Inflammatory fibroid polyp: report of two cases and review of the literature with emphasis on the molecular features and its differential diagnosis

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Abstract

Inflammatory fibroid polyp (IFP) is an uncommon benign mesenchymal polyp arising in the gastrointestinal tract. The clinical presentation can be challenging, as it depends on the size and the location of the lesion. Histopathologic examination of the polyp is the mainstay of the diagnosis as the endoscopic and macroscopic features of the lesion are not specific. Herein we describe the clinical, radiologic, pathologic, and molecular characteristics of two cases of enlarged IFPs. The first one was located in the ileum causing chronic intestinal obstructive symptoms and the other one was located in the antrum of the stomach, presented with anemia and had a synchronous villous adenoma located on the overlying mucosa. The presence of dysplastic epithelium on biopsy, along with the size and intramural location of the tumor lead to the erroneous pre-operative diagnosis of gastric adenocarcinoma. The coexistence of dysplasia or malignancy of the epithelium along with IFP is unusual and only a few cases have been reported so far. Histologically, IFP is a hypocellular submucosal tumor, consisting of spindle shaped cells with a concentric arrangement around vessels. Abundant eosinophils are seen between the tumor cells. Immunohistochemistry is an important diagnostic tool that excludes other entities like gastrointestinal stromal tumor and inflammatory myofibroblastic tumor that have an aggressive potential. At the molecular

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level, PDGFRa mutation is characteristic for IFPs and can be used to confirm the diagnosis. In conclusion, IFP is a benign mesenchymal neoplasm that may pose diagnostic difficulties both clinically and histologically.

Introduction

Inflammatory fibroid polyp (IFP) is a benign polyp that arises in almost every part of gastrointestinal tract. The clinical symptoms vary depending on the size and the location of the polyp. These tumors develop mainly in the submucosa and endoscopic features alone are not specific for their diagnosis(1). Although IFP has a distinct morphology, sometimes it can be a challenging diagnosis histologically. Immunohistochemistry is of great importance but the presence of a characteristic mutation at the PDGFRa gene confirms the diagnosis (2). Concurrent dysplasia or adenocarcinoma in the overlying epithelium is rare(3,4). Herein we report two unusual cases of large IFPs, the first one located in the ileum and the later in the stomach with a synchronous adenoma with high grade dysplasia located above the polyp. We discuss the histologic differential diagnosis and the molecular features of this benign entity.

Case report

First case: A 73-year-old woman presented with nausea, persistent vomiting and intense abdominal pain. She mentioned that these symptoms were present for the last two months with gradually increasing severity. A CT scan depicted a pedunculated mass in the ileum measuring 6,1cm in greatest diameter that caused intussusception (Figure 1A,B). The rest laboratory tests showed a mild increase in white blood cells (10.350) with 78,7% neutrophils. Eosinophils were within normal values. Segmental resection of the affected part of the ileum was performed. On macroscopic examination, a pedunculated polypoid tumor was recognized in the ileum, causing intussusception of the wall and obstruction of the lumen. The tumor measured 8cm and the cutting surface was white-greyish and gelatinous (Figure 1C).

Second case: A 59-year-old man had intermittent hematochezia the previous year and he underwent a gastroscopy, which revealed a polypoid mass in the corpus of the stomach. Biopsies were taken and analyzed elsewhere. A diagnosis of a well differentiated gastric adenocarcinoma of enteric type was rendered. CT scan revealed a mass in the corpus measuring 8,5x6x8cm with relatively unclear borders with increased uptake of contrast agent. The patient developed bloody diarrhea and was admitted to our Hospital, at the Department of Internal Medicine, where his symptoms were attributed as a side effect of the contrast agent. Cancer serum markers (a- fetoprotein, CEA and Ca19-9) were within normal levels. The rest laboratory tests showed iron deficiency and anemia. Following resolution of the diarrhea, the patient was transferred to the Department of Surgery and a partial gastrectomy was performed. We received a partial gastrectomy specimen, where a submucosal polypoid mass, located in the antrum, protruded in the lumen. The major diameter of this lesion was 8cm and the cutting surface was white-grayish and gelatinous. In the mucosa overlying the mass and in direct continuity with it, a second polyp measuring 6.5cm was also noticed, with a papillary pattern and white-grayish friable cut section.

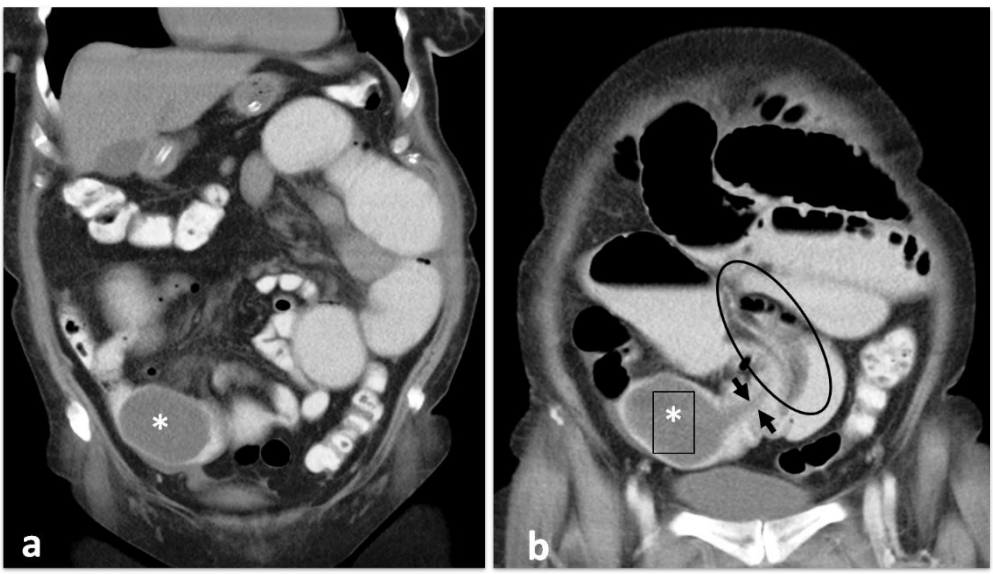

Figure 1: *Non-enhanced coronal orthogonal average thick-slab MPR(a) and contrast-enhanced coronal oblique average thick-slab MPR(b) from the first case. There is a soft-tissue endoluminal mass, measuring 6.1x4.1cm, which is locally distending the ileum (stars in a and b). The mass is pedunculated (arrows in b). The mesentery is intussuscepting at the level of the base of the stalk of the mass, which acts as the lead point (oval in b). The mass enhances mildly (~10HU) and homogeneously after IV contrast injection. Markedly distended small bowel loops with air-fluid levels proximal to the lesion (transition point) are consistent with small bowel obstruction.*

Histopathology in both cases revealed a submucosal neoplasm with moderate cellularity consisting of spindle cells in a collagenous background (Figure 2). Abundant inflammatory cells, mainly eosinophils, lymphocytes, mast cells and plasma cells, were scattered throughout the neoplasm, while eosinophils were also clustered around blood vessels. Mitotic rate was low (<1 mitosis/10HPF). Immunohistochemistry demonstrated positivity for CD34 and CD99 and no reaction for ckit, DOG1, ALK, aSMA, CK8/18 and S100. Both cases were diagnosed as IFP. A PDGFRa mutation (exone 12) was identified via PCR in the first case. In the second case, the polypoid mass above the IFP was diagnosed as a tubular adenoma with high-grade dysplasia and no invasion into lamina propria (Figure 2).

Both patients are well and free of disease, according to their oncology follow-up 24 and 16 months respectively since the diagnosis.

Discussion

IFP is a benign neoplasm of mesenchymal origin and can occur anywhere in the gastrointestinal tract. It was first described by Vanek in 1949 as a submucosal granuloma with eosinophilic infiltration.(5) The lesion is encountered in both sexes with a slight female prevalence and the mean age of the patients is 60 years old. The majority of the cases are sporadic but there are a few cases with a familial occurrence.(6) 35% of recorded cases are located in the stomach and have a predilection for the antrum.(7,8) They represent uncommon lesions, as they account for the 0.1% of gastric polyps.(9) Other reported locations are the small intestine, large intestine,

duodenum, esophagus, gallbladder and appendix.(8,10)

Originally, the nature of this lesion was considered to be reactive to trauma, allergy or infection(5) and related to Helicobacter Pylori infection.(11) Schildhaus et al, at 2008 was the first to correlate IFPs with a specific mutation in the PDGRFa gene, demonstrating the neoplastic nature of this lesion, in contrast to previous data.(2,11,12) More specifically, the mutations that these polyps demonstrate are located in the exons 12, 14 and 18 of the Platelet Derived Growth Factor Receptor Alpha (PDGFRa) gene.(5,11,13) The most common mutation is the c.2525A>T (p.D842V) in exon 18. Other mutations include deletions, deletion–insertions, duplication, and single nucleotide substitutions in exon 12.(5) Interestingly, familial and sporadic cases share the same mutations (14). There seems to be a correlation among the exons that carry the mutations with the location of the tumor.(2) Exon 12 mutations are mainly found in small intestinal IFPs and exon 18 mutations are more common in gastric IFPs. (2,13)

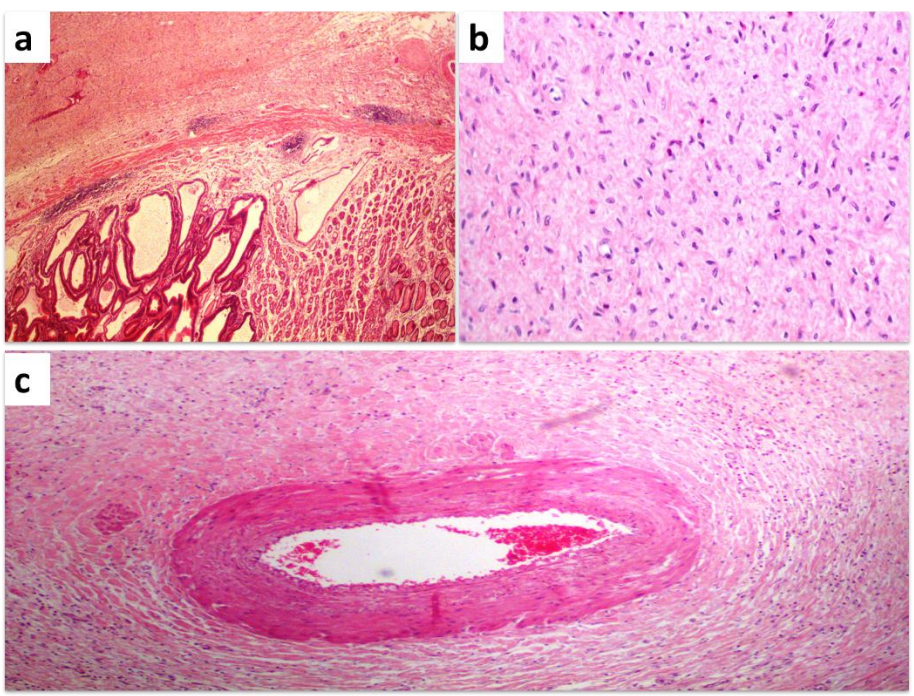

Figure 2: *Representative H&E images*

a: A submucosal lesion (upper part of the image) with smooth contours and low cellularity is seen under a gastric adenoma (lower right). (2x magnification) (case 2)

b: The neoplasm is composed mainly of spindle cells with abundant inflammatory cells and small vessels. (20x magnification) (case 1)

c: The eosinophils have a concentric accumulation around vessels (onion skin pattern) (2x magnification) (Case 2)

The presenting symptoms depend on the location and the size of the polyp. Small polyps can be asymptomatic and are discovered incidentally.(8,15) Larger lesions tend to present with bleeding from the upper GI, colicky abdominal pain, pyloric obstruction and a feeling

of early satiation.(6) A case of a patient presenting with hypovolemic shock, caused by an ulcerated IFP with a greatest diameter of 3cm has also been reported.(16) Lesions located in the small intestine can cause intussusception(6,8,15), like our first case, and present with nausea, vomiting and lower gastrointestinal tract bleeding. The polyps have a diameter ranging from to 2 to 5 cm, but there are reported cases measuring up to 9 cm. (9) Both of our cases had a 8cm major diameter.

Although the diagnosis of IFP can be postulated based on CT findings,(17) the main diagnostic tool remains the histopathologic examination of the tissue, as it is important to recognize the distinct histopathology of this lesion. Ancillary studies (i.s. immunohistochemistry and molecular analysis) are also of help. (18) Histologically, the tumor is a poorly demarcated lesion located in the submucosa. Mucosal invasion may be seen(19). The lesion can infiltrate and even partially replace the muscularis propria.(4,20) Cellularity is low to moderate. The tumor consists of haphazardly arranged spindle and stellate cells with a small amount of eosinophilic cytoplasm. The nuclei of these cells have finely distributed chromatin and inconspicuous nucleoli, usually without atypia. (13) Mitotic rate is low. The stroma can have myxoid or collagenous degeneration and is usually edematous. Inflammatory cells are often present, consisting mainly of eosinophils, plasma cells and lymphocytes.(21) The tumor contains many small thin-walled vessels that are surrounded concentrically by a hypocellular zone of spindle cells and eosinophils, which is quite characteristic for this entity (onion skin pattern). (1,9,19,21,22)

IFP is a benign entity.(17) However they cannot be distinguished clinically from adenomas and other types of polyps with more aggressive potential, so they are removed in order to exclude malignancy.(16) Interestingly, synchronous dysplasia or even adenocarcinomas can arise in the overlying epithelium and a few cases have been published.(3,4,23,24) Herein we present one such case. An incidental adenoma with high grade dysplasia was present in the mucosa overlying the IFP. Dysplastic epithelium in the biopsy along with a large mass in the wall of the stomach lead to the erroneous diagnosis of invasive adenocarcinoma in another institution. Careful examination of the biopsy that showed no evidence of invasion and attention at the double nature of the lesion on radiology could have prevented this oversight. However, the concurrent presence of dyplasia, adenoma or even invasive carcinoma with IFP highlight the need for a thorough macroscopic examination and sampling of large polyps in order not to miss synchronous malignancy. Another entity reported to accompany IFP is gastritis cystica polyposa.(25) Immunohistochemical profile of this entity is quite distinctive. The spindle cells of IFP are positive for vimentin, CD34 and PDGFRα. αSMA can be focally positive, while ckit/CD117, DOG1, desmin, S100, SOX10 and cytokeratins are negative (9).

Based on the histology and the location of the tumor, the differential diagnosis includes Gastrointestinal Stromal tumor (GIST), inflammatory myofibroblastic tumor, schwannoma, solitary fibrous tumor, leiomyoma and lipoma.

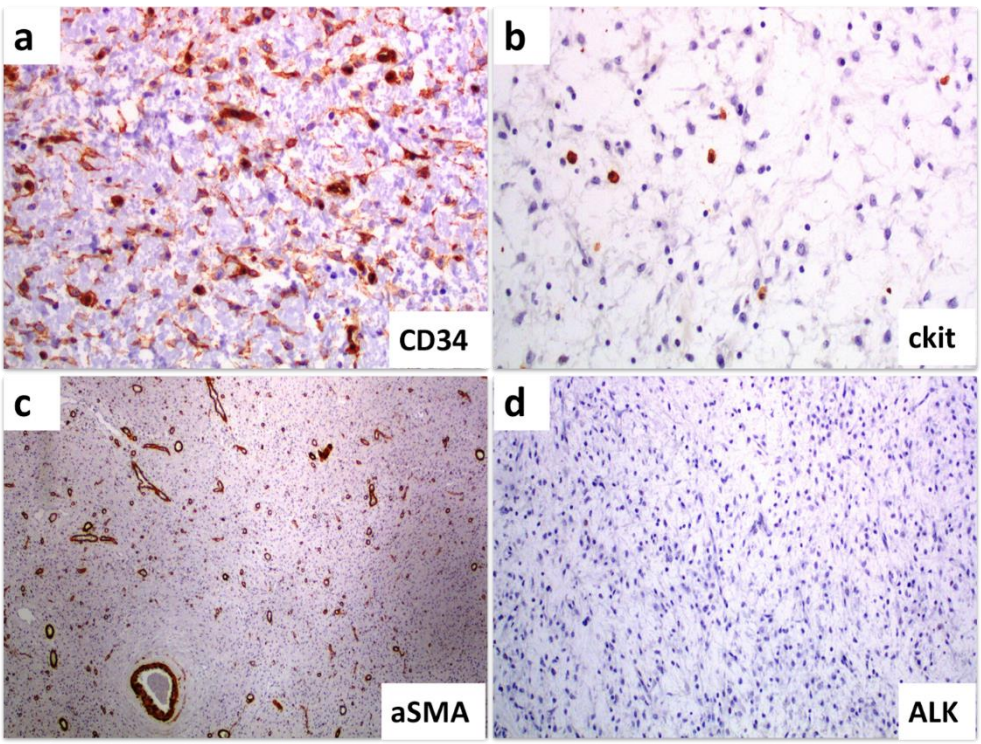

Figure 3: : *Representative images from the immunohistochemical stains*
a: The neoplastic cells are positive for CD34 (20x magnification) (case 2)
b: CKIT/CD117 staining is negative (note mast cells as an internal positive control) (20x magnification) (case2)
c: SMA is negative (musclular wall of the vessels serves as an internal positive control) (2x magnification) (case 1)
d: ALK expression was not seen (20x magnification) (case 1)

GISTs are mesenchymal tumors that share many features with IFPs including PDGFR mutations. They are derived from Kajal cells and their progenitors.(26) Histologically, they may have three phenotypes, spindle (70%), epithelioid (20%) or mixed (10%). (27) Their immunohistochemistry is quite characteristic, as in 95% of cases these tumors are positive for cKIT (CD117) and DOG1. 75-80% of GISTS have a mutation in ckit, 10% harbor a mutation in PDGFRa and the rest neoplasms have a different molecular profile.(28) It is important to differentiate these tumors from IFP as they have a more aggressive clinical behavior, while IFps are considered benign neoplasms.(9) Submucosal location, abundant stromal eosinophils, onion skin pattern and ckit/DOG1 negativity are all in favor of IFP.

Inflammatory myofibroblastic tumor is a mesenchymal tumor consisting of spindle cells with vesicular chromatin in a collagenous or myxoid stroma, where a mixed inflammatory infiltrate is intermingled with the spindle cells. However, the infiltrate contains mainly plasma cells and lymphocytes, and eosinophils are less prominent(29). The clinical presentation is with abdominal pain, bowel obstruction and fever. Laboratory findings include leukocytosis, anemia and hypergammaglobulinemia (29). Approximately 50% of these tumors have tyrosine kinase receptor gene rearrangements, involving the ALK gene, and showing ALK overexpression (29,30). In 10% of the cases ROS1 gene fusions are present(30). The neoplastic cells are positive for αSMA and desmin. DOG1, ckit, CD34, S100 and SOX10 are negative. It is important to distinguish these tumors as they

have a potential of recurrence and they can, albeit rarely, metastasize.

Schwannomas are non-encapsulated but circumscribed tumors that are surrounded by a rim of lymphocytes.(31) A mixed inflammatory infiltrate is present, being distributed around vessels. The neoplastic cells are spindle-shaped and collagen fibers lie in between them. Two growth patterns are seen: Antony type A regions are cellular and have the characteristic Verocay bodies, with palisading spindle cells while Antony type B regions are hypocellular and lack the Verocay bodies.(31,32) Immunohistochemistry is helpful for distinction from IFPs, as the spindle cells in schwannomas are S100 positive and negative for ckit, αSMA and CD34(32).

Solitary fibrous tumor is a spindle cell tumor originally described in the pleura (33). A variety of other locations have been described (34) including the stomach (35) and the ileum (36). Solitary fibrous tumor shares with IFP the onion skin perivascular pattern and the CD34 immunostain, however solitary fibrous tumors usually arise in the serosa, have a characteristic patternless pattern with hemangioperincytoma-like vessels and ropy collagen and lack an associated inflammatory infiltrate (34).

Leiomyomas are rare in the gastrointestinal tract. These neoplasms are composed of smooth muscle cells and are positive for αSMA, MSA and desmin but are negative for ckit, CD34 and S100. (37) Finally, lipomas are rarely encountered in the stomach and usually develop in the submucosa.(38) They are well demarcated, encapsulated, with smooth contours and contain mature adipose tissue.(38,39)

In conclusion, we describe the clinical, radiologic and pathologic characteristics of two cases of IFP, a benign neoplasm that may mimic a variety of mesenchymal GI tumors. GIST is the main differential diagnosis, especially in the light of their common molecular alterations. Correct diagnosis is of paramount importance as IFP is a benign entity and further therapy is not needed.

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