CASE REPORT

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Inflammatory myofibroblastic tumor of the stomach in an adult female - report of a rare case and review of the literature

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Inflammatory myofibroblastic tumor is an uncommon mesenchymal neoplasm presenting usually in children and young adults and reported in diverse locations including the lung, abdomen, retroperitoneum, pelvis, and trunk. Only a few cases involving the stomach have been reported, of which only 12 cases have been reported previously in adults. A 35-year-old female presented with complaints of abdominal pain, fever, vomiting, and loss of appetite for one month. Radiologically, a mass was seen along the greater curvature of the stomach, and was excised. Grossly, a well-circumscribed transmural tumor was seen involving the stomach wall. Histology showed a spindle cell lesion with myxoid areas and interspersed inflammatory cell infiltrate, immunopositive for vimentin and smooth muscle actin, and negative for CD34, CD117 and anaplastic lymphoma kinase-1, confirming a diagnosis of inflammatory myofibroblastic tumor. Inflammatory myofibroblastic tumor forms a rare diagnosis in the stomach and is even rarer in adults. We report here an extremely rare case of inflammatory myofibroblastic tumor involving the stomach wall in an adult, and discuss the differential diagnoses at this site.

Key words: Inflammatory myofibroblastic tumor, inflammatory pseudotumor, gastric tumor, gastrointestinal stromal tumor, inflammatory fibroid polyp

Yetişkin bir kadın hastada midenin inflamatuvar miyofibroblastik tümörü - nadir bir vakanın sunumu ve literatürün gözden geçirilmesi

İnflamatuvar miyofibroblastik tümör, genellikle çocuklar ve genç erişkinlerde görülen, akciğer, abdomen, retroperiton, pelvis ve gövde gibi çeşitli yerleşimlerde rapor edilen, nadir bir mezenşimal neoplazidir. Şimdiye kadar midede görüldüğü bildirilen az sayıda vakanın yalnız 12 tanesi yetişkinlerdedir. 35 yaşında bir kadın hasta 1 ay süren, karın ağrısı, ateş, kusma ve iştahsızlık şikayetleriyle başvurdu. Radyolojik olarak midenin büyük kurvaturunda bir kitle görüldü ve çıkartıldı. Gros olarak, mide duvarını içine alan iyi sınırlı transmural bir tümör izlendi. Histolojide miksoid alanlar ve dağınık inflamatuvar hücre infiltrasyonu gösteren iğsi hücre lezyonunun, immunhistokimyasal olarak vimentin, düz kas aktini ile pozitif, CD34, CD117 ve anaplastik lenfoma kinaz-1 için negatif boyandığı görülerek inflamatuvar miyofibroblastik tümör tanısı kesinleştirildi. İnflamatuvar miyofibroblastik tümör, mide için nadir bir tanı olmakla birlikte, erişkinlerde daha da nadir görülmektedir. Burada bir yetişkinde mide duvarını tutan son derece nadir bir olgu olan inflamatuvar miyofibroblastik tümörü sunuyor ve bu bölge için ayırıcı tanıyı tartışıyoruz.

Anahtar kelimeler: İnflamatuvar miyofibroblastik tümör, inflamatuvar psödotümör, gastrik tümör, gastrointestinal stromal tümör, inflamatuvar fibroid polip

INTRODUCTION

Inflammatory myofibroblastic tumor (IMT), referred to earlier as inflammatory pseudotumor, is an uncommon mesenchymal neoplasm of intermediate malignant potential, and presents usually in children and young adults. Since its original description in the lungs, it has been found to occur in many extrapulmonary locations as well, including the mesentry, omentum, soft tissues of the head

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and neck, retroperitoneum, liver, and urinary bladder (1,2). IMT of the stomach is rare, and only a few cases have been reported, mainly affecting children (1,3-5). To the best of our knowledge, only 12 cases of gastric IMT have been reported previously in adults (6-13). Herein, we report the 13th case of IMT involving the gastric wall in a 35-year-old female, and we review the relevant literature.

CASE REPORT

A 35-year-old female presented with complaints of dull and continuous, moderately severe abdominal pain, associated with fever, vomiting and loss of appetite for one month. There were no symptoms of reflux, no history of any alteration in bowel habits, or melena. The patient was a non-smoker and non-alcoholic. On examination, there was a smooth, firm-to-hard tender lump in the left hypochondrium. She had microcytic hypochromic anemia with a hemoglobin level of 10.7 mg/dl, hematocrit 35.6%, mean corpuscular volume 62.4 fl, and mean corpuscular hemoglobin 21.2 pg. Her platelet count was 329,000/mm^3 and erythrocyte sedimentation rate (ESR) was 20 mm/hr. Radiologically, a mass was seen invading the stomach wall along its greater curvature, abutting the pancreas. No enlarged lymph nodes were seen. Intraoperatively, a nodular encapsulated tumor was identified involving the stomach with no invasion of adjacent structures; hence, a wide local excision of the mass with a 1.5 cm peripheral rim of the normal stomach wall was done. On gross examination, a well-circumscribed lobulated tumor, measuring 11x8x7 cm, was seen in the stomach wall with a solid homogeneous, myxoid, and fleshy grey-white cut surface. The tumor was present intraluminally as a broad-based polypoidal mass and extended transmurally to form a nodular exophytic mass on the serosal surface (Figure 1). The overlying gastric mucosa appeared ulcerated. Multiple sections were taken from different areas and five-micron-thick sections were cut and stained with hematoxylin and eosin. Microscopic examination showed a spindle cell lesion with predominantly myxoid areas, admixed with an inflammatory cell infiltrate composed of neutrophils, eosinophils, lymphocytes, and plasma cells. The spindle cells were sparse in myxoid areas, and arranged in a storiform pattern in more cellular areas. The cells showed a moderate amount of eosinophilic cytoplasm and plump, round-to-oval, vesicular nuclei with prominent nucleoli (Figure 2). Very few but typical mitotic figures were seen. Numerous blood vessels resembling granulation tissue were interspersed in the tumor, and in some places the spindle cells were arranged around them. Immunohistochemically, the tumor cells were positive for vimentin and smooth muscle actin (SMA), and negative for cytokeratin (CK), CD34, CD117, and anaplastic lymphoma kinase (ALK) (Figure 3). Based on the immunostains and morphology, a diagnosis of IMT was proffered. The peripheral margin was free from tumor invasion. The patient had an uneventful postoperative course and is doing well seven months post surgery.

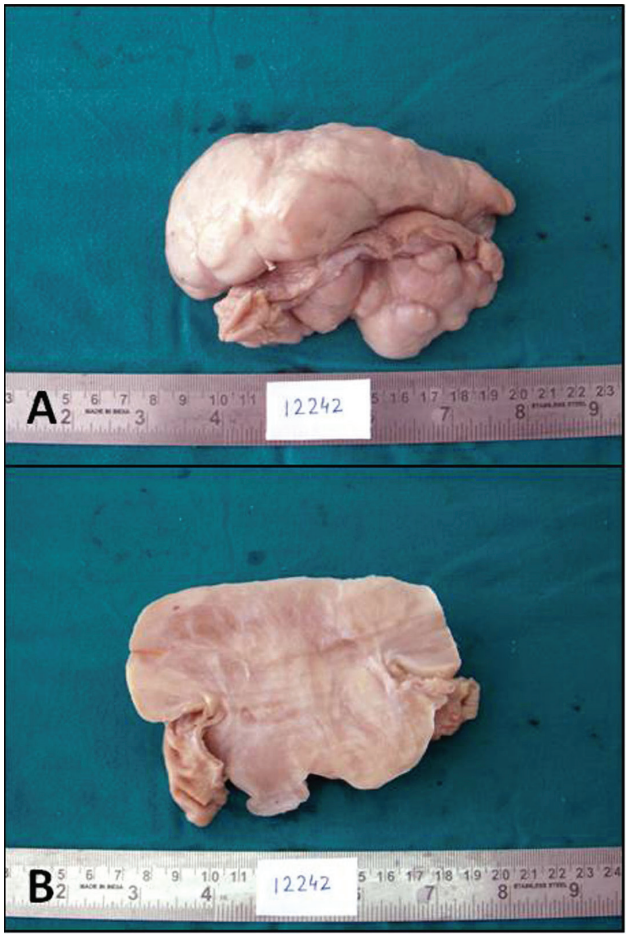

Figure 1. Gross photographs of partial gastrectomy specimen: **A)** external surface showing a lobulated polypoidal mass projecting towards the luminal surface of the stomach wall and extending transmurally to form a nodular mass on the serosal surface. A cuff of normal stomach wall is seen at the middle. The gastric mucosa overlying the tumor appears ulcerated; and **B)** cut surface of the tumor was solid, fleshy, grey-white, and homogeneous. No whorling was seen. The transmural invasion of the tumor can be clearly seen here.

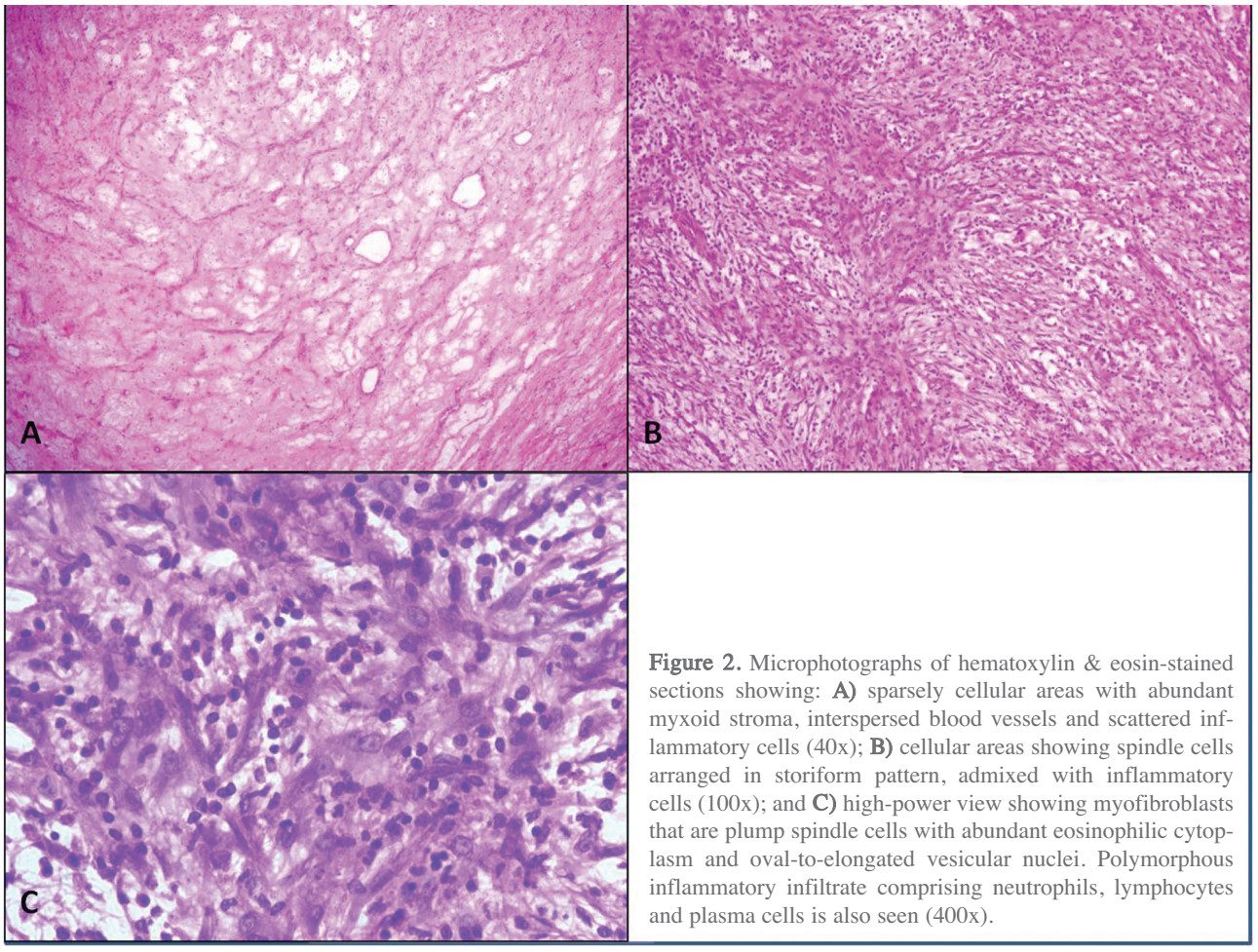

Figure 2. Microphotographs of hematoxylin & eosin-stained sections showing: **A)** sparsely cellular areas with abundant myxoid stroma, interspersed blood vessels and scattered inflammatory cells (40x); **B)** cellular areas showing spindle cells arranged in storiform pattern, admixed with inflammatory cells (100x); and **C)** high-power view showing myofibroblasts that are plump spindle cells with abundant eosinophilic cytoplasm and oval-to-elongated vesicular nuclei. Polymorphous inflammatory infiltrate comprising neutrophils, lymphocytes and plasma cells is also seen (400x).

DISCUSSION

Inflammatory myofibroblastic tumor (IMT), also historically known as inflammatory pseudotumor, plasma cell granuloma, plasma cell pseudotumor, xanthomatous pseudotumor, pseudosarcomatous myofibroblastic proliferation, and inflammatory myofibrohistiocytic proliferation, has evolved over time, from being considered initially a benign reactive inflammatory process to a neoplasm of intermediate biological potential, with frequent recurrences and occasional metastasis (1,2,14). Besides affecting the lung, in which it was originally described, IMTs have also been found in diverse extrapulmonary locations (1). In contrast to pulmonary IMT, which occurs in mid-adulthood, extrapulmonary IMT affects children and young adults within the first two decades of life, and is rare after 30 years. It shows a slight female preponderance (F:M=1.4) (1,14). Intraabdominal IMTs have been reported to occur, in decreasing order of frequency, in the omentum, mesentry, liver, stomach, bowel wall, and spleen (1). Gastric IMT, in contrast to other IMTs, shows a marked female preponderance (M:F= 1:4), and is seen to occur in children from 4 months to 15 years (mean age: 7 years) (3,4). To date, to the best of our knowledge, there are only 12 published reports in the English literature of gastric IMT in adults, and our case, affecting a 35-year-old female, forms the 13th such case reported in an adult (Table 1) (6-13).

Gastric IMTs are often large (3 to 10 cm), infiltrate surrounding organs frequently, and can present with abdominal pain, hematemesis, melena, and palpable abdominal lump (3,4). As in other pulmonary and extrapulmonary IMTs, fever, weight loss, normocytic to microcytic hypochromic anemia, thrombocytosis, elevated ESR, and hypergammaglobulinemia are commonly present in gastric IMT as well. These features are seen to abate after surgery of the tumor and reappear when the tumor recurs, and hence can serve as adjuncts in the follow-up (1-3). IMT can occur in any part of

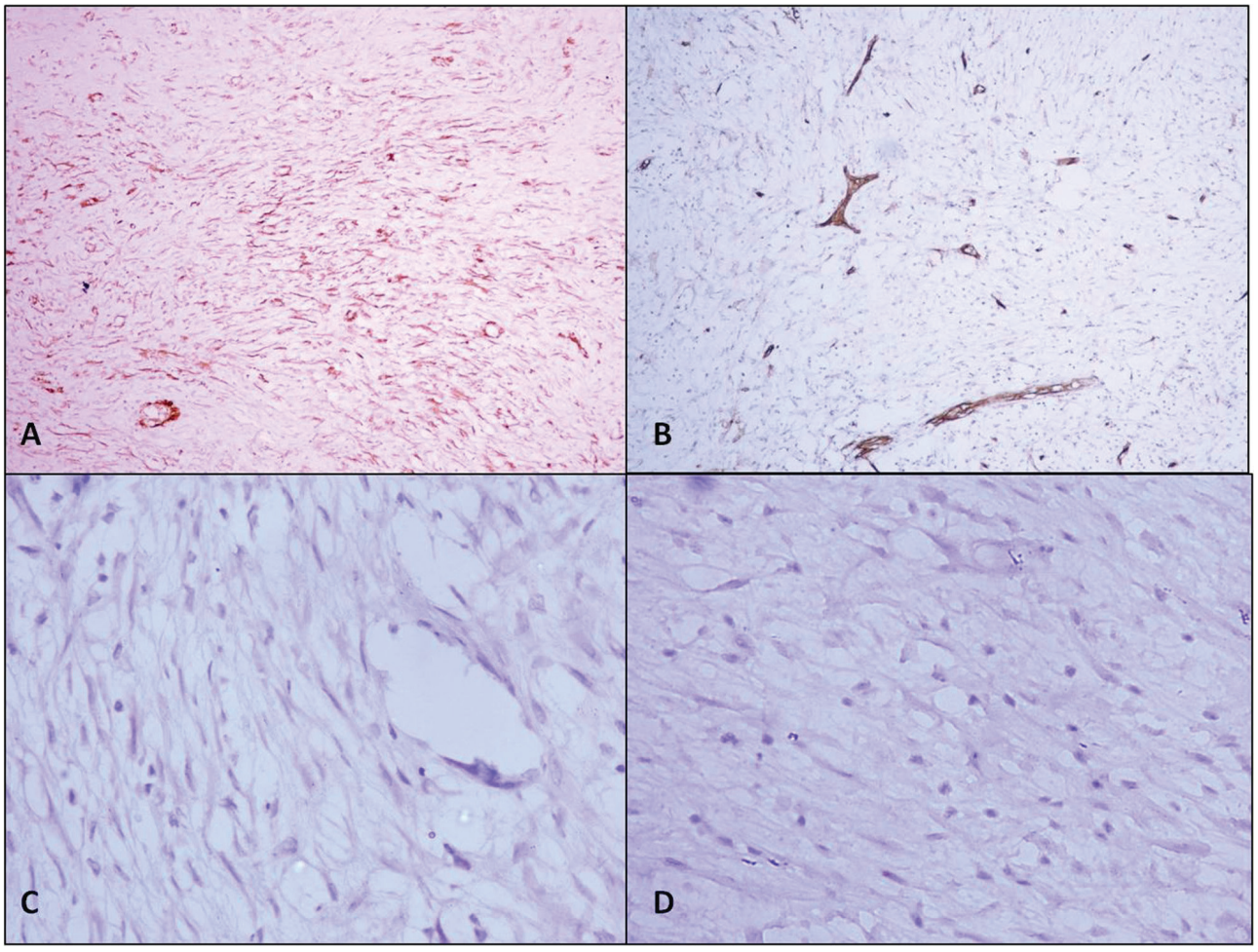

Figure 3. Microphotographs of immunohistochemical stains showing: **A)** diffuse cytoplasmic immunopositivity for SMA in tumor cells. Smooth muscle of blood vessels acting as internal positive control (100x); **B)** tumor cells immunonegative for CD34. Here, endothelial cells of blood vessels are acting as internal positive control (100x); and **C)** and **D)** tumor cells imunonegative for CD117 and ALK, respectively (400x).

the stomach (3,4). As we can see from Table 1, a majority of the previously reported cases, including the present case of adult gastric IMT, also presented with similar clinical features of abdominal pain, lump and anemia. A female preponderance was seen (F:M=8:5=1.6), with a highly variable age range (19-80 years, mean age: 43.77 years). In most patients, the tumor was large (range: 1.5 cm - 11 cm, mean: 7.08 cm), and was located at any site in the stomach.

The exact etiopathogenesis of these tumors is unknown. About 50-75% of extrapulmonary IMTs show ALK gene rearrangements, supporting their neoplastic origin (2). Various mechanisms of tumor development have been proposed, including exaggerated inflammatory response to infections by organisms (such as Epstein-Barr virus, cytomegalovirus, *Escherichia coli, Helicobacter pylori (H. pylori), Campylobacter jejuni,* actinomycetes, and *Pseudomonas veronii)*, surgery, radiotherapy, chemotherapy, and steroid use (1,4,11,15). In four out of the seven previously reported cases of adult gastric IMT, there was a history of peptic ulcer disease and/or *H. pylori* infection, while the information was not available in five cases (Table 1). These findings thus support an inflammatory origin of the tumor, and add another neoplasm to the list of tumors that can occur due to *H. pylori* infection, such as gastric cancer, gastric lymphoma, colon cancer, and pancreatic cancer (16). However, in our patient, there was no documented evidence of either peptic ulcer disease or *H. pylori* infection.

As the clinical and radiological features are nonspecific, the diagnosis of gastric IMT comes to

Table 1. Review of patient characteristics in adult gastric IMT

Cases	Age/ sex	Presenting symptoms/ signs	History of PUD/*H. pylori*	Location	Size	Operative procedure	Histology	ALK status	Adjuvant chemotherapy	Follow-up
1. Kojimahara et al. 19936	19/F	Vomiting, weight loss, mild anemia	Absent	Lower end of esophagus to LC	9 cm	Total gastrectomy	T	NA	None	Asymptomatic at 2.5 yrs
2. Al-Taie et al. 20027	45/F	Abdominal pain	Present	Body	6 cm	Excision	T	NA	None	NA
3. Kim et al. 2004[8]	26/M	Palpable lump, normochromic microcytic anemia	Absent	Distal esophagus to body, lymph nodes, pancreas, spleen, peritoneal dissemination	8 cm	Total gastrectomy with excision of other organs	T	NA	None	Peritoneal seeding with 7 cm mass in rectovesical pouch at 5 weeks
4. Leon et al. 2006[9]	50/F	Persistent vomiting, weight loss, history of partial gastrectomy	Present	PW	7 cm	Subtotal gastrectomy	T	NA	None	Asymptomatic at 2 yrs
5. Park et al. 2008[10]	55/F	Sharp acute abdominal pain, no other complaints, N/N anemia, raised ESR	Present	GC	8.5 cm	Gastric wedge resection	T	Negative	None	No recurrence
6. Shah et al. 2008[11]	80/F	Epigastric discomfort, anemia	Present	Prepyloric region	1.5 cm	Excision	T	NA	None	Asymptomatic
7. Albayrak et al. 2010[12]	56/F	Hematemesis, melena, with nausea and vomiting, anemia	Absent	Gastric cardia	11 cm	Partial gastrectomy	T	Negative	None	Asymptomatic at 8 months
8. Shi et al. 2010[13]	36/M	Abdominal pain and mass	NA	Antrum, LC	4.5 cm	Partial gastrectomy	T	Positive	None	NED at 5 yrs
9. Shi et al. 2010[13]	42/M	Abdominal pain and mass, upper GI hemorrhage	NA	Upper body, GC	8 cm	Partial gastrectomy	T	Positive	None	Recurrence at 12 months, then NED at 11 months after second surgery
10. Shi et al 2010[13]	40/M	Abdominal mass	NA	Upper body, AW	6.3 cm	Partial gastrectomy	T	Positive	None	NED at 3.3 yrs
11. Shi et al 2010[13]	45/M	Abdominal pain and mass	NA	Angle	5.5 cm	Partial gastrectomy	T	Positive	None	NED at 2.6 yrs
12. Shi et al 2010[13]	40/F	Abdominal pain and mass	NA	Lower body, PW	5.8 cm	Partial gastrectomy	T	Positive	None	NED at 4 yrs
Present case	35/F	Abdominal pain, lump, vomiting, fever, anemia	Absent	GC	11 cm	Wide excision	T	Negative	None	Asymptomatic at 7 months

AW: Anterior wall, ESR: Erythrocyte sedimentation rate, F: Female, GC: Greater curvature, LC: Lesser curvature, M: Male, N: None, NA: Not available, NED: No evidence of disease, PUD: Peptic ulcer disease, PW: Posterior wall, T: Typical.

light only after histopathological examination of the excision specimen (8,12). Due to the submucosal location of the tumor, endoscopic biopsies frequently reveal only normal or inflamed gastric mucosa, eluding pre-operative diagnosis (5,7,9,11, 12).

Three histological patterns have been described in the landmark study by Coffin et al. (1): a myxoid vascular pattern resembling nodular fasciitis, a compact spindle cell pattern with a fascicular or storiform cellular arrangement, and hypocellular collagenized pattern resembling scar or desmoid. In any case of IMT, an admixture of all of these patterns may be present in different areas, or any one pattern may predominate. The present case displayed the first two patterns, predominantly the first, i.e. myxoid vascular, and a smaller component of storiform cellular pattern in some sections.

Tumor cells are immunopositive for vimentin, SMA, muscle specific actin, and desmin and focally for CK and KP-1 (1). They are negative for CD117, S-100, and estrogen receptor. About 60% of IMTs overexpress ALK proteins, which can be detected by immunohistochemistry and form a specific marker if positive (2,15). In a recent study by Coffin et al. (2), it was shown that older patients more frequently have ALK-negative tumors, and such tumors are more likely to show atypical histological features, such as hypercellularity, prominent fascicular architecture, focal herringbone pattern, necrosis, abundant ganglion-like cells, multinucleated or anaplastic giant cells, marked cellular and nuclear pleomorphism, and atypical mitoses. However, they found that presence of these atypical features did not indicate aggressive behavior or metastases, and thus they are not presently considered an adverse prognostic factor.

Significantly, all cases of metastatic IMT included in the study, though very young (age range: 5-16 years, mean: 12.2 years) were ALK-negative. ALK-positive tumors, on the other hand, were seen more frequently in younger patients and were associated with local recurrence. Other factors for recurrence described in the study were abdominopelvic sites, larger size, incomplete resection, multinodular masses, and older age. Factors for metastases included younger age, larger size, both abdominopelvic and pulmonary sites and, as mentioned, ALK negativity (2). Of the 13 cases of adult gastric IMT, ALK immunohistochemistry was performed in eight cases, and was found to be positive in five. Three cases (including our case) were negative for ALK; however, none of these cases showed atypical histology (Table 1). Our patient, due to the intraabdominal location, large size, older age, and ALK negativity, is being kept under close follow-up, even though the tumor did not display any atypical features.

As surgical excision is usually curative, it is important to accurately diagnose IMT to avoid unnecessary aggressive treatment (1,2). The differential diagnosis of IMT in the stomach ranges from various benign to malignant conditions, including inflammatory fibroid polyp (IFP), gastrointestinal stromal tumor (GIST), leiomyoma, and leiomyosarcoma. Lesions that would be included in the differential diagnosis of IMT at other sites, such as nodular fasciitis, myofibroma, sclerosing inflammatory lesions, inflammatory malignant fibrous histiocytoma, dedifferentiated liposarcoma, fibromatosis, and follicular or interdigitating dendritic cell sarcoma, are rare or unknown in the stomach. IFP, GIST, abdominal fibromatosis, and smooth muscle tumors do not display the systemic signs and symptoms seen in IMT patients. IFP is a benign tumor-like lesion which, similar to IMT, shows spindle-shaped myofibroblasts with admixed inflammatory infiltrates, in a collagenous or myxoid stroma. However, they only rarely invade the muscularis, and show a predominance of eosinophils and fibrosis. Also, the tumor cells in IFP show an onion skin-like pattern around blood vessels and glands, which is absent in IMT. Immunohistochemically, most cases of IFP show positivity for CD34 and negativity for SMA, while the opposite is true for IMT (17). In the present case, IFP was thus ruled out by the transmural location, lack of onion skinning on histology, immunopositivity for SMA, and immunonegativity for CD34. GISTs, which are mesenchymal tumors of the gastrointestinal tract (GIT), can often be confused macro- and microscopically with IMT. However, they show only scattered inflammatory cells, and have a different immunohistochemical profile, i.e., they are nearly always positive for CD117 (c-kit) and DOG1, frequently for CD34 and variably for SMA. They are immunonegative for ALK, desmin and keratin (18). In the case under discussion, the presence of extensive inflammatory infiltrates, systemic symptoms, and absence of CD117 helped in differentiating the tumor from GIST. Smooth muscle tumors such as leiomyoma and leiomyosarcoma commonly occur in the GIT. Absence of cellular atypia, atypical mitosis and necrosis ruled out a leiomyosarcoma in our case. Leiomyomas can show areas of myxoid change and occasional eosinophilic infiltrates and can show a similar immunohistochemical profile (SMA and desmin positive) as ALK-negative IMT. However, in contrast to IMT, they do not demonstrate marked lymphoplasmacytic infiltrates and sparsely arranged spindle cells with granulation tissue type of blood vessels, which were seen in the present case. Also, leiomyomas show whirling and numerous scattered CD117-positive mast cells, which were absent in the present case (18).

Alternative or adjunctive treatments with chemotherapy and/or radiotherapy have been tried in IMT at other sites (2). However, no benefit of these has been proven in gastric IMT, as the prognosis is generally good and recurrences rare; hence, surgery is the treatment of choice. Though neither metastasis nor death has been reported in gastric IMT, long-term follow-up is recommended due to the unpredictable nature of the disease and lack of well-defined prognostic criteria (3-5). From Table 1, we can see that similar to our patient, all the gastric IMT cases reported in adults were treated surgically, and no adjunctive chemotherapy was given. Recurrence has been reported in only one patient, who underwent a second surgery and was asymptomatic at nearly one year after the second surgery.

To conclude, gastric IMTs are rare in adults and may simulate malignancy due to their infiltrative nature. As they nearly always follow a benign clinical course, IMT should be considered in the differential diagnosis of stomach wall masses associated with anemia in adult females. Appropriate immunohistochemical evaluation is helpful in differentiating IMT from other spindle cell lesions

that can involve the stomach. Though there is still debate about adverse prognostic factors in IMT, patients with abdominopelvic location, large size, aggressive histology, and ALK negativity should be closely followed for early detection of recurrence or metastasis.

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