ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 8, Issue – 2, April – 2023 , Page No. : 162 – 166

ALK 1 Negative Mesenteric Inflammatory Myofibroblastic Tumor with Atypical Spindle Nodular Area

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Citation this Article: Yadav Neha, Patil Divya, Bhalekar Surekha, Dive Prakash, "ALK 1 Negative Mesenteric Inflammatory Myofibroblastic Tumor with Atypical Spindle Nodular Area", IJMSIR- April - 2023, Vol – 8, Issue - 2, P. No. 162 – 166.

Type of Publication: Case Report

Conflicts of Interest: Nil

Abstract

Inflammatory Myofibroblastic Tumor (IMFT) is a rare neoplastic lesion that is primarily found in the pulmonary system like the lungs of children and young adults but can also occur in other organs such as the liver, spleen, and mesentery but is rare in the gastrointestinal tract. Symptoms vary depending on the location of the tumor and can be non-specific. Generally, have a benign clinical course, but intra-abdominal and retroperitoneal tumors have a higher rate of local recurrence and distant metastasis. We report a rare case of anaplastic lymphoma kinase 1 (ALK-1) negative IMFT in the mesentery of a 42-year-old male with an atypical spindle to epithelioid nodular area in the tumor.

While ALK negativity combined with an atypical spindle nodular area raised suspicions of aggressive behavior, smooth muscle actin, and CD30 negativity helped confirm the non-malignancy. Our case suggests the importance of smooth muscle actin as a significant and better marker for the diagnosis of IMFT.

Keywords: ALK-1, Gastrointestinal, Inflammatory myo fibro blastic tumor Mesentery, Smooth muscle actin.

Introduction

Inflammatory Myofibroblastic Tumor (IMFT) is a rare spindle cell neoplastic lesion with unpredictable bio logical behavior with an occasional tendency towards the invasion of surrounding tissue, and local recurrence. Previously known as inflammatory pseudotumor, plasma cell granuloma, inflammatory myo fibro blastoma, or inflammatory myo fibro blastic proliferation.[1-3,7] Primarily found in the pulmonary system, IMFT can also develop in other organs, such as the gastrointestinal tract, mesentery, stomach, omentum, intestine, kidneys, liver, mediastinum, retroperitoneum, renal pelvis, spleen, esophagus, and lymph nodes.[3,7] IMFT's clinical presentation is non-specific and difficult to diagnose.[8] The World Health Organization classifies IMFTs as tumors of intermediate biological potential since both local recurrence and metastases are possible. [4,7] Elevated recurrence risk factors are extrapulmonary

origin, size >8 cm, and local invasion, mostly within 2 years of the initial surgery.[4]

Case Report

A 42-year-old man complained of hypogastric pain and dyspepsia, worsened by eating and relieved by antacids. He had a single fever episode in the last 8-10 days, with no other symptoms. No significant medical or family history was reported. On physical examination, vitals were stable, flat, and umbilical inverted abdomen, and a palpable 4 x 4 cm mass with a well-defined margin and hard consistency was felt in the infra umbilical region, with tenderness in the hypogastric, right iliac fossa, and right umbilical region. Lab tests revealed normal platelets, WBC, Hb, renal, and liver function.

Abdominal and pelvic ultrasound found a 5.1 x 3.5 cm hypoechoic lesion in the midline of the umbilical region and small bowel wall thickening (6 mm). CT scan (plain + contrast) showed a lobulated, enhancing mass in the mesentery of the central abdomen with mild adjacent fat stranding and desmoplastic reaction along infero-medial surface (Fig. 1). The patient had a resection and anastomosis via midline incision laparotomy to excise the mesenteric mass located 20 cm from the ileocecal junction.

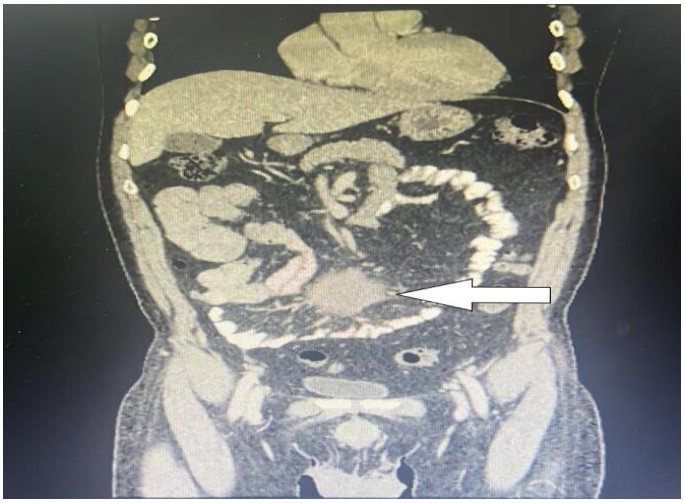

Figure 1: CT scan reveals lobulated, enhancing mass in the mesentery of the central abdomen.

The histopathological study included a 58 x 7 cm segment of the small intestine with attached mesentery (Fig. 2). The serosal and mucosal surfaces were unremarkable. A 6.5 x 6 x 3 cm bosselated tumor was present in the mesentery, 16 cm from proximal and 22 cm from distal resection margins. The external surface was well-circumscribed, firm, creamy white, and focally congested.

The cut surface was whitish-yellow, homogeneous, and had a 1 cm nodular area, without necrosis or hemorrhage. The tumor was 3 cm from the corresponding small intestine.

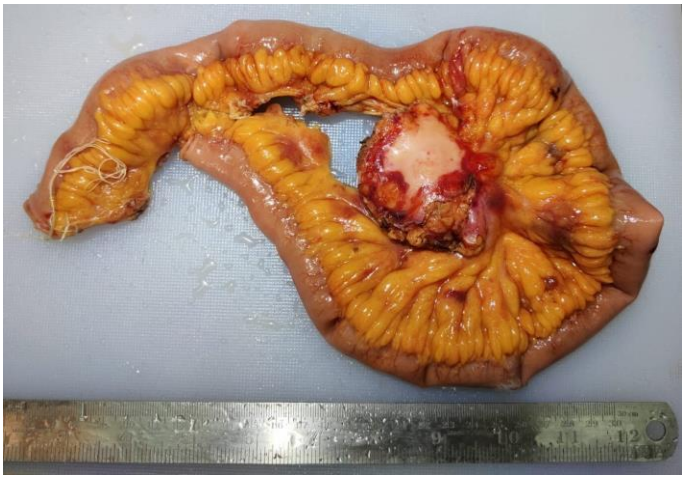

Figure 2: The resected segment of the small intestine with a bosselated tumor in the mesentery.

On microscopic study, the mesenteric mass shows an ill-circumscribed tumor. The tumor cells were arranged in vaguely storiform, fascicular patterns admixed with dense fibro collagenous and myofibroblastic stroma (Fig. 3). Moderate chronic inflammatory cell infiltrate and lymphocytic cell aggregates were seen. It also shows a well-circumscribed and well-demarcated hypercellular nodular area having spindle to epithelioid cells with hyperchromatic to vesicular nuclei, some having prominent nucleoli and indistinct cytoplasmic border admixed with moderate chronic inflammatory cell infiltrate predo minantly composed of lymphocytes,

plasma cells, and histiocytes (Fig. 4). Few dilated blood vessels were observed. Mitosis in the nodule was 2-3/HPF. There was no evidence of necrosis or hemorrhage in the tumor as well as in the nodule. The tumor involved mesenteric fat with few entrapped hypertrophic nerve bundles.

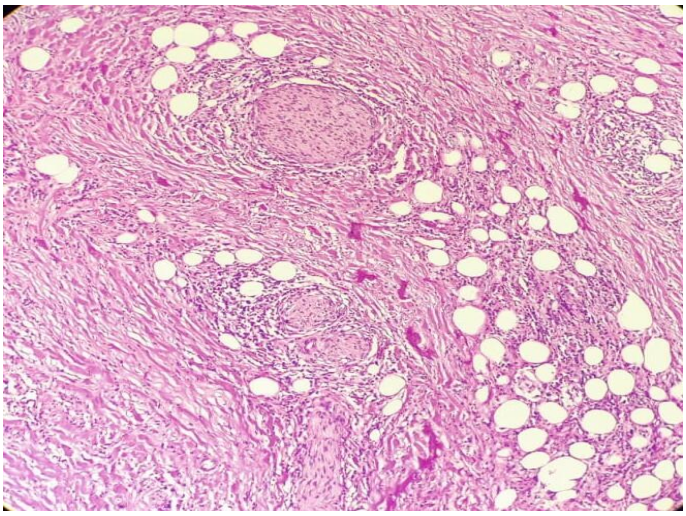

Figure 3: Tumor cells arranged in vaguely storiform, fascicular patterns admixed with dense fibro collagenous and myofibroblastic stroma with moderate chronic inflammatory cell infiltrate. (H&E: 4x)

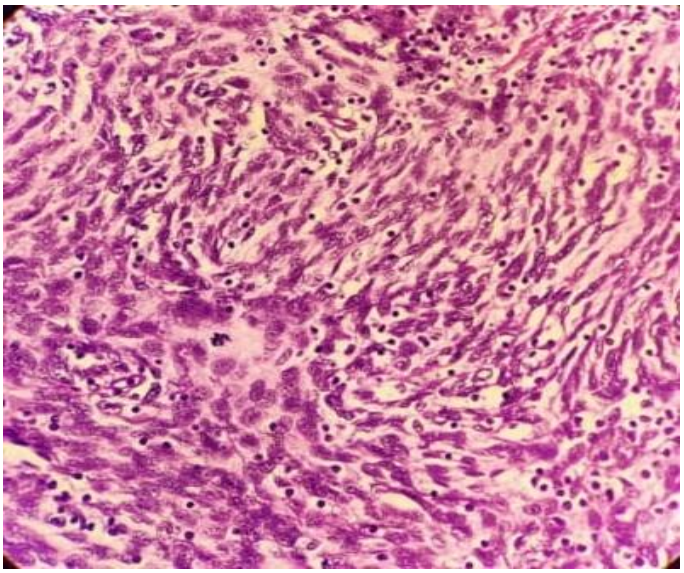

Figure 4: Atypical nodular area having spindle to epithelioid cells with hyperchromatic to vesicular nuclei, some having prominent nucleoli and indistinct cyto plasmic border admixed with moderate chronic in flam matory cell infiltrate. (H&E: 40x)

His to morphologically, proximal and distal resection margins of the intestine and adjacent section were free of tumor and unremarkable. On immuno histochemistry, tumor cells were negative for ALK, and CD30 and show diffuse and strong tram track positive staining pattern for smooth muscle actin (SMA) in the myofibroblastic cells (Fig. 5). However, the nodular areas showing atypia were negative for ALK, CD30, and SMA. The final pathologic diagnosis was IMFT.

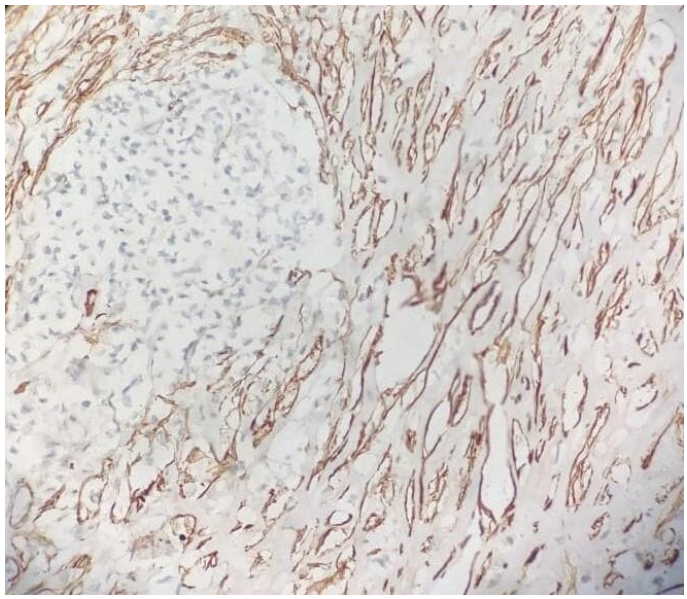

Figure 5: Strong tram track positive staining pattern for smooth muscle actin in the myofibroblastic cells but negative in nodular area.

Discussion

An IMFT is a rare mesenchymal solid tumor, first described by Dr. H. Brunn in 1937 as a lung tumor, predo minantly appearing in pediatric patients and young adults but can develop in older ages with no predilection for any sex. [1-3,8] Some tumors in IMFTs over-express oncoprotein due to the clonal rearrangement of the ALK gene on chromosome 2p23 and the expression of p80. Abnormalities in chromosome 2p have been found in up to 60% of patients younger than 10 years, indicating a

neoplastic nature. [1,10] The etiology of IMFT remains unknown but associated to occur after trauma, surgery, or oncogenic viruses such as Epstein-Barr and Human Herpes. [2,3]

A 38-case series found the stomach to be the most common extrapulmonary site (34%).[1] Intra-abdominal tumors typically present with non-specific symptoms, such as abdominal pain, obstruction, and growth retardation in children. Constitutional symptoms may include fever, night sweats, weight loss, and malaise. [2,9] Laboratory abnormalities are rare but may include anemia, throm bocytosis, elevated erythrocyte Sedi mentation rate, and hyper gamma globulinemia. [1,9] Aneuploidy may indicate local invasive behavior and recurrence.[10] Atypia of spindle cells in pulmonary lesions may indicate aggressiveness.7 Similarly, atypical spindle cells in our extra-pulmonary case of IMFT may also be aggressive. Only a small risk of distant metastasis has been reported. [7,9]

Typical histopathological findings of IMFT include spindle cell proliferation with areas of myxoid change and hypocellularity, showing a collagenous background with mixed inflammatory cell infiltrates. [1,9] Spindle cells of the IMFT express markers corresponding to the myofibroblastic nature of these cells, such as vimentin and SMA. [4,7]

Differential diagnosis endoscopically includes malig nancy and submucosal tumor and radiologically included solitary fibrous tumors and fibro matoses. [3] In flam matory fibroid polyps, fibromatoses, gastro intestinal stromal tumors, leiomyoma, leiomyo sar coma, and schwan noma have similar pathological findings with IMFT. [3,5]

Complete surgical excision is the preferred treatment, followed by long-term monitoring with physical exams and imaging. [2,11] Radio therapy and chemo therapy (cisplatin, doxorubicin, and methotrexate) have not shown significant benefits. Using steroids and non-steroidal anti-inflammatory medications is controversial. [1,3,11]

Immunohistochemistry for ALK is a crucial marker for IMFT diagnosis and shows ALK gene rearrangement, but around 50% of cases, including ours, are ALK-negative and have other gene rearrangements, mainly of ROS1, ETV6, and/or NTRK3.2 Although ALK-1 protein could not be demonstrated in our case, negative results are not strictly against IMFT.[1,3,4,10] On the other hand, the patient's age and site of the lesion are also uncommon for IMFT cases.[7] In a large study, 68% of cases showed kinase fusion, supporting the roles of targeted therapy with tyrosine kinase inhibitor drugs, including crizotinib. 6 ALK positivity is associated with a less aggressive clinical course, but its relationship to prognos is unclear. [3,5]

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