] found that there were overlapping genome methylation patterns in CFT and IMT, and they concluded CFT and IMT probably represent two ends of the spectrum of a single entity with CFT being the burnout stage of IMT; this theory is not yet proven.

Retroperitoneal fibrosis may be confused with IMTs but tends to have wide-spread fibrosis and lacks mass forming ability when compared to IMT. Retroperitoneal fibrosis are characterized with prominent sclerosis, phlebitis and entrapped surrounding structures which are not seen in IMTs. Pseudo-tumors associated with atypical mycobacterial infections have been reported to mimic IMTs [3]. Clinically, these can be differentiated by the fact that the patients are immunocompromised and pseudo-tumors are mostly present in lymph-nodes. There have been rare case reports of abdominal pseudo-tumors secondary to Mycobacterium tuberculosis clinically and histologically mimicking IMTs, but granulomas or epithelioid cells gave a clue and acid-fast stain, or PCR confirmed the diagnosis in them [12]. Abdominal tuberculosis is uncommon in western countries but in India we frequently encounter this. It is pertinent to diagnose tuberculosis appropriately as it would entirely change the course of management. Inflammatory leiomyosarcoma, Hodgkin’s lymphoma and xanthogranulomatous inflammations are other differential diagnosis. Clinical background, histology, and immune-phenotyping aids in arriving at correct diagnosis.

Soft tissue sarcomas are staged by two staging systems; one is AJCC staging system and another is musculoskeletal tumor society staging system [1]. But IMTs are not included in the AJCC staging system [13].

Surgical excision is the mainstay of treatment for both primary and recurrent tumors and it is curative in the majority. Vital point of decision on management of IMTs is the identification of ALK mutation. Approximately 50% of IMTs harbor clonal rearrangements of ALK gene at 2p23 [14]. Various patterns of ALK immunoreactivity associated with different fusion patterns have been reported [15]. Marino-Enriques et al (16) in their case series of abdominal IMTs with RANBP2-ALK fusions and aggressive clinical behavior demonstrated epithelioid morphology and a unique pattern of nuclear membrane or perinuclear ALK immunoreactivity and termed them as ‘Epithelioid Inflammatory Myo-fibroblastic Sarcoma’.

IMTs with ALK mutation have responded to Crizotinib; an ALK inhibitor. Crizotinib has been tried on inoperable, metastatic, recurrent and locally aggressive IMTs. Only IMTs with ALK mutations showed response to Crizotinib [17], but this was not a reliable feature, responses ranged from no response to complete response and doses required to achieve the same response also varied [2,17]. The underlying mechanism of this behavior is not yet elucidated. Crizotinib can be tried as a neoadjuvant therapy for inoperable, ALK positive, IMTs; even partial response would make tumors amenable to surgery. Postoperative adjuvant Crizotinib therapy has shown improved outcomes in such patients [17].
Inoperable cases of IMT who are not the candidates for Crizotinib therapy can be treated with Doxorubicin and Ifosfamide [18] or Vinorelbine and Methotrexate regimen [19] with some expectant success. Kevin Johnson et al. [20] combined Vincristine and Celecoxib to Doxorubicin and Ifosfamide and showed complete remission. Diop B. et al. [21] demonstrated tumor remission with steroid and NSAIDs in an incompletely resected recurrent mesenteric IMT. In our case series one of the cases was given steroids after incomplete resection, showed complete remission with no recurrence in next five years. The rationale behind using steroids or NSAIDs is based on the findings that the mediators of angiogenesis, VEGF and COX-2 are expressed in IMTs and may play an important role in their growth. [22]. Radiotherapy can be tried as adjuvant therapy in unresectable cases in combination with chemotherapy.

The overall prognosis of IMTs is good [20]. Abdominal and retroperitoneal IMTs are more aggressive than other extrapolmonary IMTs with recurrence rates of 23% to 37% [7, 23]. Multiple lesions in different anatomical sites have been reported, some of them with Multifocal disease [23]. There are also reports of clear metastatic lesions resulting in patients’ death [16, 24]. The correlation between clinical-pathological character and prognosis remains imperfect, but identification of ALK fusion mutation improves predictability of its aggressiveness.

CONCLUSION
IMTs are not pseudo-tumors, but mesenchymal tumors of borderline malignant potential. Clinically IMTs mimic other soft tissue tumors and pseudo-tumors which can be differentiated by pathology and immunophenotyping. IMTs with RANBP2-ALK fusion mutation behave aggressively and are now termed as ‘Epithelioid Inflammatory Myofibroblasts Sarcoma’. Surgery is the treatment of choice for primary as well as recurrent cases. Crizotinib is the chemotherapy of choice in ALK mutant IMTs, as the primary modality of treatment or adjuvant therapy depending on the case scenarios. Doxorubicin, Ifosfamide, vincristine, vinorelbine, methotrexate and radiotherapy are the other alternatives for the inoperable cases which do not show ALK mutation. Steroids and NSAIDs are adjuvants for aggressive, recurrent and metastatic cases. IMTs are mostly benign, but they can be locally aggressive, recurrent, and metastatic. Overall prognosis is good with some exceptions of death caused by metastatic IMTs.

AUTHORS’ CONTRIBUTIONS
All the authors have equally contributed to data collection, data analysis and its interpretation, in drafting and revising the content. All the authors have approved the final version to be published, and all the authors are equally accountable to all aspects of the draft published.

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