gastrointestinal disorders

MDPI

Review

Mesenchymal Tumors of the Gastrointestinal Tract—Beyond GIST—A Review

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Abstract: Sarcomas are rare lesions and encompass a wide variety of entities, depending on their nature. In recent years new entities have been described and new knowledge, especially that provided by molecular studies, has been increasing. This makes it very difficult to be updated with all the described entities, since only some of the centers have the desired ancillary studies for the correct diagnosis. Some lesions are extremely rare and may appear once or twice during the lifetime of a general pathologist. When we refer to sarcomas of the gastrointestinal tract, the gastrointestinal stromal tumor (GIST) is the most well-known lesion that the pathologist will most frequently find in daily practice. This paper aims to comprehensively review the sarcomas associated with the gastrointestinal tract, emphasizing histopathology and going beyond GIST. This review highlights the histopathology of rare types of sarcomas so it may increase awareness of common and rare lesions, prompting an easy and effective diagnosis.

Keywords: sarcomas; gastrointestinal tract; diagnosis

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1. Introduction

The gastrointestinal tract (GI) exhibits benign and malignant lesions with variable degrees of frequency. Lesions of an epithelial nature, such as polyps and carcinomas, are the most common, especially in the large bowel [1]. Mesenchymal lesions are rarer and encompass a wide variety since they can originate from muscle, neural, vascular, or fibroblastic tissue [2]. Of all the mesenchymal lesions, the most frequent and best known is the gastrointestinal stromal tumor (GIST) [3].

However, the GI tract houses a wide diversity of mesenchymal lesions, some of which are very rare and will probably never be seen by most pathologists. The increase in knowledge generated by next-generation immunohistochemistry and sequencing has provided us with new and fascinating entities [4].

This paper aims to perform a comprehensive review of the mesenchymal lesions of the GI tract, excluding GIST, focusing on pathological evaluation and genetics, with some relevant clinical background. The paper also excluded mesenchymal lesions originating in the liver and pancreas, focusing only on the "GI tract".

2. Inflammatory Myofibroblastic Tumor

The inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal tumor commonly found in children and young adults, usually in the lungs. Still, in some rare cases, it may be present in the GI tract. The colon and small intestine are the most frequent locations, followed by the stomach [5]. Its etiology is unknown, despite some case reports stating there

is an association with infection by the Epstein–Barr virus and immune dysregulation [6]. Regarding its pathogenesis, up to two-thirds of cases have rearrangements of the *ALK* gene at the 2p23 position with several partners. The *RANBP2::ALK* fusion is the most common, with rare cases with *RRBP1::ALK*; in about 5% of cases *ROS1*, *NTRK3*, *PDGFRB*, and *RET* fusions are identified [7]. In most cases, *ALK* fusions were assessed by Fluorescence In Situ Hybridization (FISH), so the fusion partner was not known. However, in recent years several comprehensive genetic sequencings have been performed; these have discovered new fusion partners and added new data and possible therapeutic targets [8].

As stated before, most cases occur in the small bowel [9] and stomach [10], but any part of the GI tract may be affected; even in the gallbladder, according to case reports [11]. Clinical features are variable, from abdominal pain to obstruction. In circa 50% of patients, there is leukocytosis anemia and hypergammaglobulinemia [12].

On gross examination, the tumor size is usually variable, and an IMT may be up to 12 cm in length [13]. Histological examination shows uniform, plump spindle cells with pale cytoplasm organized into loose fascicles. The supporting stroma may be collagenous or myxoid and is usually associated with plasma cells and lymphocytes, with fewer eosinophils and neutrophils. The amount of stroma is variable, with some tumors not having much stroma. Mitotic activity is scarce and usually there is no necrosis [13,14]. An epithelioid variant is described, with round cells and large eosinophilic cytoplasm, supported by an abundant myxoid stroma with many neutrophils. Interestingly, this epithelioid variant usually has a *RANBP2::ALK* fusion and, less commonly, a *RRBP1::ALK* fusion [15].

The differential diagnosis may be wide since it encompasses almost every spindle cell lesion of the GI tract; however, the combination of morphology (especially inflammation) with ALK staining/fusion, provides the diagnosis.

A morphological example of an IMT can be seen in Figure 1.

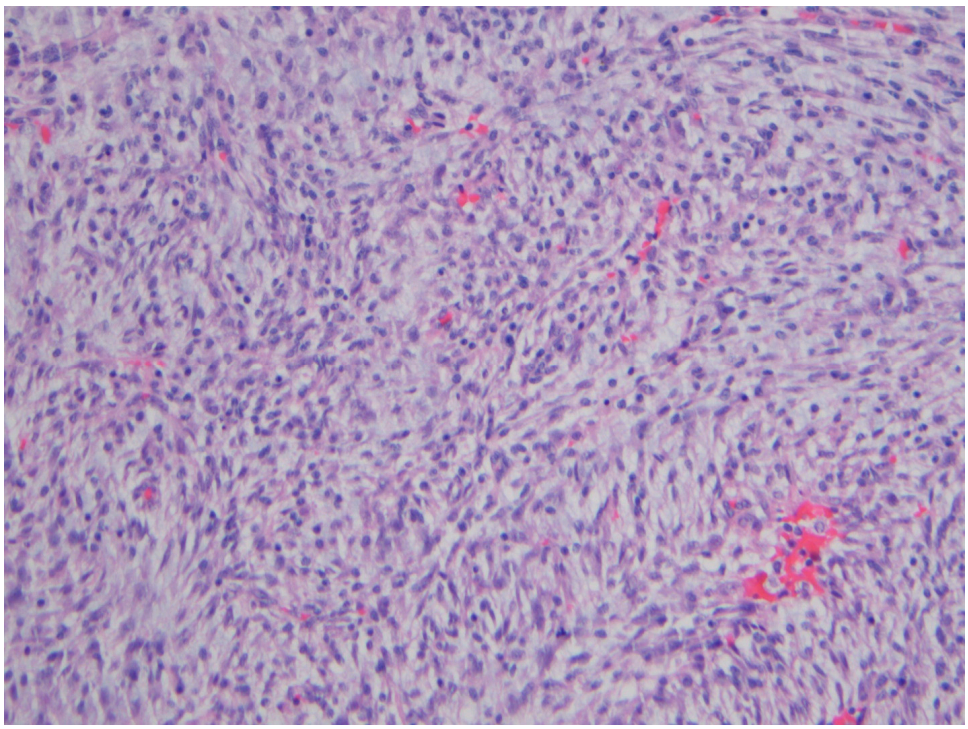

Figure 1. An example of an inflammatory myofibroblastic tumor: uniform, spindle, and plump cells form randomly oriented fascicles. Stroma is vaguely myxoid, without necrosis.

3. Desmoid Fibromatosis

Desmoid fibromatosis is a locally aggressive, non-metastasizing neoplasm [13]. It usually develops in the mesentery of the small bowel, and therefore it is considered a GI-

associated lesion. It has an infiltrative growth pattern and on radiology evaluation in some cases it may be mistaken for a more aggressive tumor [16].

Symptoms are rather unspecific; most commonly, abdominal pain is present. Both sexes are equally affected, and there is a broad range of higher incidences between 30 and 40 years [17]. There are multiple causes, but circa 15% are associated with mutations in the adenomatous polyposis coli (*APC*) gene and in these patients it usually presents at a younger age [18]. Tumors can be large, up to 31 cm [19].

Almost all tumors have a dysregulated WNT/β-catenin pathway [20]. Patients with germline mutations usually have an *APC* or *CTNBB1* mutation (mutually exclusive), which is the initiating event. In rare cases, with somatic changes, there is an accumulation of the β-catenin in the cytoplasm, which causes increased transcriptional effects [21].

Histologically, it is composed of long fascicles of spindle cells with ovoid nuclei without atypia or necrosis. The background is variable and can present with myxoid areas or keloidal fibers [22]. The hallmark for diagnosis is nuclear staining for β-catenin [23].

Molecular pathology may be necessary for the diagnosis, and in about 95% of cases a mutation in the exon 3 of β-catenin is found [24]. The *APC* mutations are usually located at codon 1444 [25]. Some authors advise that a colonoscopy should be performed even in the absence of a mutation in *CTNBB1* in apparently sporadic tumors, as it may be associated with a non-recognized form of desmoid fibromatosis [26].

Treatment is surgical, comprising a complete excision. In cases of incomplete resection, there is a high rate of recurrence [27]. Chemotherapy with anthracycline and hormonal therapy may be performed before surgery for tumor shrinkage and to allow a more conservative surgery; or after surgery in cases of incomplete resection [28,29]. A genetic study has a role in prognosis since mutations of the *CTNNB1 p.S45F* have a worse recurrence-free survival [30]. Currently, some target therapies are under investigation in clinical trials [30] but these are not yet widely available in clinical practice.

Diagnosis is usually straightforward, but a differential diagnosis of GIST must be kept in mind. The correct immunohistochemistry provides the right diagnosis.

A typical fibromatous desmoid tumor can be seen in Figures 2–5.

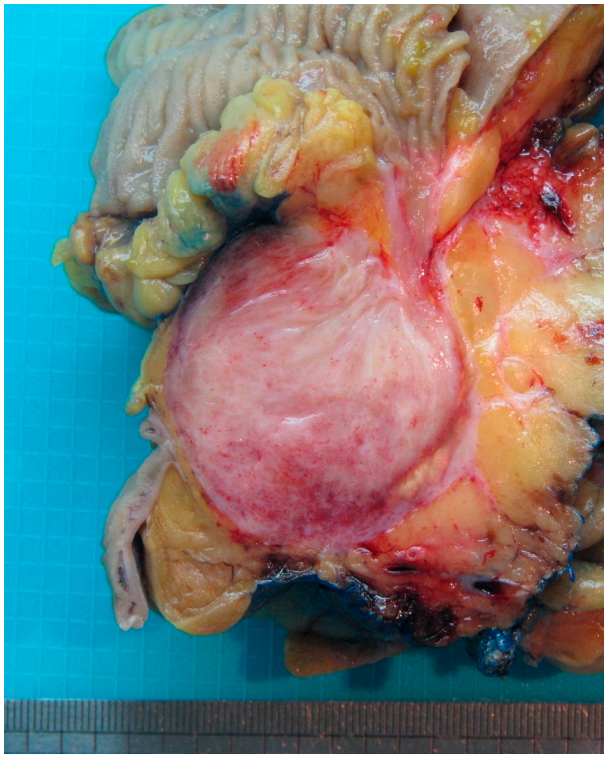

Figure 2. Gross picture of mesenteric fibromatosis, showing a white/pink mass with moderately defined borders.

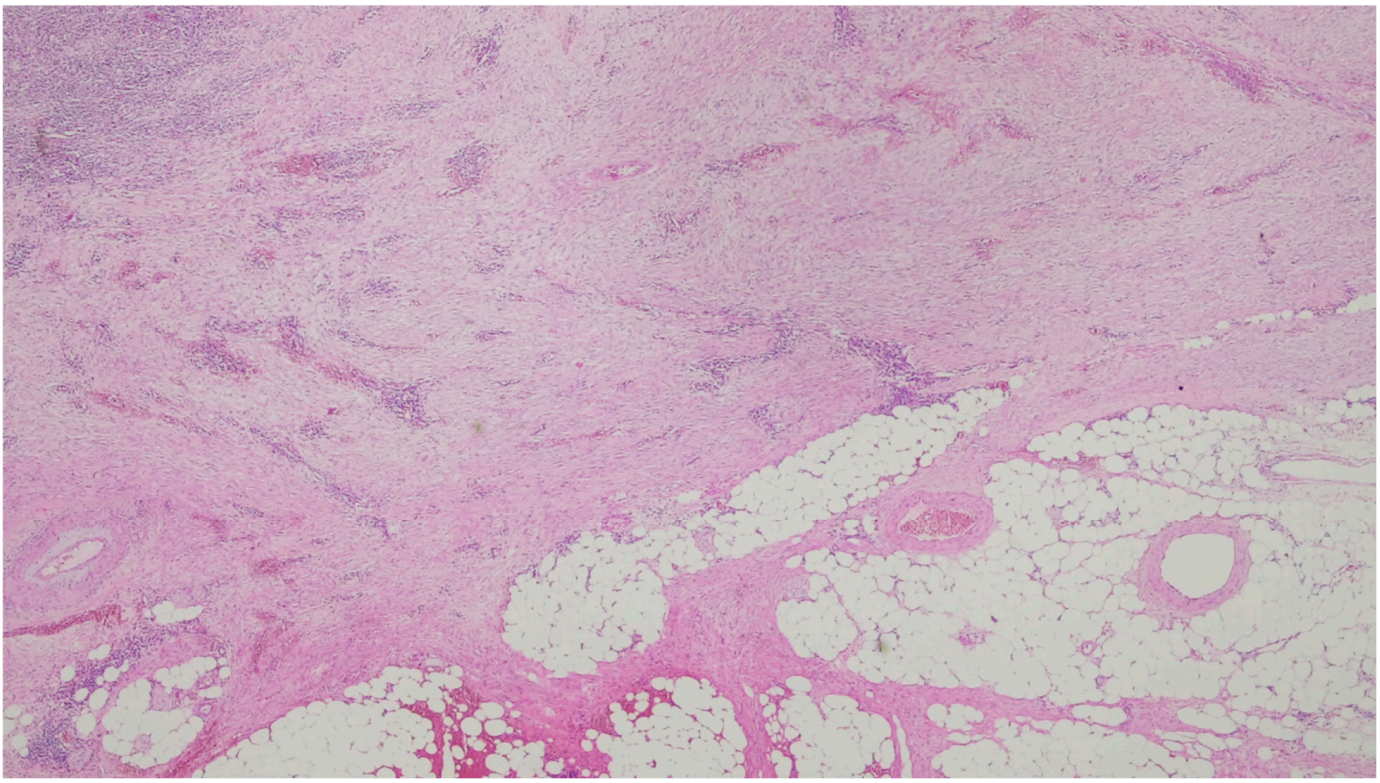

Figure 3. The lesion has poorly defined boundaries and entraps local adipose tissue.

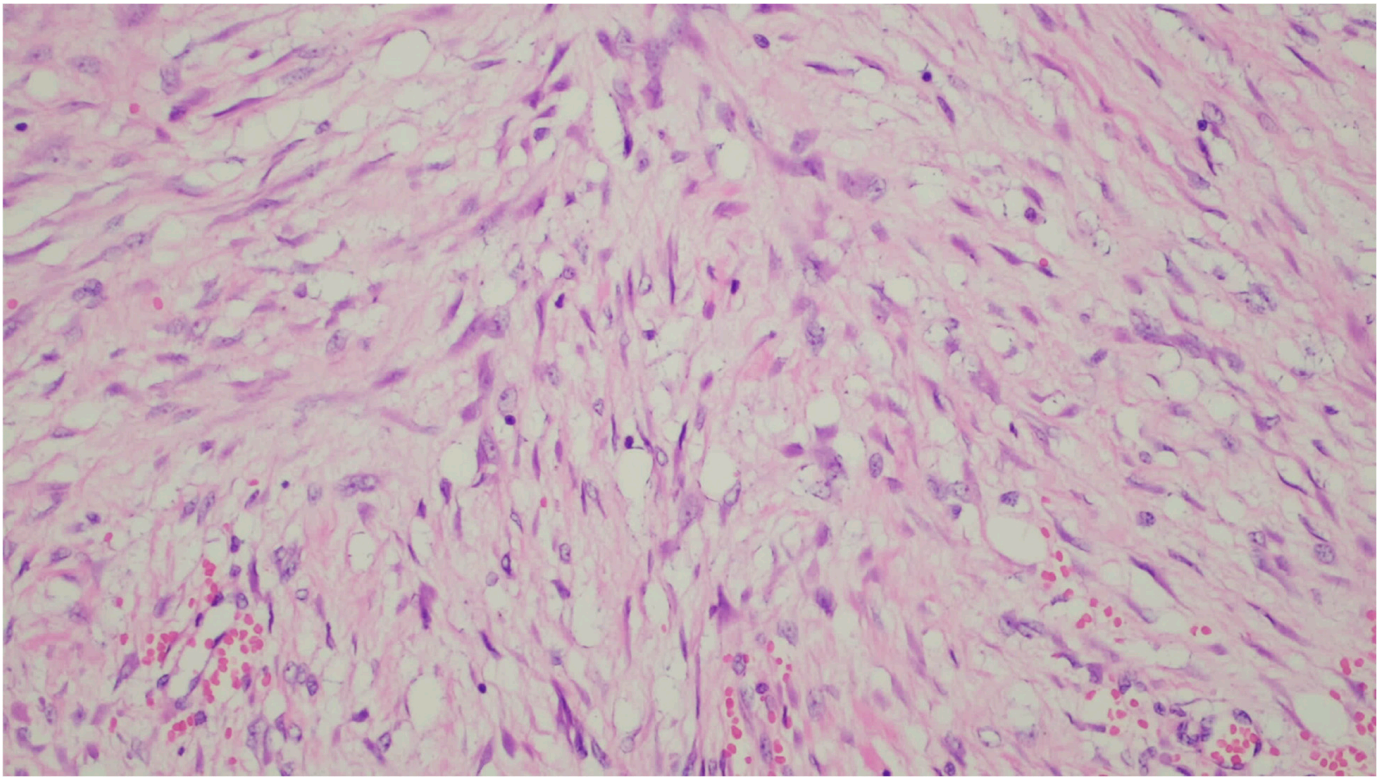

Figure 4. Spindle cells without atypia, sometimes with small nucleoli.

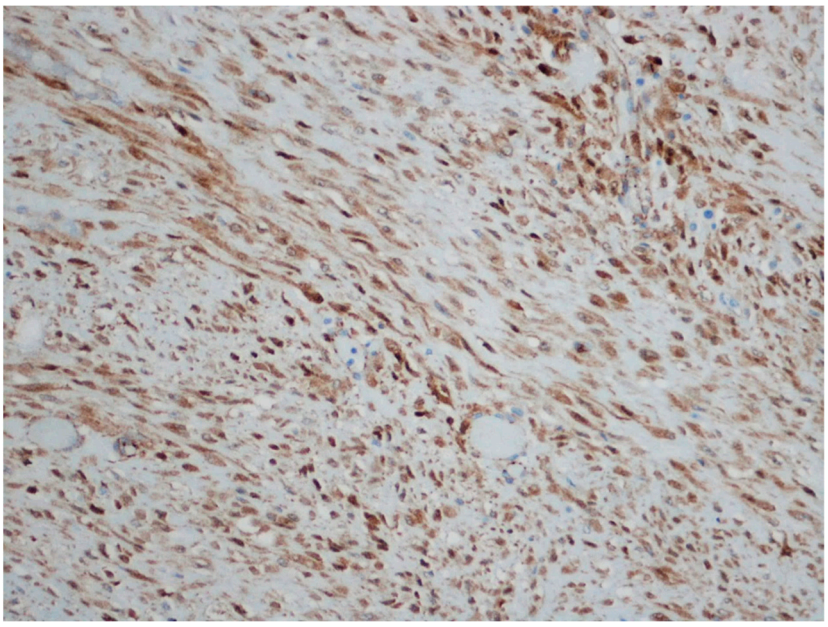

Figure 5. A nuclear beta-catenin immunohistochemistry stain is the hallmark of pathological diagnosis.

4. Solitary Fibrous Tumor

The solitary fibrous tumor is fibroblastic in nature, and is more common in pleural locations [31]. However, it has been described in various anatomical sites, including the GI tract [32].

Usually, it is seen in adults within a wide age range (20 to 70 years). Both sexes are equally affected; symptoms are unspecific, are usually associated with compression and sometimes hemorrhage [33].

Its pathogenesis is defined by a *NAB2::STAT6* fusion, in which the repressor domain of NAB2 is replaced by an active domain of STAT6, resulting in constitutive activation of RGR-mediated transcription [34].

Recent studies in thoracic tumors have found three groups of fusions: a predominant *NAB2ex4::STAT6ex2*, the *NAB2ex6::STAT6ex16*, and the *NAB2ex6::STAT6ex17* (n = 16), which were associated with different clinical features [35]. Recently, a variant called *STAT6::TAD* was associated with higher mitotic count and lower recurrence-free and overall survival due to increased expression of FGF2 [36].

Grossly, tumors are well circumscribed and can measure up to 25 cm. Morphologically, they are composed of ovoid/spindle cells arranged in poorly defined fascicles, supported by thin-walled vessels dilated in a staghorn pattern. Stromal hyalinization is also a characteristic feature and may be prominent. Myxoid changes, cystic dilation, and hemorrhage may be present [13]. A subset of solitary fibrous tumors exhibit a mature adipose tissue component—the so-called lipomatous solitary fibrous tumor [37]. Immunohistochemistry shows positivity for CD34 and STAT6; the latter considered with high specificity and sensibility [38] and allows the differential diagnosis with GIST.

Treatment is surgical, and the majority of tumors behave benignly. About 10% have an aggressive course. Features associated with worse outcomes are older age, larger size, high cellularity, necrosis, cytological atypia, and high mitotic activity [39].

A study by the French sarcoma group incorporates clinical data, pathological features, and history of radiotherapy to predict survival, recurrence, and distant metastasis [40]. Recently, some cases of dedifferentiated solitary fibrous tumors have been described, and in these cases, chemotherapy seems to be the best choice of treatment [41]. Malignant behavior in solitary fibrous tumors is hard to predict. While most have a benign clinical course, a significant group can recur or metastasize, sometimes after 10 years [42]. Images of SFT can be seen in Figures 6 and 7.

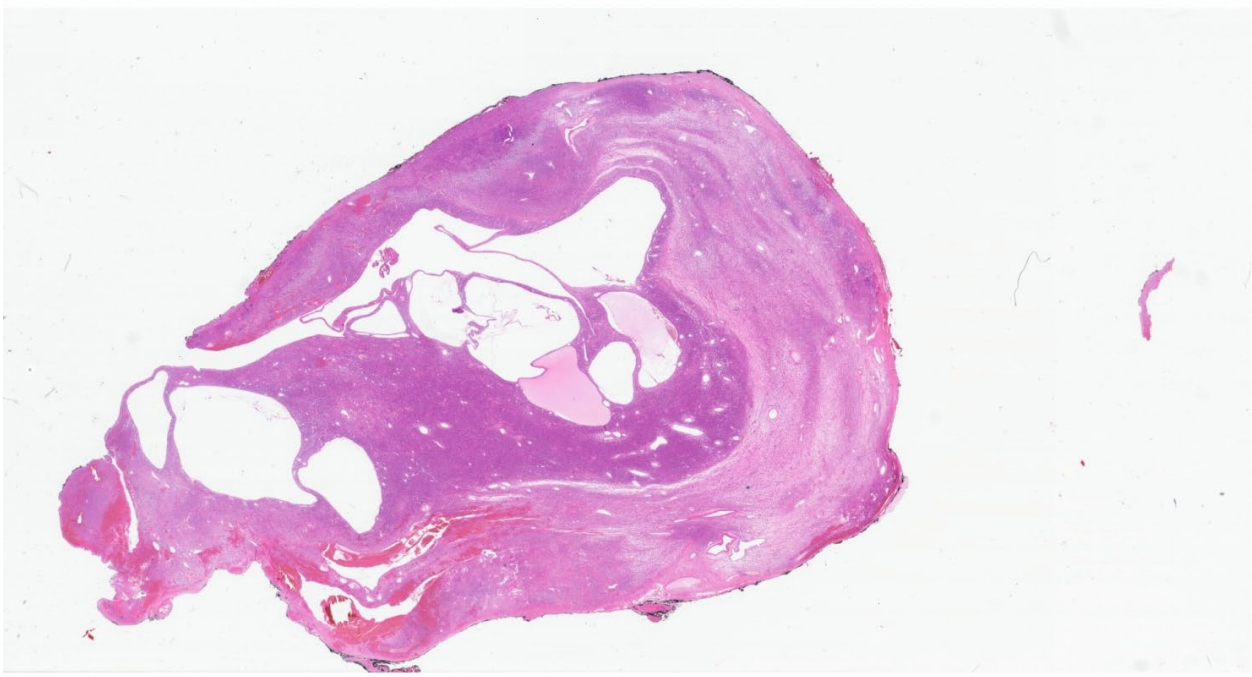

Figure 6. Low-power view of a solitary fibrous tumor with central cystic spaces.

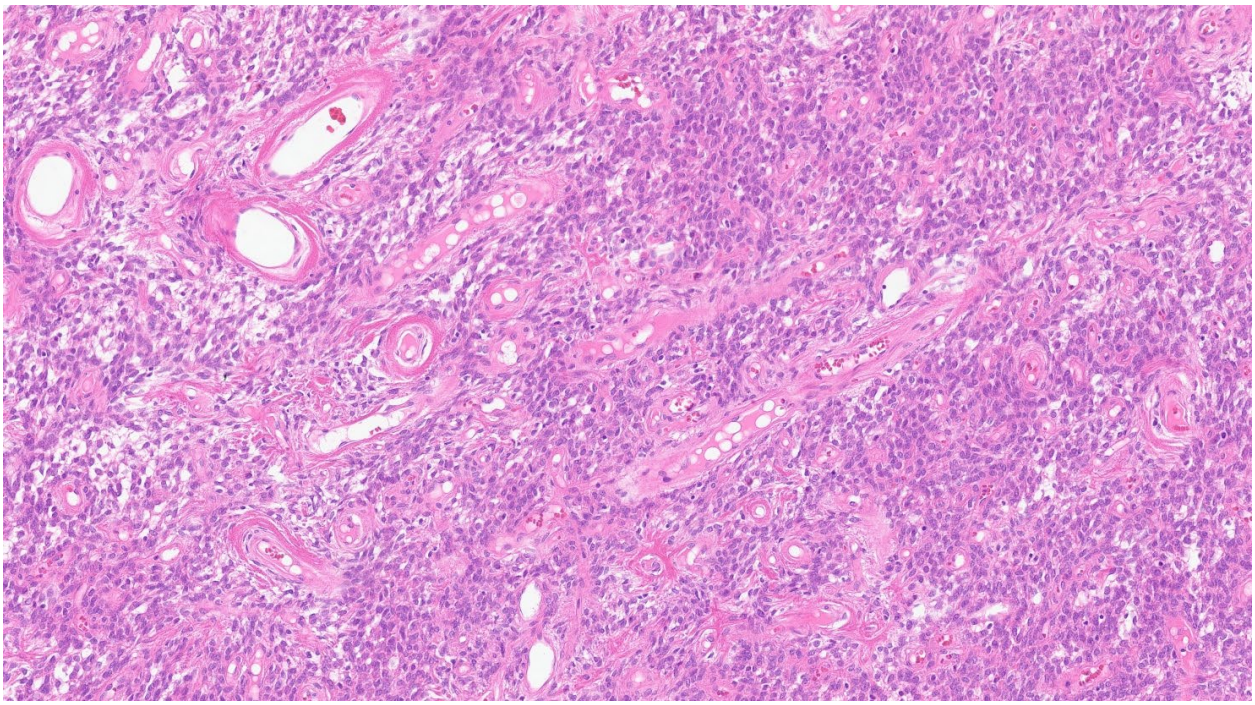

Figure 7. Higher power shows oval to spindle cells in a background of a mild fibrotic stroma and with hyalinized blood wall vessels.

5. Lipoma

Lipomas are benign lesions composed of mature adipose tissue. They are relatively common in soft tissues and may appear in any location in the GI tract [43].

Most lipomas appear in the submucosa and the caecum/ascending colon. Some rare cases can appear in the subserosa and mucosa. The latter is sometimes associated with Cowden syndrome [44].

Clinically, lipomas are commonly asymptomatic and represent incidental findings; however, in some cases—especially when the tumor is in the caecum or is large in size— they can cause obstruction [45]. Ulceration and hemorrhage may be referred by patients [46].

Morphologically, lipomas in the GI tract are identical to their soft tissue counterparts: mature adipocytes of uniform size without atypia. If they exhibit prominent capillary vessels with microthrombi, the designation of angiolipoma may be applied [13].

The histology of these lesions can be seen in Figures 8 and 9.

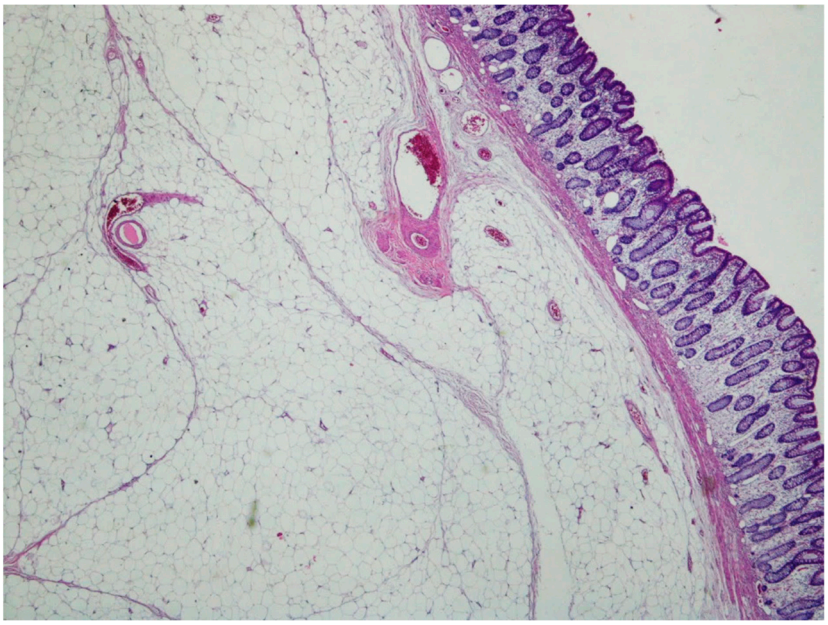

Figure 8. A typical submucosal lipoma in the colon. Note the colonic normal mucosa in the right part of the figure.

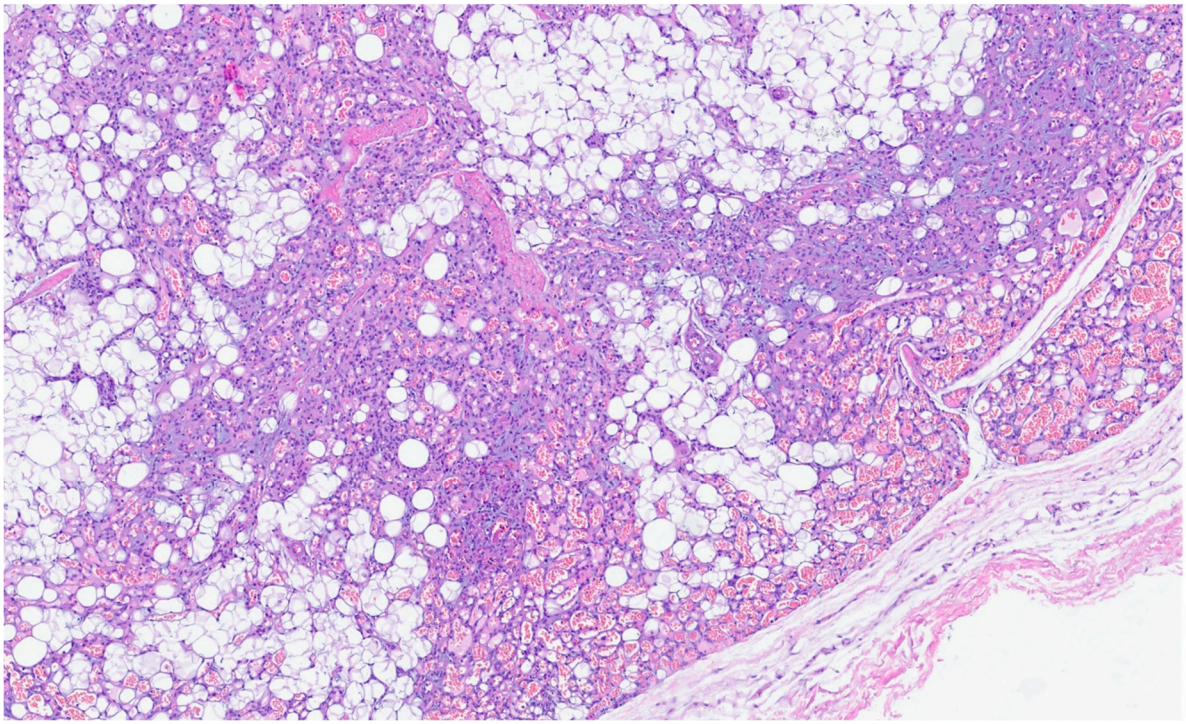

Figure 9. A typical angiolipoma with small blood vessels and thrombi. Some myxoid changes are also apparent.

6. Inflammatory Fibroid Polyp

Inflammatory fibroid polyp is a benign fibroblastic neoplasm. Typically polypoid in appearance, with some rare sessile lesions, they show a predilection for the stomach (antrum), followed by the ileum [47].

Usually, they are incidental findings, with large tumors being discovered in investigations due to abdominal pain, hemorrhage, or obstruction [48]. Some small lesions in the intestine may cause intussusception [49].

Most of the tumors are sporadic in origin, with some cases demonstrating a familial predilection due to germline *PDGFRA* mutations [50]. These mutations usually occur in exon 18 in the stomach and exon 12 in the small intestine [51].

The tumors vary in gross size; most are usually less than 3 cm, but in some cases they can be up to 7 cm [52].

Histological morphology is typical. The lesion is usually centered in the submucosa and composed of a proliferation of spindle and stellate cells in a haphazard distribution. The stroma is vaguely myxoid and contains inflammatory cells, namely eosinophils. Small to intermediate blood vessels with concentric fibrosis are also a characteristic part of the spectrum [13].

Immunohistochemistry demonstrates a consistent positivity for CD34 and PDGFRA [53]. Due to CD34 positivity, the main differential diagnosis is with GIST and SFT, but inflammatory fibroid polyp is negative for DOG-1 and STAT6.

This lesion is benign, and surgery/endoscopic dissection is the curative choice [54]. Typical histology is depicted in Figures 10 and 11.

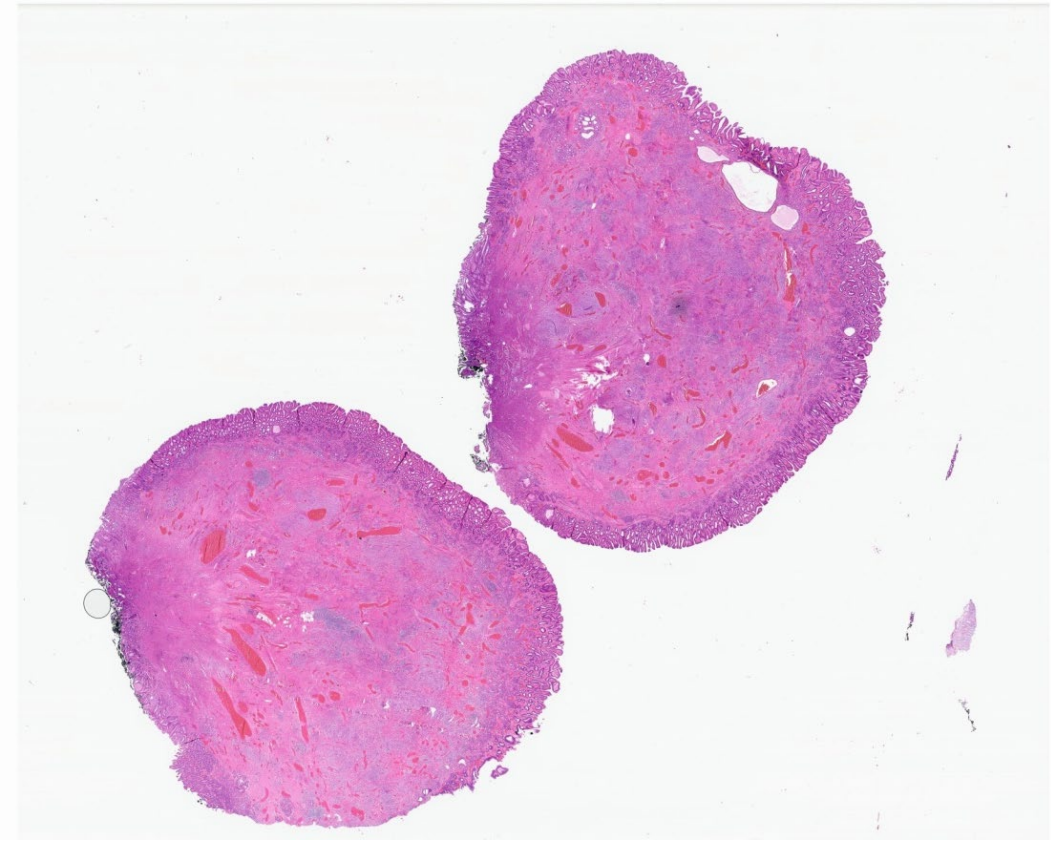

Figure 10. A typical inflammatory fibroid polyp in the stomach. Notice the lesion centered in the submucosa.

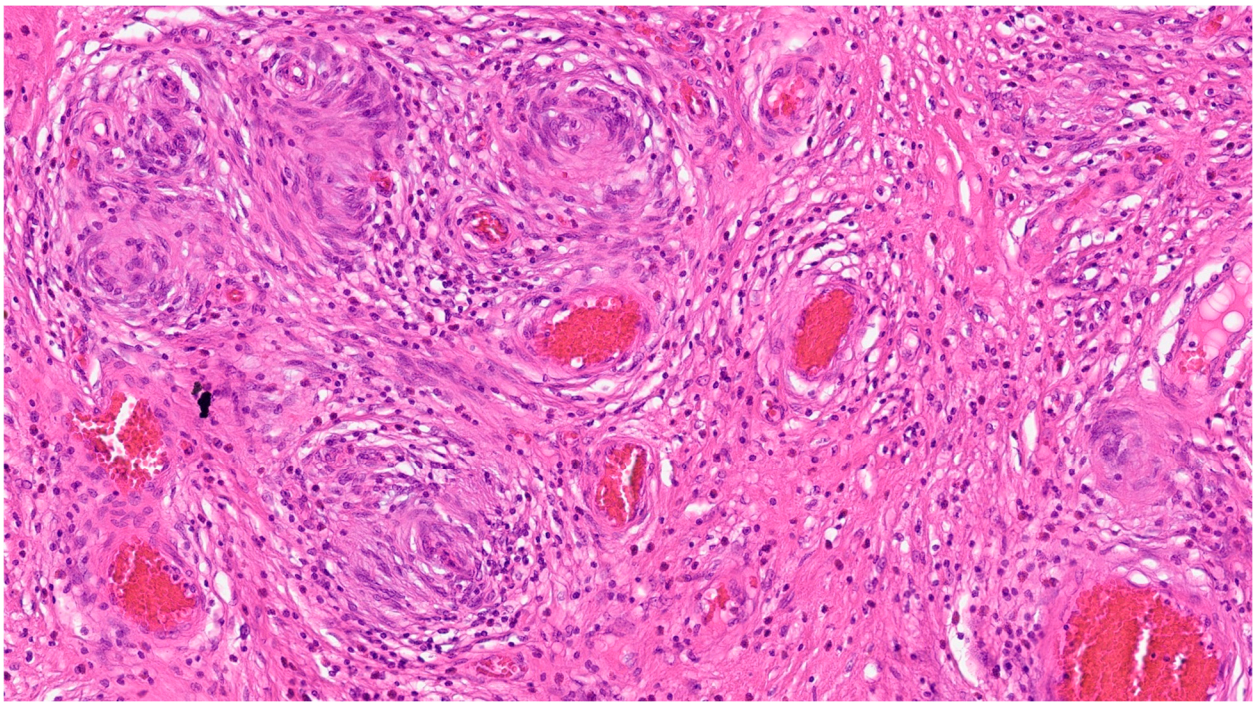

Figure 11. A high-power view shows spindle cells associated with eosinophils and concentric perivascular fibrosis, imparting an "onion skin" morphology.

7. Plexiform Fibromyxoma

This is a rare entity with benign behavior that arises in the antrum and pyloric region and, sometimes, in the duodenum [55]. Recently, a case was described in which the esophagus was affected [56]. Both sexes are equally affected, and the age range is wide, and includes children [57].

Symptoms are usually related to GI obstruction, with some being asymptomatic [58]. Grossly, this lesion appears as a gelatinous mass centered in the muscularis propria that can protrude to the serosa or to the mucosa with ulceration [59]. Lesions vary in size; with large lesions measuring up to 15 cm [60].

The histomorphology of these tumors is rather typical: bland spindle cells, supported by a myxoid/fibromyxoid/collagenous stroma and with a rich vascular network of thin-walled vessels in a multinodular pattern. Immunohistochemistry has a limited role; it is usually limited to smooth muscle actin positivity, and has more value in establishing the differential diagnosis [13].

Recently, *MALAT1::GLI1* fusions have been detected, as well as *GLI1* polysomy in a subset of tumors [61]. This makes it distinct on a molecular basis from myxoid GISTs, which is the main differential diagnosis, but the true meaning of this genetic change is still unknown [57].

8. Leiomyoma

Leiomyomas are benign mesenchymal tumors with smooth muscle differentiation. They are the second most common mesenchymal neoplasms of the GI tract [62], occurring more frequently in the esophagus (10%), colon, and rectum (together 80%); they are rarer in the stomach and the small intestine [63–65]. Data about prevalence are not known, but they are rare, and autopsy studies point to an incidence of 0.006–0.008% of esophageal leiomyomas [66]. Most commonly, they are found incidentally [62]. Depending on the location in which they arise, they can be polypoid or intramural.

Colorectal leiomyomas usually arise from the muscularis mucosae, are more frequently small-sized and pedunculated; rarely, they can appear as ulcerated lesions [62,67]. They are found more often in men (2.4:1 M:F) between the ages of 38 and 85 years, with a median of

62 years, and are located predominantly in the rectum and sigmoid colon [65]. The age of appearance may reflect when patients start to undergo colonoscopies. Rarely, they can be intramural in the colon and rectum [65].

Esophageal leiomyomas arise from the muscularis propria, and are intramural and larger [67]. Esophageal leiomyomas appear more frequently in younger men, with a median age of 30 to 35 years. They are more common in the lower third of the esophagus, are usually larger than colon leiomyomas because of their intramural origin, and they have a median size of 5.3 cm [63]. In a study of 342 patients whose esophagi were completely excised, 27 had leiomyomas, representing an incidence of 7.9%; none of them were clinically detected and more commonly arose from the inner circular layer of the muscularis propria [13].

Grossly, leiomyomas are white, well delimited, and have a firm consistency. Histologically, leiomyomas are composed of well-differentiated fascicles of bland, fusiform cells with elongated nuclei with tapered ends with eosinophilic cytoplasm. The histological features are similar, irrespective of where they arise. Mitotic activity and necrosis are absent. Atypia may be present in symplastic leiomyomas [65]. Leiomyomas stain positively for muscle markers—such as α-SMA, desmin, and h-caldesmon—and do not express S100, CD34, KIT, or DOG1, which is important in the differential diagnosis of other fusiform neoplasms in the GI tract, such as schwannoma, gastrointestinal stromal tumors, and inflammatory fibroid polyps [13].

These are benign neoplasms with no risk of recurrence or metastasis, and enucleation of the lesion is the treatment of choice [65].

The typical morphology can be seen in Figures 12 and 13.

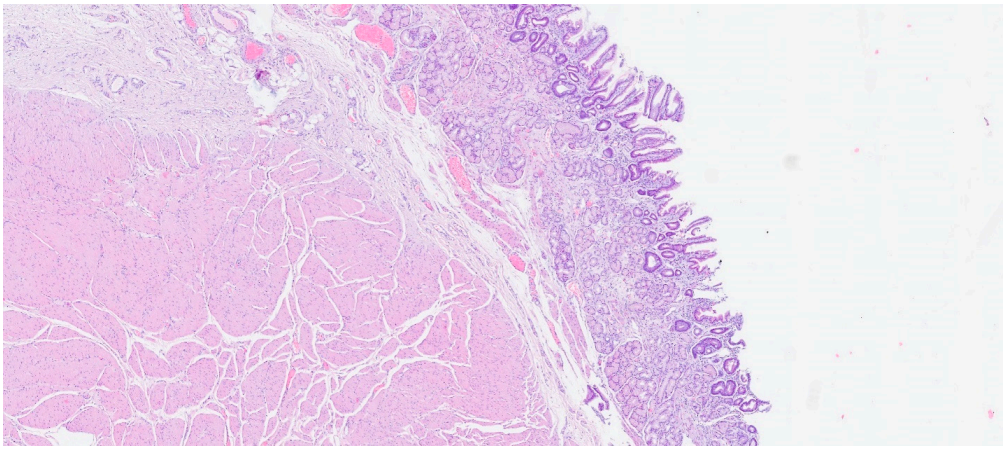

Figure 12. A submucosal leiomyoma of the ampulla of Vater.

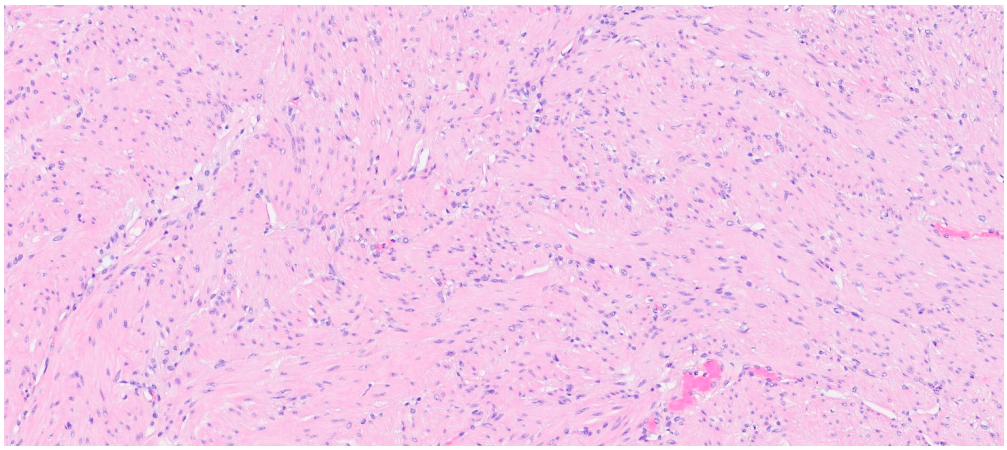

Figure 13. Leiomyoma composed of well-differentiated fascicles of bland, fusiform cells with elongated nuclei with eosinophilic cytoplasm.

9. Leiomyosarcoma

Leiomyosarcoma is a rare, malignant neoplasm with smooth muscle differentiation; in the GI, they are extremely rare. According to the SEER database [62], in a 15-year period (2001–2016) in the United States, a total of 523 patients were diagnosed with GI leiomyosarcoma. In a single institution study, Agaimy et al. [68] found three cases of leiomyosarcomas out of 262 mesenchymal lesions over 12 years.

According to one study, the median age at diagnosis is 58.5–66 years (18–94 years) [63,64]. It is most frequently found in the small intestine (31.7%), followed by the duodenum, the ileum and jejunum, the stomach (28.3%), and the colon (26.4%) [8]. It has an equal incidence in males and females [62].

In the largest study of LMS of the GI, the mean tumor size varied. In the esophagus it was 10.2 $\pm$ 4.5 cm, in the stomach it was 6.45 $\pm$3.7 cm, in the small intestine it was 10.6 cm $\pm$ 6, and in the colorectum it was 6.7 $\pm$ 5 [64]. In a study by Yamamoto et al. [63], where they reported seven leiomyosarcomas of the GI, three were elevated and ulcerated with transmural involvement, two were in the submucosa with ulceration of the overlying mucosa, and two had extramural growth. Grossly, LMS are usually described as lobular masses, and are sometimes polypoid or ulcerated, with a grey, beige, or pink-tan mass [64,68].

Morphologically, they are composed of fascicles of spindle cells with atypia, centrally placed cigar-shaped nuclei, and eosinophilic fibrillary cytoplasm with high mitotic counts. LMS are positive for muscle markers, and α-smooth muscle actin closely followed by muscle-specific actin were reported to have the highest sensitivity (86% and 71%, respectively), these tumors are negative for c-kit and DOG1 [63]; however, desmin shows higher specificity as GISTs may have α-smooth muscle actin staining [65]. Loss of smooth muscle marker expression is associated with a worse prognosis [66,67].

In a study that involved multiple institutions, 407 smooth muscle tumors of the GI were studied, irrespective of whether they were initially diagnosed as leiomyoma or leiomyosarcoma, several pathological features were assessed, and some were found to be linked to a more aggressive course, such as moderate-to-severe atypia, high cellularity, abnormal or lack of differentiation, tumor necrosis mucosal ulceration, lamina propria involvement, and serosal involvement [65]. In another study, where only leiomyosarcomas were considered, tumors $\geq$ 5 cm were associated with shorter survival, and no association was found between the mitotic count and prognosis [63].

Usually, these patients present with unspecific symptoms; thus, around 40% have regional or distant involvement at diagnosis. Yamamoto et al. reported a 14% local recurrence rate and a 43% metastasis rate in their series; it is estimated that between 25 and 50% of patients died because of the disease [63]. In the analysis of the SEER data, the 5-year overall survival was 77.3%, and the cancer-specific survival was 90.3%. The grade and stage of the tumor were the only factors significantly affecting survival in the multivariate analysis [62].

The mainstay treatment for patients with resectable disease is surgery, as it is correlated with a better prognosis [64].

A typical morphology of a leiomyosarcoma can be observed in Figure 14.

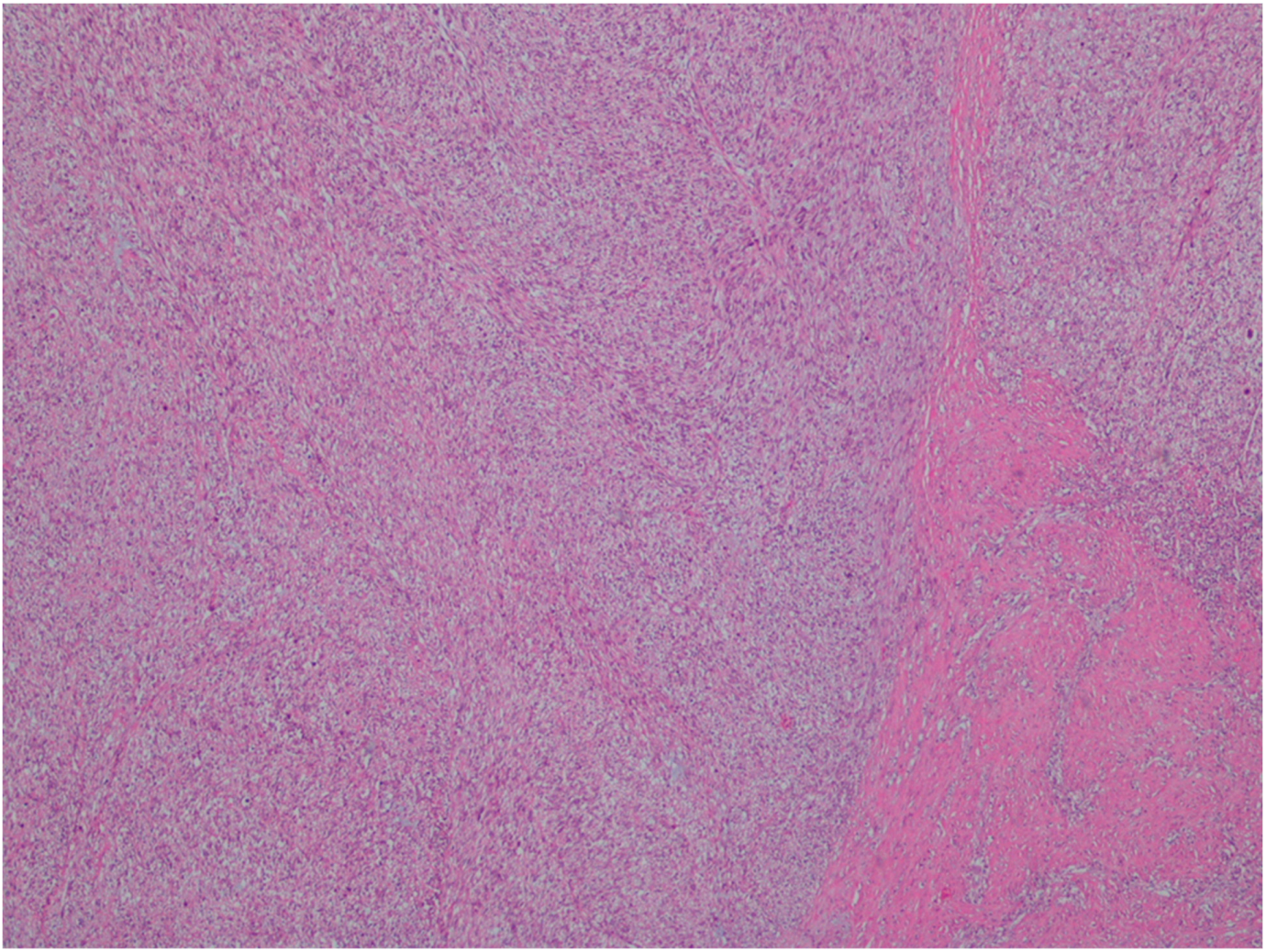

Figure 14. Leiomyosarcoma. When compared to the benign counterpart (leiomyoma), there is more cellular density and nuclear atypia.

10. Hemangioma

Hemangiomas of the GI are uncommon, they can appear as a single or multiple lesions, and occur anywhere throughout the GI tract [13,69]. Far more common are vascular malformations [70,71].

The most common location of hemangiomas is the small intestine [70]. The colorectum is a rare place of appearance and of all hemangiomas located here, about 50% appear in the rectum [13]. In the stomach, vascular malformations are more common than true hemangiomas [71]. There is a wide range of incidence for true hemangiomas, from being congenital to appearing in the eighth decade of life [71].

Clinically, the most common presentation is occult or acute GI bleeding; other presenting symptoms include abdominal pain, bowel obstruction, and perforation, but they can also be incidental. Grossly, the majority appear as intraluminal lesions, but polypoid lesions may occur [70].

Due to its morphological heterogeneity, many different terms have been used to describe hemangiomas, and vascular malformations may correspond to the same entity [71]. A classic morphology is represented in Figure 15.

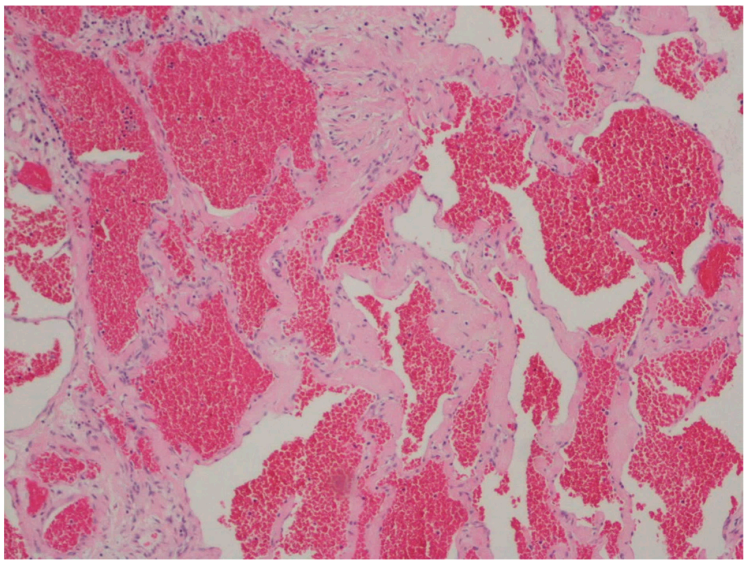

Figure 15. A cavernous hemangioma; notice the large and dilated vessels with thin walls.

11. Lymphangiomas

Lymphangiomas are benign mesenchymal tumors that, rarely, can be found throughout the GI tract, accounting for less than 5% of lymphangiomas [72]. They most commonly appear in the small intestine and less commonly in the colon and esophagus [13]. Usually, they occur in children and young adults and are equally distributed among genders [73].

Clinically, the patients may appear with anemia or acute abdomen. They can also be found incidentally during endoscopy or colonoscopy [74].

It has been suggested that these lesions may be congenital, or arise due to inflammation or trauma [73]. Grossly, they can range from small lesions to large masses [74].

Histologically, they are composed of thin-walled, cystically dilated lymphatic spaces lined by endothelial cells with lymph fluid [73] (see Figure 16). When lymphangiomas are multicentric or extensively infiltrating, this is called lymphangiomatosis [13]. Immunohistochemically, lymphangiomas stain for D2-40 and CD31 and show variable expression of CD34 [71].

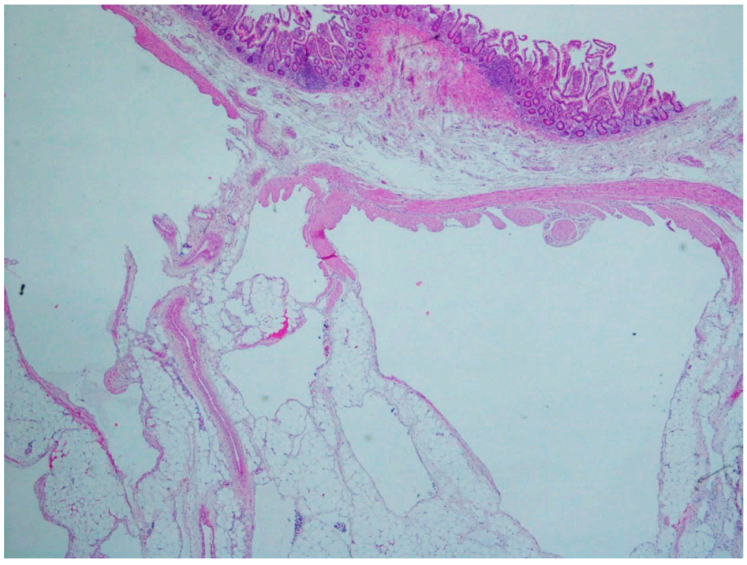

Figure 16. Cystic lesion with spaces lined by a layer of endothelial cells located in the duodenum; notice the normal duodenal mucosa in the upper part of the picture.

12. Kaposi Sarcoma

Kaposi sarcoma (KS) is a vascular neoplasm derived from the lymphatic endothelium that can arise anywhere along the GI tract [13]. There are four different epidemiologic types: classic KS, iatrogenic/immunosuppressive KS, AIDS-related KS, and endemic KS [75].

Human herpesvirus 8 (HHV-8) has been identified as the causative agent. In Europe and the United States, KS usually manifests in the context of immunosuppression, such as post-transplantation or as a complication of AIDS. Between a quarter and half of AIDS patients can have visceral lesions, sometimes without cutaneous manifestations of KS [76–78] and it is frequently asymptomatic [78]. When symptomatic, the most common manifestations are diarrhea, abdominal pain, and GI bleeding [79]. The GI tract is the most common extracutaneous site for Kaposi in AIDS [13,75]. It stands out as the most prevalent gastrointestinal tumor in AIDS cases.

There is a wide age range for KS diagnosis. In a study by Zheng et al. [79], a multi-institutional analysis of 46 cases of KS of the GI was carried out; they found that incidence ranged from 25 to 72 years (median 34 years), with a male predominance.

Although it can involve any part of the GI tract, involvement of the upper tract is more common, especially the stomach, duodenum, and esophagus [78].

Macroscopically, KS in the GI typically presents as red, blue, or brown nodules/mass-like lesions, erythematous lesions, ulcers, and macules [13,79].

Histologically, KS is characterized by a proliferation of blood vessels and spindle cells with minimal atypia organized in vague fascicles, slit-like spaces with extravasated red blood cells with hemosiderin deposition, which is associated with lymphocytic and plasma cell infiltrate. The PAS shows hyaline globules, and there is a variable mitotic activity [75]. Multiple variants of KS have been reported, which may make the diagnosis considerably more difficult [79]. Seven morphologic patterns have been described as occurring in the GI tract, apart from the conventional KS morphology. Two are spindle cell patterns (GIST-like and inflammatory myofibroblastic tumor-like) and five patterns without spindle cells (lymphangioma/lymphangiectatic-like, mucosal hemorrhage/telangiectatic-like, mucosal inflammation-like, granulation tissue-like, and mucosal prolapse-like). The majority of cases were of the non-spindle variant [13].

Endothelial markers such as CD31, CD34, ERG, and D2-40 help ascertain a vascular differentiation of the neoplasm, and the antibody against the latent nuclear antigen 1 (LNA-1); a protein in HHV-8 confirms the diagnosis [75,80].

The differential diagnosis can include bacillary angiomatosis and angiosarcoma.

Enteric KS is usually clinically silent and has low morbidity, and the involvement of the GI tract does not influence survival [13].

13. Angiosarcoma

Angiosarcomas are malignant mesenchymal neoplasms that recapitulate endothelial cell differentiation [81]. Primary angiosarcomas are rare in the GI tract and are reported mainly in the setting of metastatic disease [13,82]. In an extensive review of the literature on primary angiosarcomas of the GI tract, Schizas et al. reported 110 cases published in the English literature [83].

Primary angiosarcomas present with non-specific symptoms such as GI bleeding, abdominal pain, mass or ascites, and acute abdomen, and the interval between the symptoms and the diagnosis is estimated to be greater than six months [83].

Grossly, angiosarcomas can have a variable appearance, from firm greyish-white tissue to markedly hemorrhagic tissue with cystic spaces; they form hemorrhagic, often ulcerating masses. The tumor size ranges from 1.5 to 19.5 cm (median 4–6 cm) [13,83]. Angiosarcomas in the GI tract have a male predominance and more commonly affect adults, with a peak in the seventh decade of life [83]; it can, rarely, affect children. The majority of cases are described in the small (44.5%) and large intestine (35.5%), and less commonly in the stomach (4.5%) and esophagus (2.7%) [83]. Predominantly, angiosarcomas are unifocal,

but multifocality has also been described [83]. Angiosarcomas can arise de novo or can be secondary to radiation, most commonly after ten years.

Cytogenetically, angiosarcomas have complex karyotypes [84], which are usually aneuploid without any characteristic point mutation or gene fusion [13]. There are low levels of alterations in TP53 and the PIK3CA/AKT/mTOR pathway [85].

Recurrent somatic mutations involving genes that regulate the angiogenic signalling pathways and endothelial cell receptors are found in angiosarcomas [13,86], with increased expression of vascular endothelial growth factor and its receptors [87] and mutations in *KDR*, *PTPRB,* and *PLCG1* [88,89]. *KDR* mutations have been reported in both primary and secondary angiosarcomas, and may be a target of specific kinase inhibitors. PLCG1/KDR mutations are mutually exclusive [88]. *MYC* amplification or high expression is seen in less than 10% of sporadic angiosarcomas [88]; it is much more common in secondary angiosarcoma related to breast cancer and lymphedema [88]. However, recent studies have detected *MYC* amplification in almost one-third of primary breast angiosarcomas [90] and 25% of visceral angiosarcomas [91]. Particularly in younger patients, CIC fusions have been described, and the presence of CIC alterations is associated with inferior disease-free survival [88]. Rare mutations have been described in *RAS*, *PIK3CA*, *TP53*, *FLT4*, and *TIE1* [88].

There is a wide variation in morphology, from a well-formed network of vessels to sheets of epithelioid and spindle cells without a clear formation of vessels. The endothelial cells are often atypical. They are high-grade neoplasms with high mitotic activity and coagulative necrosis. The endothelial cells are spindled, hobnailed, or epithelioid, and may form papillary-like projections [13]. In the GI, a predominance of an epithelioid morphology is common [88]. Epithelioid angiosarcomas usually show a solid architecture and atypical epithelioid cells with abundant cytoplasm, mimicking carcinoma, melanoma, or lymphoma [13]. Less commonly, they can appear to be low-grade with well-formed vascular channels with minimally atypical spindled cells [13]. Endothelial markers are essential to establish the vascular nature of the tumor. Angiosarcomas usually show staining for vascular markers, such as CD31, factor VIII [92], FLI1, podoplanin [93], and ERG positivity [94]. The expression of CD34 is variable [13], and as it becomes more poorly differentiated, it is more probable to lose CD34, or for its expression to be decreased. The use of CD31 and CD34 identifies almost all angiosarcomas, even poorly differentiated ones [13]. FLI1 and ERG have a high specificity and sensitivity, although some carcinomas and melanomas may express them [94,95]. In angiosarcomas, especially epithelioid type, expression of keratins may be present [96].

Due to its epithelioid morphology, several differential diagnoses might be considered, including melanoma, sarcomas, and poorly differentiated carcinoma.

No association between angiosarcoma and immunosuppression or HIV positivity has been found [87].

Metastasis at presentation is found in primary angiosarcomas of the small intestine and colon in 44.9% and 53.8% of patients, respectively. The main sites involved are the liver and lungs [83]. Median survival varied between two and three months. The prognosis is unfavorable, with survival usually being below one year [97].

Local disease is treated with surgical resection, chemotherapy, and radiation therapy [13].

14. Glomus Tumor

Glomus tumors are composed of cells developed from the neuromyoarterial apparatus in the glomus body, representing less than 2% of soft tissue tumors [81]. Glomus tumors occur most commonly in the upper extremities in the subungual region. Rare cases can appear in the digestive tract and can be mistaken for neuroendocrine tumors, gastrointestinal stromal tumors, or metastasis [98]. They are rarer than GISTs, with an estimated incidence of one in 100 of that of GISTs [99]. Most glomus tumors are benign but they can exhibit malignant behavior with infiltrative growth and metastasis [100].

In the GI tract, they are most commonly found in the stomach [99] and can be found in the esophageal junction and duodenum. In a series by Miettinen et al. [99], just one out of 32 GI glomus tumor was not in the stomach, but was located in the cecum.

It probably has an equivalent incidence between genders. However, the paper by Miettinen showed a strong female predominance (72%) with a female–male ratio of 1.6:1, and the age of the patients ranged from 19 to 90 years (median age 55 years). Glomus tumors have been found in patients as young as 8 years [100].

The most common presenting symptom is upper GI bleeding, with melena being the most common consequence; other common symptoms are anemia and weakness. The tumor in the cecum mimicked appendicitis. Glomus tumor of the GI tract is typically a single lesion, but 10% of patients have a multifocal disease. Inactivating mutations of the glomulin gene are associated with multiple familial glomus tumors [81].

Grossly, they are reported as being circumscribed and intramural, with sizes varying between 1.3 and 7 cm (median 2.5 cm). The consistency is described as soft to rubbery and sometimes spongy. The color is white to pink and frequent hemorrhage occurs; ulceration of the mucosa is a common finding [99]. Presenting signs are non-specific with GI bleeding and ulcers.

Histologically, they involve the muscularis propria and are similar to the ones found in the soft tissue. Most are multinodular, separated by bands of smooth muscle. Dilated veins are present in the periphery of the lobules and the tumor periphery. A fibrous band of tissue around the tumor is a common finding. Surrounding the tumors is smooth muscle and a fibrous capsule [99]. The cells that make up these neoplasms have a distinct appearance, with a round and uniform shape and sharply defined borders that can be accentuated by PAS or toluidine blue [81]. They are organized in sheets and nests surrounding vascular spaces; cytoplasmatic clearing is a common finding. Mitotic activity is low, with less than five mitosis per 50 HPF. Foci of myxoid and hyaline change are common, especially in the center of the tumor. Vascular space involvement is also a common finding, especially at the periphery of the tumor; but this alone is not associated with metastasis [100].

The cells are positive for vimentin, smooth muscle actin, calponin [99], TLE1 [101], and often for h-caldesmon. Desmin is variable, and S100 and c-kit are absent [102]. Weak staining for synaptophysin is sometimes observed, which is important to keep in mind in the differential diagnosis of neuroendocrine tumor, paraganglioma, leiomyosarcoma, and lymphoma.

Fusions of *CARMN::NOTCH* with the partners *NOTCH1* (3%), *NOTCH2* (52%), and *NOTCH3* (9%) genes have been described in both benign and malignant soft tissue glomus tumors [103]. This has also been confirmed in glomus tumors of the upper GI tract, where it was found at a higher incidence than the glomus tumors of the extremities, with the detection of the fusion transcript *CARMN::NOTCH2* in 88% of cases [98]. In this series, the only two cases that did not have the *CARMN::NOTCH2* had a specific morphology. All the cases with the fusion could be detected by the *NOTCH2* antibody, which was negative for gastrointestinal stromal tumors, neuroendocrine tumors, desmoid tumors, inflammatory fibroid polyps, and leiomyosarcomas [98]. A small subset of angioleiomyomas and myofibromas harbors the same fusion [104]. *BRAF V600E* mutation and *KRAS G12A* mutation have been described in glomus tumors of the soft tissue [105]. In a subset of malignant glomus tumors, BRAF V600E expression has been noted [106]. Recurrent alterations in *ATRX*, *CCND1*, and *CDKN2A* were also described for malignant glomus tumors [107].

Papke et al. studied features associated with adverse outcomes in gastroesophageal glomus tumors. Glomus tumors with cytologic atypia, two or more mitoses per 10 HPF, and tumors 5 cm or bigger should be considered malignant. Complex copy number alterations were found in the malignant glomus tumors but not in the benign [107]. Folpe et al. previously had defined criteria for the classification of atypical and malignant glomus tumors in the soft tissue [108], which included deep location, a size $\geq$ 2 cm, moderate to high nuclear grade with $\geq$5 mitosis/50 HP.

The majority of glomus tumors are benign, and excision is the treatment of choice. A glomus tumor is represented in Figure 17.

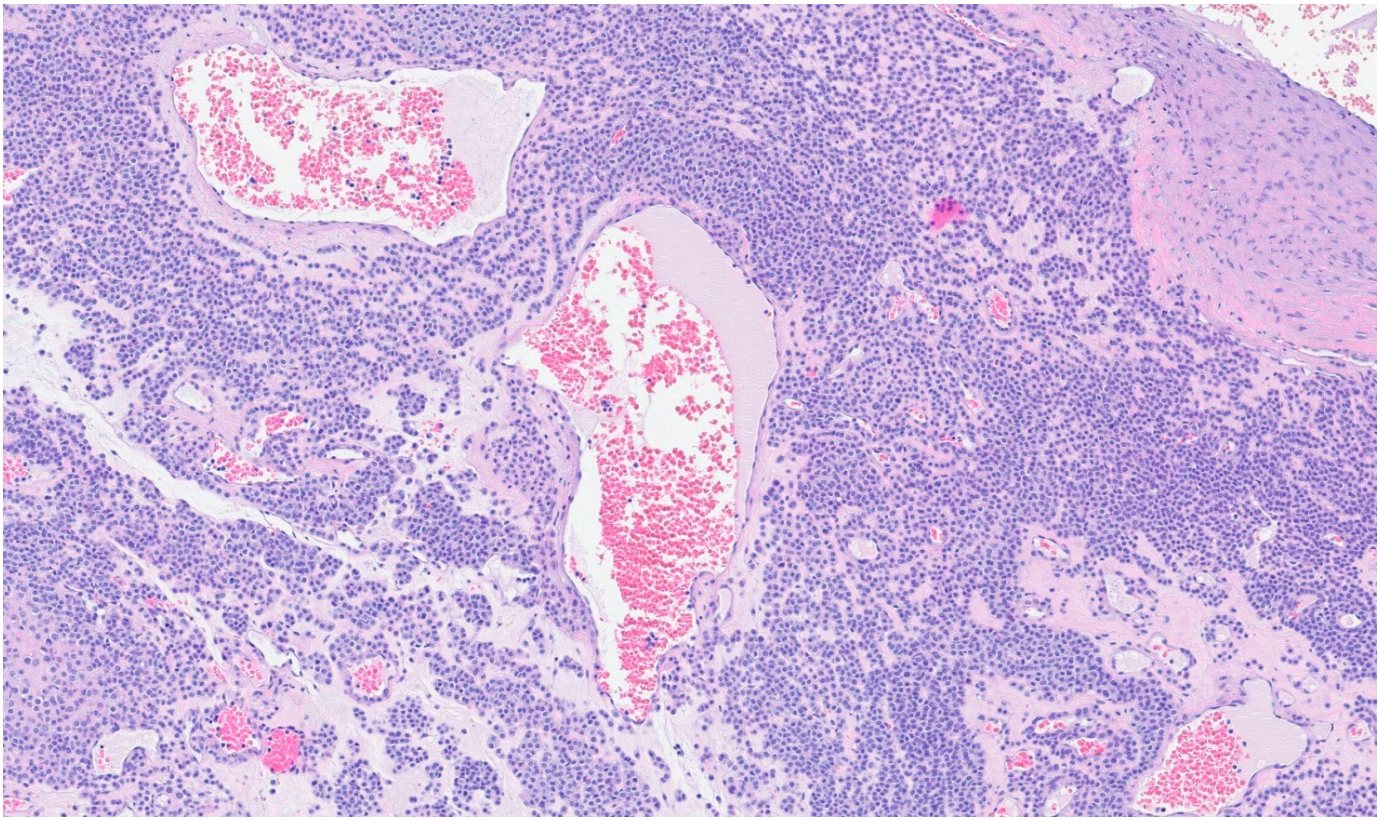

Figure 17. Glomus tumor. There is a proliferation of glomus cells in the perivascular compartment.

15. Schwannoma

Schwannomas are benign lesions originating from the nerve sheath cells that are common in the soft tissue [81].

Regarding the GI tract, they usually form intramural masses and typically arise in the stomach [109]. Most commonly, they are incidental findings, although some may cause GI bleeding or mass-like symptoms [110]. Endoscopy has a pivotal role in the diagnosis and in obtaining tissue for pathology examination [111].

The majority are sporadic, but some cases may be associated with neurofibromatosis type 2; in these cases, they show loss of heterozygosity at *NF2*. The most frequent type of schwannoma in this context is the plexiform type [112].

On gross examination, they are well circumscribed, usually in the submucosa, with a wide size range; cases of lesions measuring up to 7 cm have been described [113].

Histologically, they are similar to the soft tissue counterpart, with spindle cells distributed in hypo- and hypercellular areas. Older lesions may show cystic changes, hemorrhage, and hyaline thick-walled blood vessels. A particular subtype of schwannomas in the GI tract is the reticular subtype. Schwannomas have a peculiar peripheral lymphoid cuff. Immunohistochemistry is consistent with Schwannian differentiation, with S100 and SOX10 positivity (Figures 18 and 19).

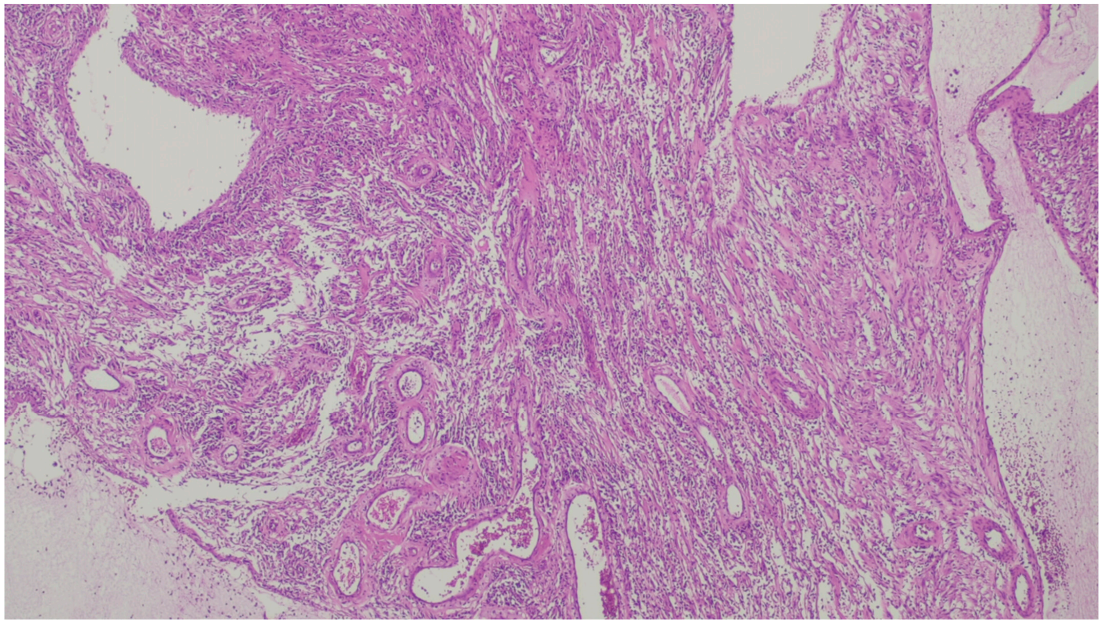

Figure 18. The lesion is composed of spindle cells with dilated blood vessels and hyalinized walls.

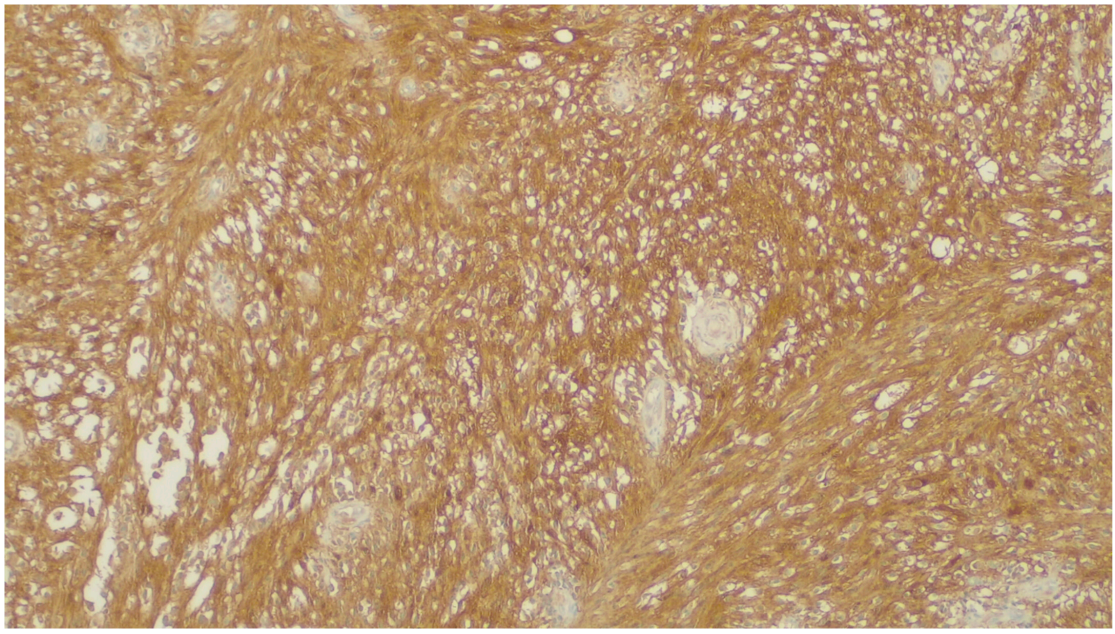

Figure 19. The lesion has a diffuse staining for S100.

16. Granular Cell Tumor

A granular cell tumor is a lesion with neuroectodermal differentiation, composed of cells with epithelioid morphology and granular cytoplasm due to a high quantity of lysosomes [13].

Up to 10% of the lesions arise in the GI tract; the esophagus being the most common location, especially in the lower part [114]. Some cases are described in other locations, namely the large bowel and perianal region [115].

The majority of cases are of small dimensions and, thus, are discovered incidentally. They can appear at any age but are more common around the sixth decade of life [114].

Most cases are sporadic, with some cases associated with neurofibromatosis type 1 [116], Noonan syndrome [117], and LEOPARD syndrome [118]. In syndromic cases, the granular cell tumor usually develops in a non-GI location.

Recent genetic studies have shown mutations (in circa 70% of cases) in *ATP6AP1* and *ATP6AP2*; namely, inactivating mutations inducing an oncogenic driver and generating intracytoplasmatic granules [119].

Grossly, there are small yellowish nodules, usually under 3 cm. Histology exhibits a poorly defined lesion, with monotonous and epithelioid cells with abundant eosinophilic and granular cytoplasm. The cells are arranged into cords and nests, sometimes growing under the squamous epithelium of the esophagus, which shows pseudoepitheliomatous hyperplasia. The nucleus is frequently eccentric, small, and regular, as seen in Figure 20.

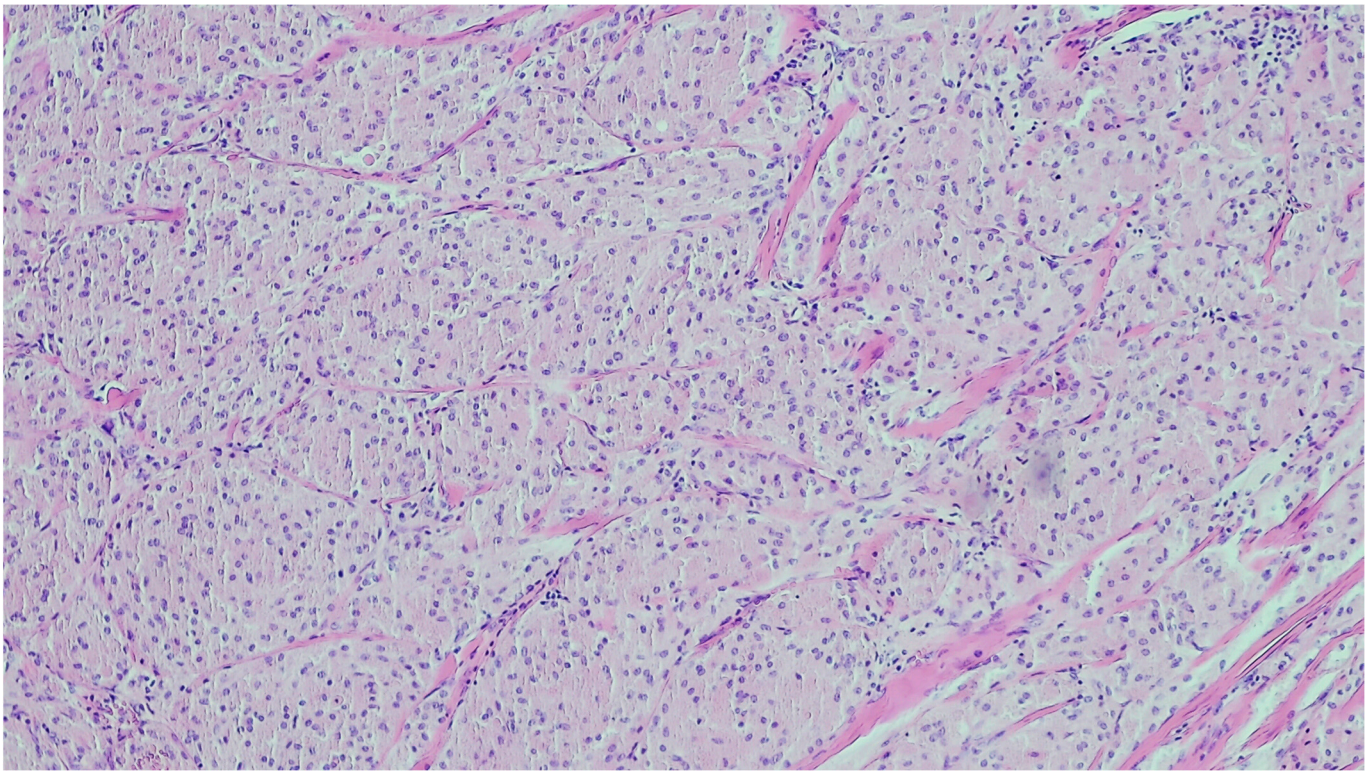

Figure 20. In this case, the lesion has a nested appearance. The cells have a large, eosinophilic, and granular cytoplasm.

Some malignant cases are described, usually presenting with nuclear pleomorphism, mitosis, necrosis, and sometimes sarcomatous transformation [13,81].

Immunohistochemistry shows positivity for S100 and calretinin [13]. Excision is the treatment of choice with good results. There are no established guidelines in malignant cases, but the use of pazopanib monotherapy, a potent oral tyrosine kinase inhibitor, has been reported with success in soft tissue tumors [120,121].

17. Perineurioma

Perineurioma is a benign lesion composed of cells with perineurial differentiation [13].

The majority of lesions are discovered incidentally during colorectal cancer screening, with the rectosigmoid colon being the most common location. Some cases may be identified in the stomach. They have a female predominance and appear in middle-aged adults [122].

Some cases have been associated with *NF1/2* mutations [123] and serrated polyposis with *BRAF V600E* mutations [124].

They appear as small polypoid lesions. On microscopic evaluation, they show expansion of the *lamina propria* by uniform and bland spindle cells, entrapping colonic crypts. Some lesions can focally infiltrate the *muscularis mucosa*, but they are commonly well-defined. The cells have a whorled architecture and sometimes wavy nuclei. Mitosis and necrosis are absent. Immunohistochemistry reveals positivity for EMA, claudin-1, and GLUT1 [13].

18. Ganglioneuroma

The lesion encompasses a benign tumor composed of a mixture of mature ganglion cells, satellite cells, and nerves. In cases of multiple lesions or those associated with a syndrome, the term ganglioneuromatosis is employed [13].

Most cases occur in the large intestine, with a predilection for the left side and rectum. No gender preference is observed, and the age range is wide [125,126].

Usually, they present in colorectal cancer screening as small polypoid lesions (inferior to 2 cm) and can be solitary, multiple, or diffuse. Multiple and diffuse lesions have a strong association with multiple endocrine neoplasia (MEN) type 2B or neurofibromatosis type 1; the latter is less common [127]. Multiple ganglioneuromatosis polyposis is frequently associated with Cowden syndrome, with *PTEN* mutations [128].

Microscopically, the polypoid lesions show an expansion of the *lamina propria* by ganglion and Schwan cells, accompanied by eosinophils, sometimes with cystic colonic glands. Ganglioneuromatosis is characterized by an exuberant proliferation of nerves and ganglion cells. In these cases, the cells may also form nodules and have a transmural involvement. Immunohistochemistry is not contributive and shows neural and Schwann differentiation [13]. An example can be seen in Figure 21.

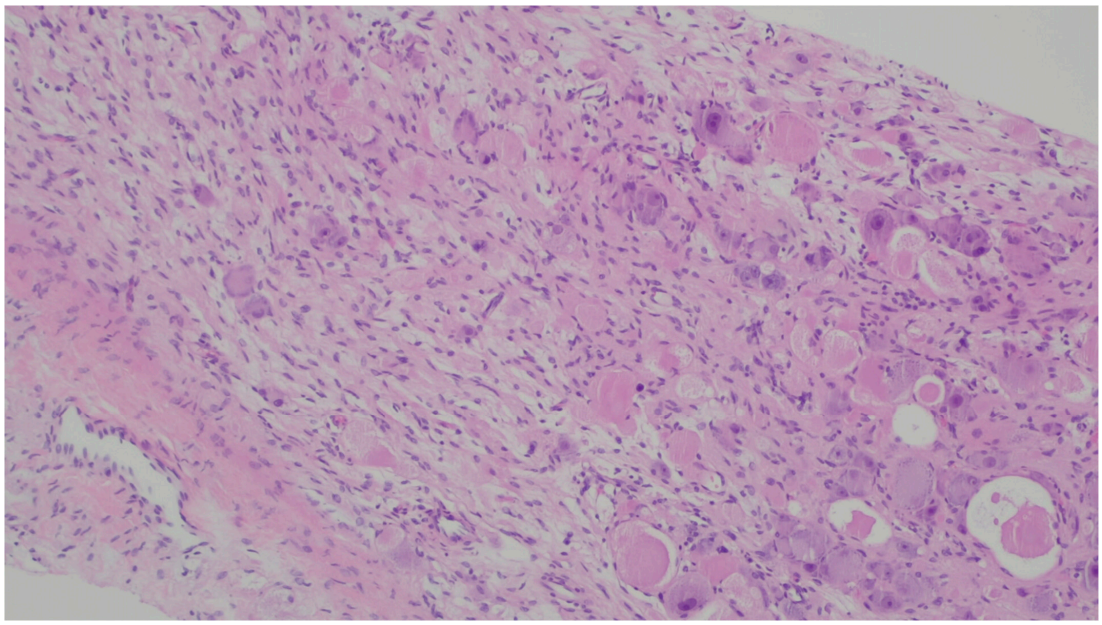

Figure 21. Ganglion cells with eosinophilic cytoplasm dispersed among a background of Schwann cells.

19. PEComa

The family of perivascular epithelioid cell tumors (PEComa) is a group of mesenchymal neoplasms composed of epithelioid cells that express both smooth muscle and melanocytic markers [81]. The term perivascular epithelioid cell was first suggested by Bonetti et al. to describe a cell type with both melanocytic and muscular characteristics [129].

PEComas are a family of tumors encompassing several entities that were once thought to be separate entities but are now considered related, including angiomyolipoma, lung lymphangioleiomyoma, and clear cell sugar tumor of the lung [81].

In patients with tuberous sclerosis, 80% of patients by the age of 10 develop renal angiomyolipomas, which are often multiple or bilateral, and almost 40% of women with this syndrome are affected with lymphangioleiomyomatosis. Other PEComas are usually sporadic [130].

PEComas are genetically heterogeneous [81]. About two-thirds of cases show deletions or mutations of the *TSC2* gene or with a lower incidence *TSC1* gene, leading to its inactivation; this can occur both in sporadic cases and in cases associated with tuberous

sclerosis [131]. Of cases with *TSC2* mutation, two-thirds have *TP53* mutation [132]. *TFE3* rearrangement may occur in 20% of the PEComas [132]. *TFE3* rearrangements and *TSC1/2* inactivation seem to be mutually exclusive [132].

They are rare neoplasms, and less than 100 cases have been reported in the GI tract [133]. The most common locations are the colon, liver, and small intestine. The stomach and other GI organs are rare sites for PEComas to arise [81]. The presenting symptoms are not specific, and include abdominal pain, GI bleeding, and weight loss.

Grossly, PEComas are circumscribed and encapsulated with a cut surface that varies from pale tan to greyish brown. Depending on their size, they can be intramural, and centered in the mucosa and submucosa; or transmural, involving the mesentery. Pedunculated PEComas have also been described [134–136].

In the biggest series conducted to date, Doyle et al. [133], reported a total of 35 cases of GI PEComas. The age at presentation varied between 7 and 70 years, with a median age of 45. The most common location was the colon (54%), more commonly the right colon, followed by the transverse, small bowel (35%), stomach (6%), gallbladder, and omentum (3% each). In this series, the tumor size ranged from 0.8 to 22 cm, with a median of 6.2 cm. In 31 patients, follow-up was available, with a median duration of 36 months. Local recurrence was not reported, but 13 patients developed metastatic disease. Five patients were reported to have died from the disease; the median time from the diagnosis to death was 22 months (ranging from 2–48 months).

There is uncertainty in how to predict the behavior of these neoplasms. They can have a benign behavior, uncertain malignant potential, or a malignant behavior. A risk stratification method has been proposed by Folpe et al. [108,137]. Some histological features have been associated with metastatic disease, such as marked nuclear atypia, diffuse pleomorphism, and $\geq$2 mitoses per 10 HPFs [133]. A tumor size above 6 cm seems to be associated with metastatic potential, but this finding did not reach statistical significance; the presence of atypical mitosis was not associated with metastasis [133].

Histologically, GI PEComas are morphologically similar to PEComas that develop elsewhere in the body. Most have a nested, trabecular, and alveolar architecture, surrounded by a delicate vasculature [81], with frequent perivascular condensation; however, PEComas can have a surprisingly diverse morphologic appearance. The cells are usually epithelioid with round to oval nuclei with a granular eosinophilic cytoplasm; a minority of spindle cells can be seen. Occasional multinucleated giant cells can be present [108]. The mitotic activity usually is low. The subset of PEComas associated with TFE3 translocation can have a striking similarity with alveolar soft part sarcoma, with a pseudoalveolar architecture.

PEComas are characterized by positivity for muscle markers (α-SMA and desmin) and melanocytic markers. HMB-45 is the most sensitive marker, followed by Melan-A, and MiTF as the least sensitive [108]. The epithelioid cells stain more extensively for melanocytic markers than the spindle cell component when present. In the TFE3-rearranged PEComa group, TFE3 expression is achieved by immunohistochemistry [138]. Up to one-third can stain for S100, and rare cells can stain for pancytokeratins and c-kit [108].

Treatment of PEComas with mTOR inhibitors has demonstrated a significant clinical response [139,140].

The PEComa morphology and immunohistochemistry are represented in Figures 22–25.

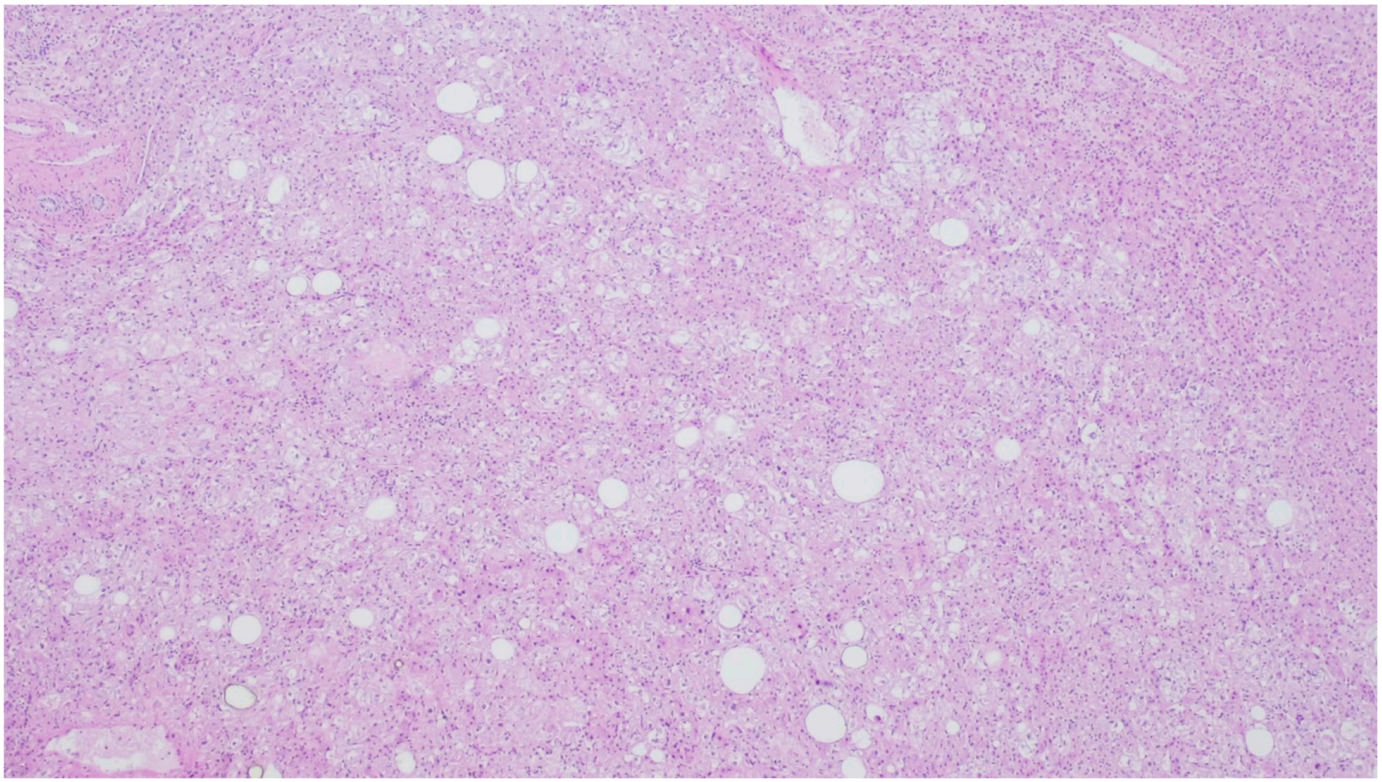

Figure 22. PEComa. The tumor is composed of cells with eosinophil cytoplasm, with evident lipomatous and vascular elements.

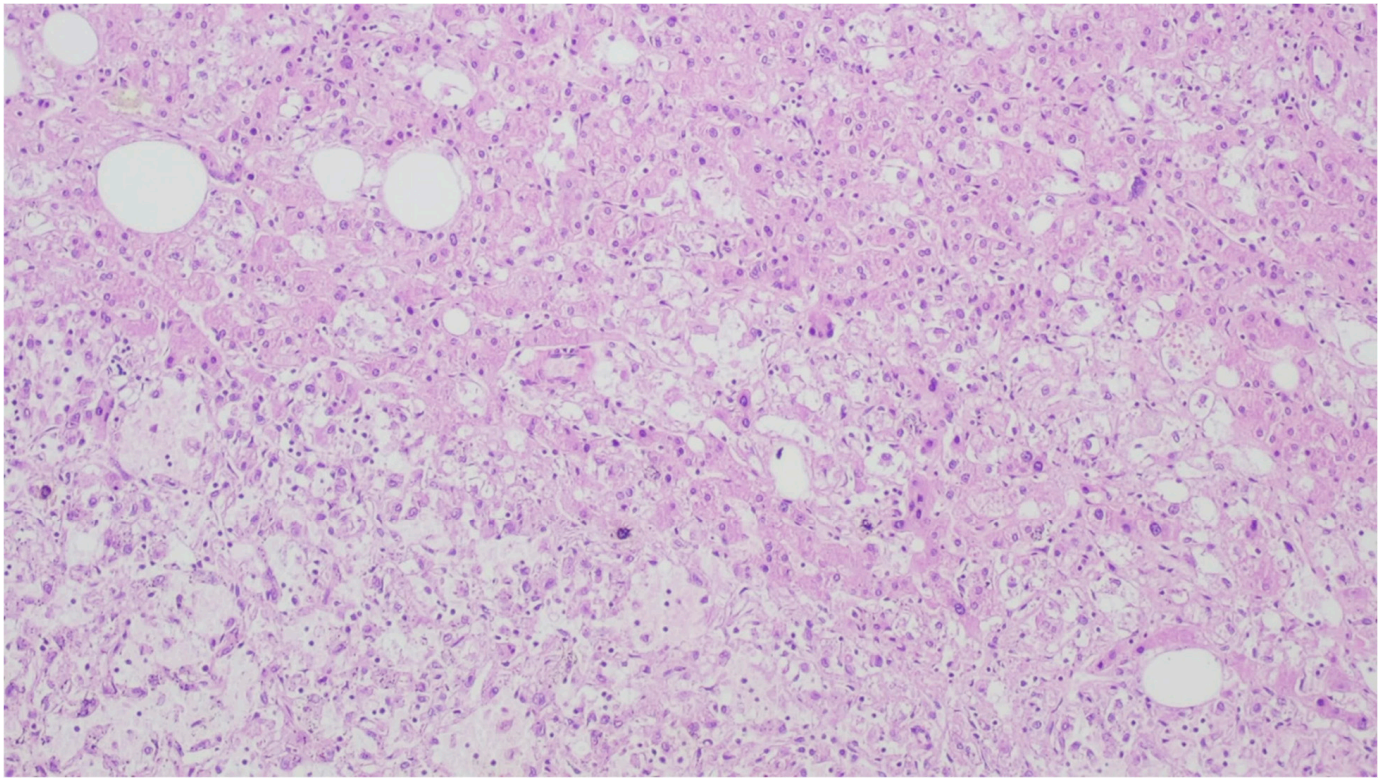

Figure 23. On higher magnification, some cells are mildly pleomorphic; sometimes with clear cytoplasm.

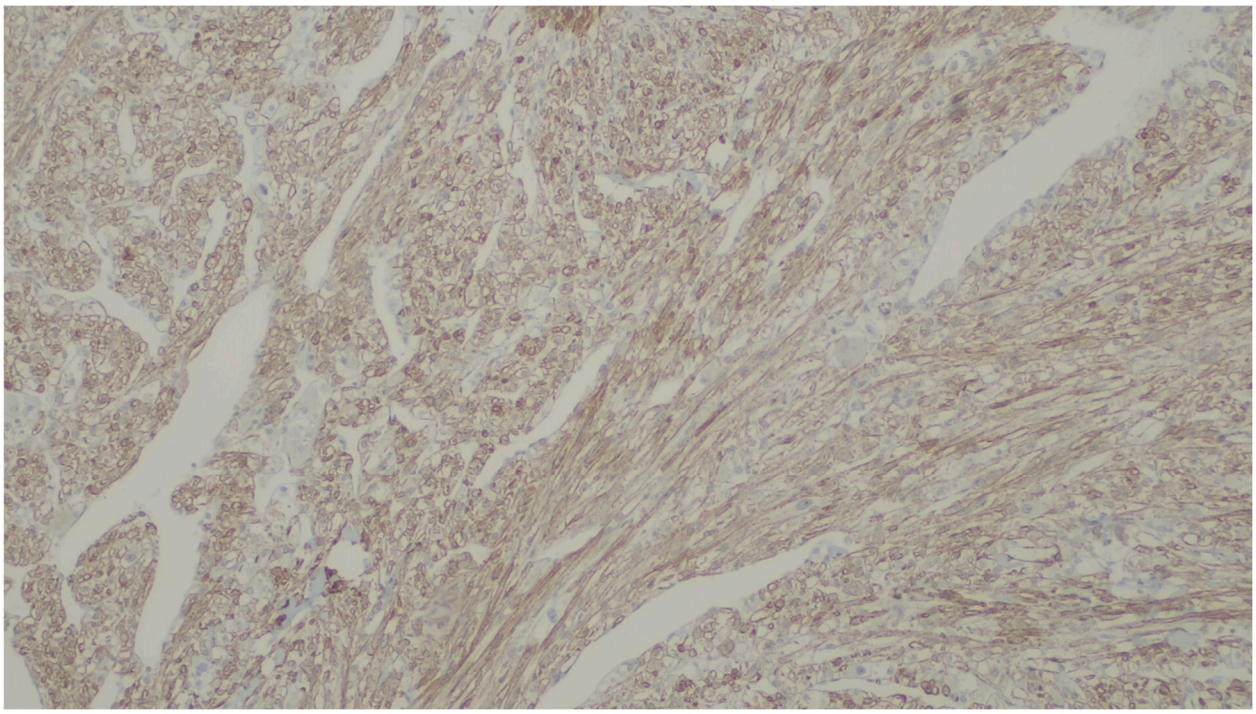

Figure 24. The lesions can have a diffuse staining for muscular markers (α-SMA).

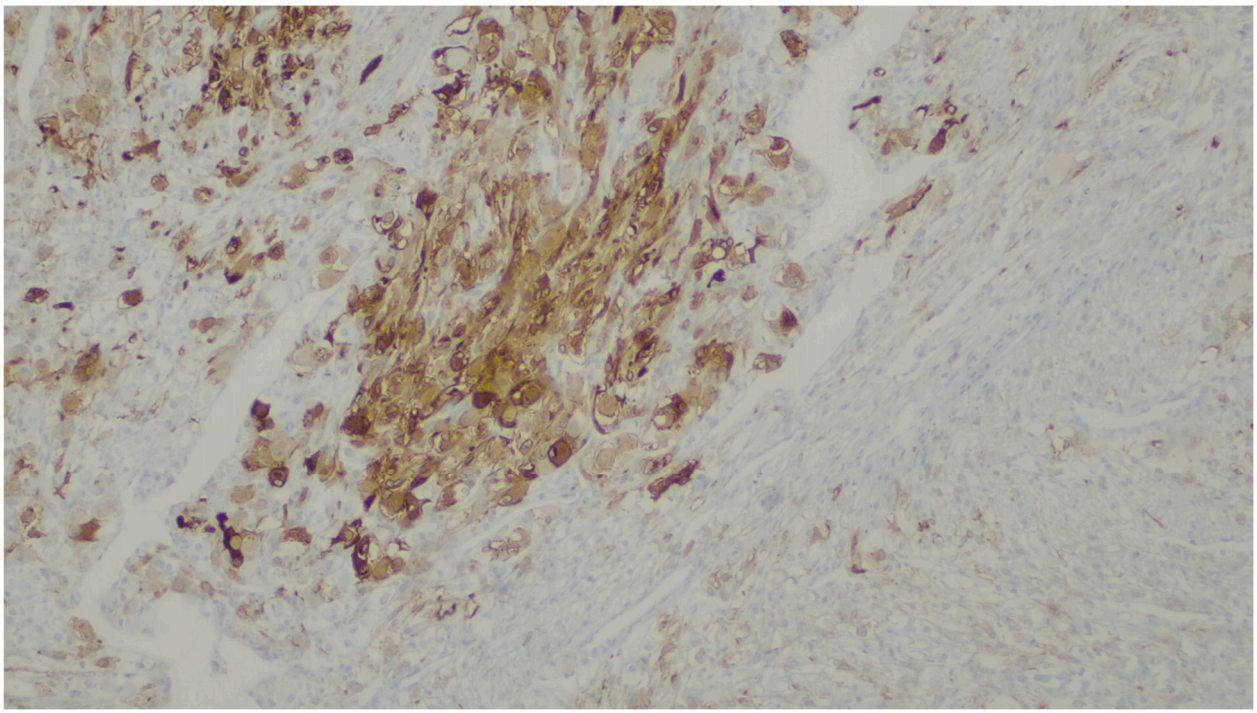

Figure 25. Lesions usually exhibit heterogeneous staining for melanocytic marker (Melan-A).

20. *NUTM1*-Rearranged Colorectal Sarcoma

NUT carcinomas are aggressive tumors that occur typically in the midline region in teens and young adults. They are commonly metastatic at the time of presentation, and are associated with a dismal prognosis [141].

Nuclear protein of the testis (NUT) carcinomas harbor fusions of *NUTM* with *BRD4* (71%) and *BRD3* (14%). Other uncommon partners are *NSD3*, *ZNF532*, and *ZNF592*. The cell of origin is unknown, and the most common locations are the head, neck, and thorax [142].

Rearrangements of *NUTM1* are not limited to NUT carcinomas and have been described in poromas and porocarcinomas [143], embryonal tumors of the central nervous system [144], and undifferentiated sarcomas [145]. Sarcomas with *NUTM1* rearrangements often show fusions involving the *MAX* family genes or *CIC* [146,147].

NUTM1-rearranged sarcoma is considered a distinct entity within the group of *NUTM1*-rearranged tumors. *NUTM1*-rearranged colorectal sarcoma is a recently described neoplasm with predominant spindle cell morphology and variable epithelioid/rhabdoid morphology with an *MXD4::NUTM1* fusion [145]. In a paper by Van Treeck et al. [145], five patients with this rare entity were described. Four out of five patients were female, with age of presentation ranging from 38 to 67 years (median 51 years).

Grossly, the tumors were circumscribed, whorled, white to tan in color, with a size ranging from 2.5 to 20 cm. The tumors presented in the colon and the ileocecal valve region, and four had metastasis at presentation; three had lymph node involvement and one had liver involvement. Morphologically, the lesions were centered in the submucosa, infiltrated the mucosa and the *muscularis propria*, and were described as having three distinctive patterns: intersecting fascicles with uniform cells pattern, a hyalinized/nested pattern, and an epithelioid and rhabdoid pattern. Mitotic activity was low. Immunohistochemically, *NUTM1*-rearranged sarcomas have a nuclear expression of NUT, variable keratin expression and expression of CD117 and DOG1, and retained expression of SMARCB1 and SMARCA4 [148].

GIST, synovial sarcoma, sarcomatoid carcinomas, sarcomatoid mesothelioma, and rhabdoid tumors should be considered in the differential diagnosis. The expression of NUT or *NUTM1* rearrangement is key for the diagnosis [146].

21. Mesenchymal Tumors Associated with *NTRK* Rearrangements

Eight cases of mesenchymal tumors with NTRK1 or NTRK3 rearrangements were described by Atiq et al., who identified three different groups of tumors. One was infantile fibrosarcoma with involvement of the GI tract, another was low-grade spindle cell S100+ and CD34+ neoplasms associated with NTRK1 fusions, and the third was unclassified high-grade spindle-cell sarcomas with NTRK1 fusions [149]. These tumors were morphologically and immunohistochemically different from GISTs, notably by the absence of DOG1 and KIT expression by immunohistochemistry [149].

Previously, two spindle-cell sarcomas with NTRK fusions involving the GI tract had been reported in quadruple wild-type GISTs [150,151].

22. Synovial Sarcoma

Synovial sarcoma is a high-grade lesion that is extremely rare in the GI tract. It has a morphological overlap with its soft tissue counterpart and is characterized by an *SS18::SSX1/2/4* rearrangement [13].

In the GI tract, it is usually described in the stomach, albeit rarer cases were referred to in other locations. It appears in middle-aged to older adults, without gender predilection, and can be a polypoid or an ulcerated lesion [152].

Morphologically, they are monophasic with uniform spindle cells with scarce matrix or biphasic with glandular elements. High-grade sarcoma features with pleomorphic features and mitosis can be present and are associated with a poor prognosis [153].

Immunohistochemistry is similar to the soft tissue counterpart; tumors may have focal positivity for keratins and EMA in monophasic lesions and strong staining in the biphasic version [81]. A recent antibody for SS18/SSX has demonstrated excellent correlation with molecular findings.

Data are scarce, but small lesions with low-grade features seem to have an excellent prognosis after complete excision, while high-grade lesions are associated with aggressive behavior [154].

Figures 26–29 represent synovial sarcoma morphology and molecular features.

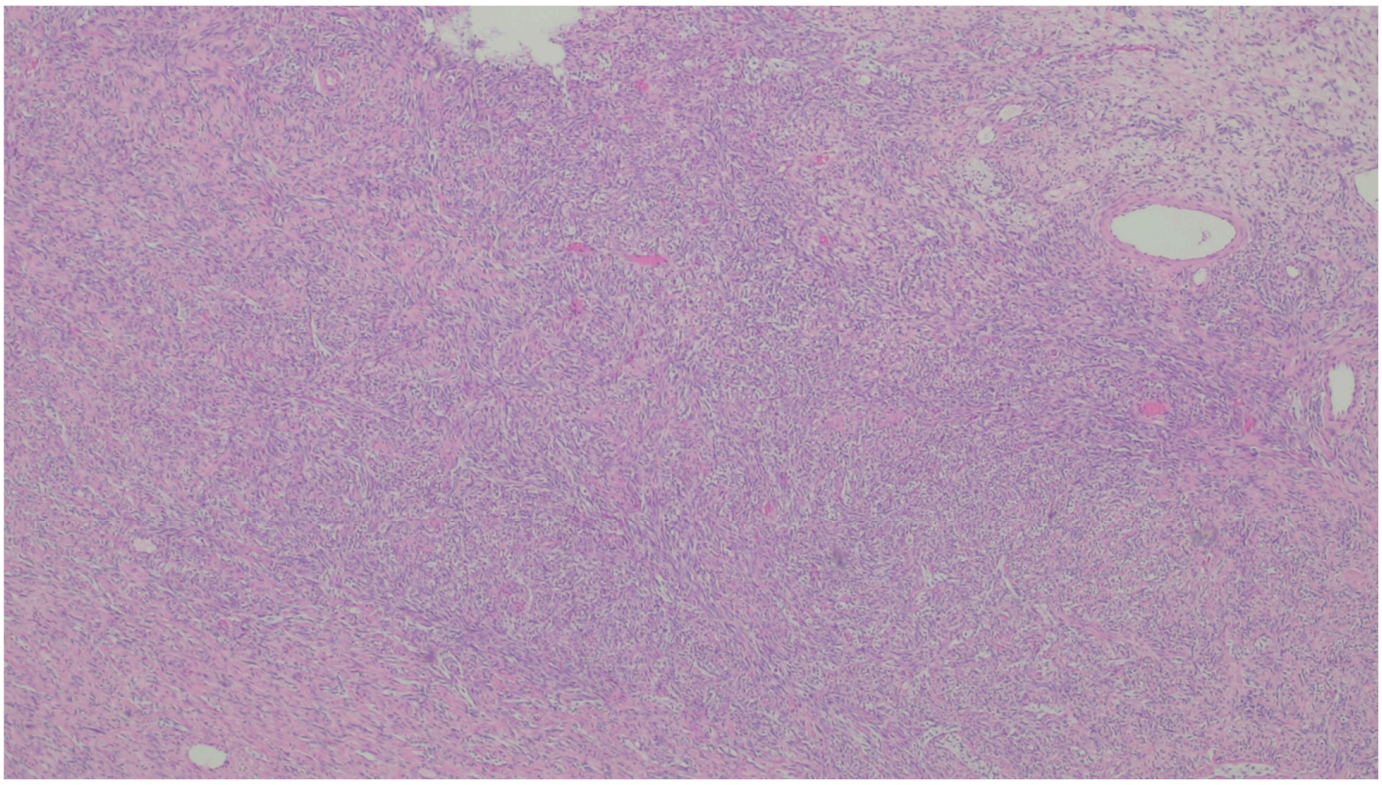

Figure 26. A low-power view showing a dense cellular lesion in a haphazard pattern.

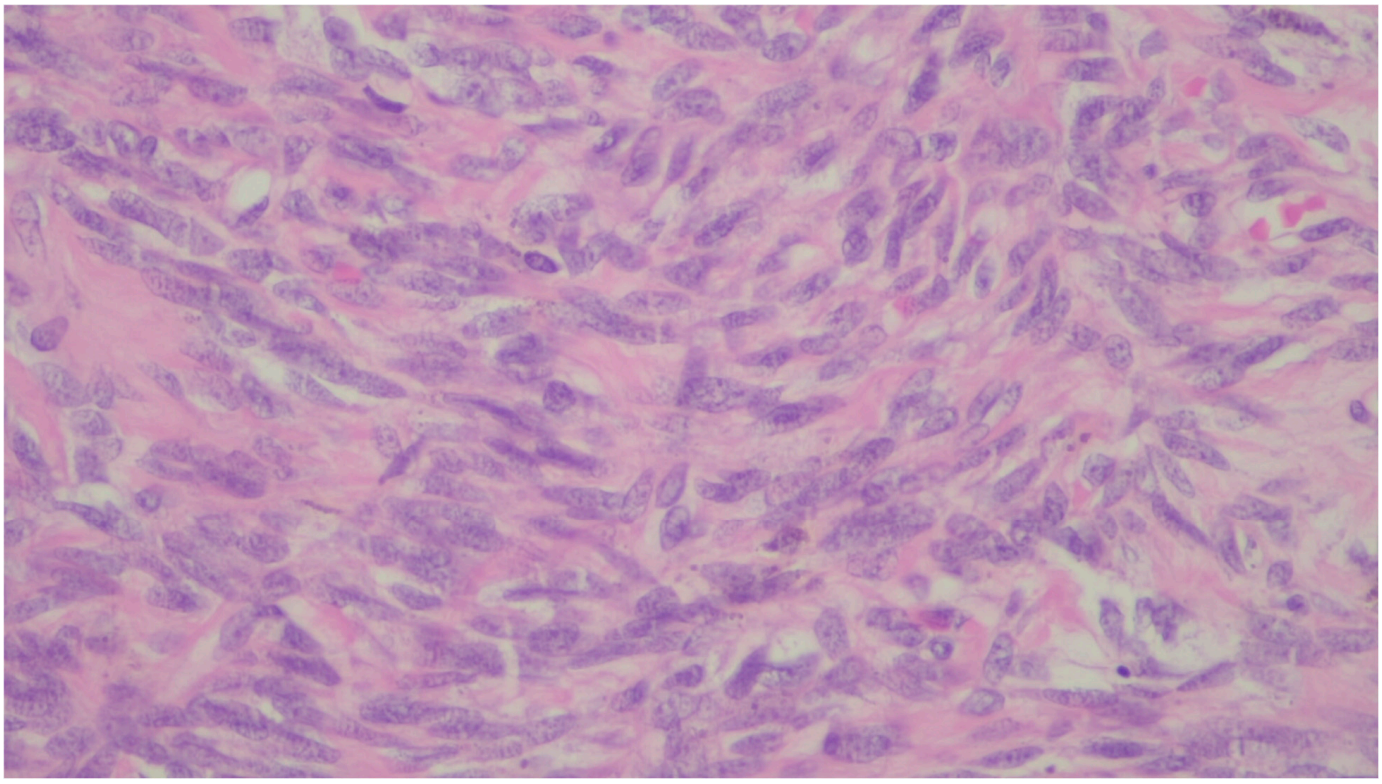

Figure 27. The lesion is composed of spindle cells, somehow monotonous in a fibrous stroma background.

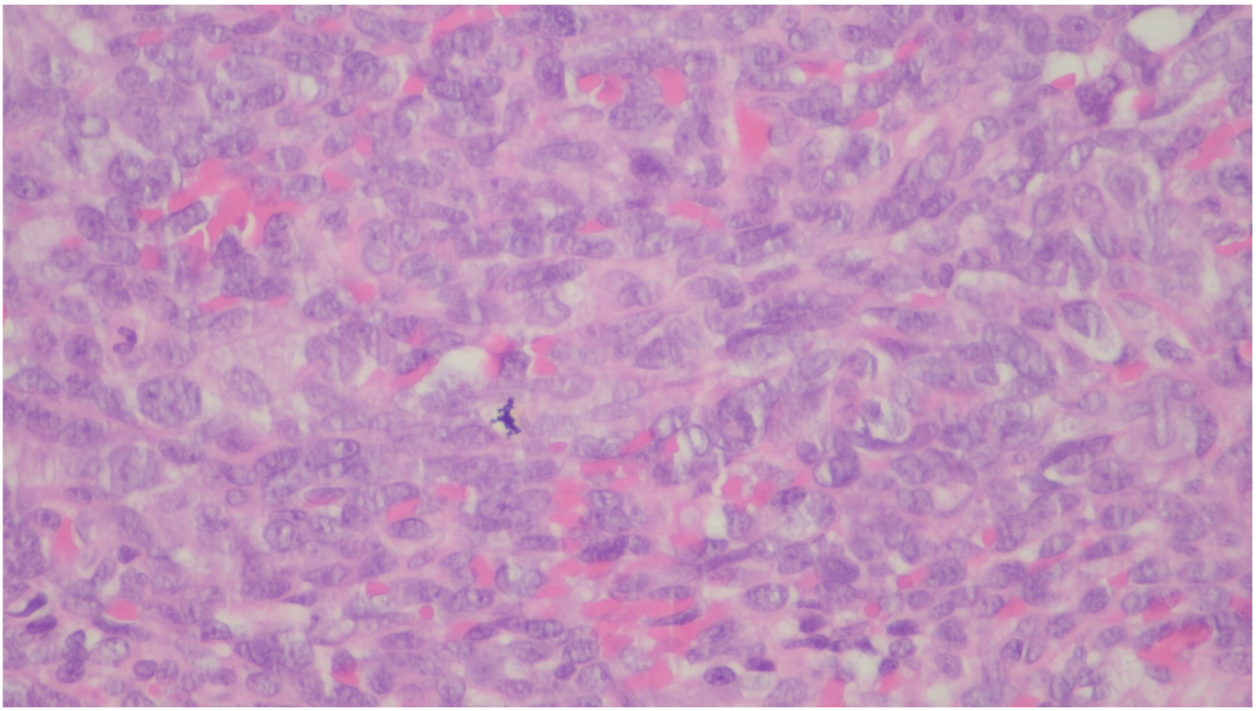

Figure 28. Mitotic activity is evident.

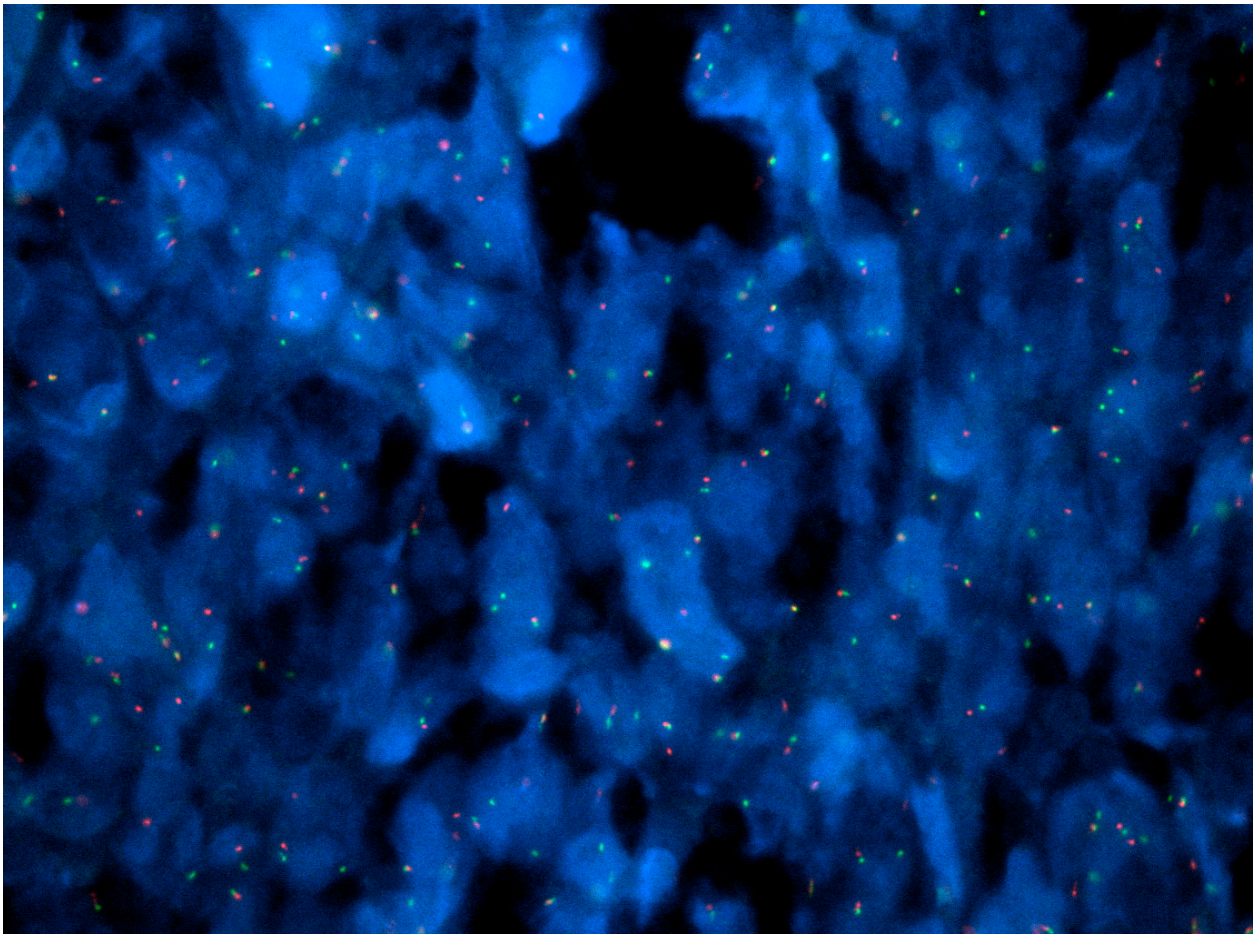

Figure 29. A break-apart FISH probe exhibits the typical translocation, leading to the correct diagnosis.

23. Gastrointestinal Clear Cell Sarcoma/Malignant Gastrointestinal Neuroectodermal Tumor

The last entry of this paper stands for a less common lesion with neuroectodermal differentiation and a gene fusion involving the *ESWR1* gene.

This tumor usually arises in young adults but can appear in older age groups. It is highly aggressive, with a tendency for metastases in the lymph nodes and the liver, which are frequently present at diagnosis. The size of the tumor varies, and tumors of up to 15 cm, polypoid or mural in appearance, with ulceration resembling carcinomas have been reported.

Histology shows a nested or pseudopapillary pattern and sometimes a spindle phenotype. Nuclei are large with prominent nucleoli, and cytoplasm is eosinophilic and, in rare cases, clear. Osteclastic-like giant cells are present in 50% of cases. Mitotic activity is common.

Morphology is represented in Figures 30 and 31.

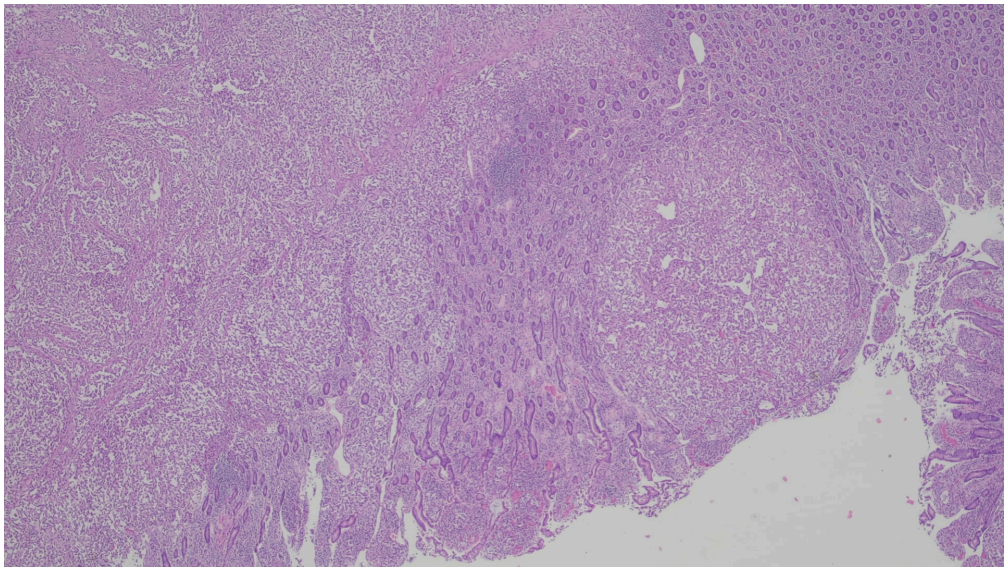

Figure 30. Ileum with ulceration and submucosal involvement by a solid and nested tumor.

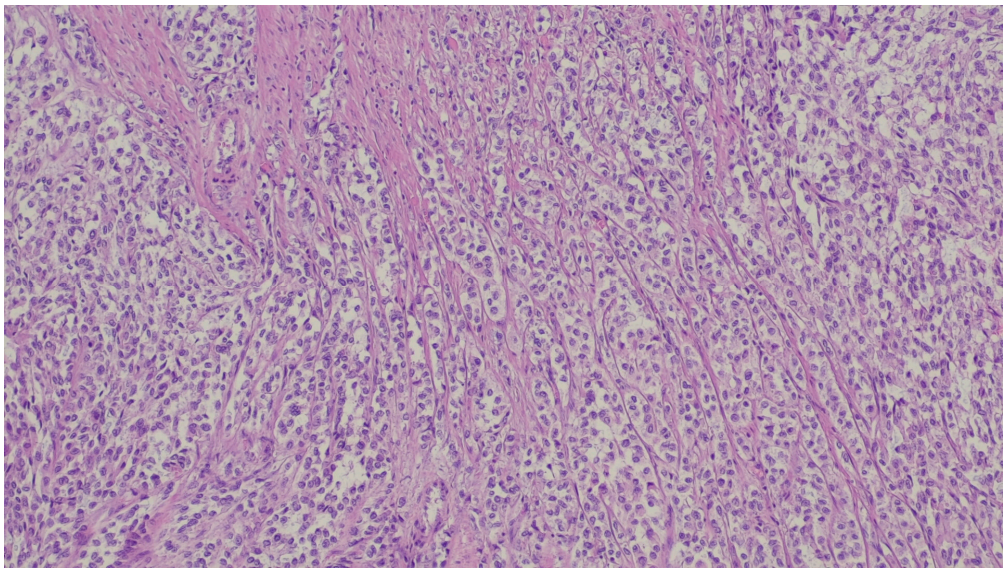

Figure 31. The tumor is composed of cells with clear or eosinophilic cytoplasm and rather monotonous nuclei.

Immunohistochemistry shows a neuroectodermic differentiation with S100 and SOX10 positivity. It is a matter of debate whether the gastrointestinal clear cell sarcoma/and the malignant gastrointestinal neuroectodermal tumor are different tumors or the same tumor with two faces. Tumors with positive melanocytic markers (Melan-A, HMB45, or MiTF) are

considered clear cell sarcomas, while tumors with negativity for these markers are called malignant gastrointestinal neuroectodermal tumors.

Most cases contain *EWSR1* fusions, namely *EWSR1::ATF1* or *EWSR1::CREB1*. This gene alteration allows the differential diagnosis of metastatic melanoma.

A summary of the lesion features is displayed in Table 1.

Table 1. Summary of the lesions, with focus on demographics, site, clinical presentation, histology and relevant immunohistochemistry.

Entity	Demographics	Site	Clinical Presentation	Histology	Immunohistochemistry
Inflammatory myofibroblastic tumor	Children and young adults	Colon and small intestine	Variable, from abdominal pain to obstruction	Uniform, plump spindle cells with pale cytoplasm organized into loose fascicles; colagenous or myxoid stroma with inflammation, mainly lymhocytes and plasma cells	α-SMA, ALK positive
Fibromatosis	30 and 40 years	Mesentery of the small bowel	Abdominal pain	Long fascicles of spindle cells with ovoid nuclei without atypia or necrosis	B-catenin
Solitary fibrous tumor	Adults, with a wide range of ages	Anywhere in the GI tract	Symptoms are unspecific, usually associated with compression and, sometimes, hemorrhage	Ovoid/spindle cells arranged in poorly defined fascicles, supported by thin-walled vessels, dilated in a staghorn pattern	STAT6
Lipoma	Adults	Anywhere in the GI tract	Asymptomatic; some cases in the ileocecal valve with obstruction	Mature adipose tissue	S100, Rb1 is retaned, CD34 is negative
Inflammatory fibroid polyp	Adults	Stomach	Incidental findings; some cases with abdominal pain, hemorrhage, or obstruction	Proliferation of spindle and stellate cells in haphazard distribution in the submucosa	CD34; PDGFRA
Plexiform fibromyxoma	Wide range of age	Antrum and pyloric region	Asymptomatic; some cases with ulceration	Bland spindle cells, supported by a myxoid/fibromyxoid/collagenous stroma and with a rich vascular network of thin-walled vessels in a multinodular pattern	SMA and, occasionally desmin positive. ALK, CD34, keratins, KIT, and DOG1 are negative
Leiomyoma	Wide range of age	Esophagus, colon, and rectum	Asympromatic	Well-differentiated fascicles of bland, fusiform cells with elongated nuclei with tapered ends with eosinophilic cytoplasm	α-SMA, desmin, caldesmon
Leiomyosarcoma	Very rare in the GI tract	Small intestine	Abdominal pain, obstruction	Of fascicles of spindle cells with atypia, centrally placed cigar-shaped nuclei, and eosinophilic fibrillary cytoplasm with high mitotic counts	α-sma, desmin, caldesmon
Hemangioma	Uncommon	Anywhere in the GI tract	Occult or acute GI bleeding	Large and dilated vessels with a thin wall	CD31, CD34 and ERG
Lymphangiomas	Children and young adults	Small intestine	Anemia or acute abdomen	Thin-walled, cystically dilated lymphatic spaces lined by endothelial cells with lymph fluid	D2-40, CD31, CD34
Kaposi sarcoma	25 to 72 years (median 34 years), with a male predominance	Stomach, duodenum, and esophagus	Frequently asymptomatic, when symptomatic, the most common manifestations are diarrhea, abdominal pain, and gi bleeding	Proliferation of blood vessels and spindle cells with minimal atypia organized in vague fascicles, slit-like spaces with extravasated red blood cells with hemosiderin deposition, associated with lymphocytic and plasma cell infiltrate	CD31, CD34, ERG, D2-40, HHV-8
Angiosarcoma	Male predominance and more commonly affect adults with a peak in the seventh decade	Small and large intestine	GI bleeding, abdominal pain, mass or ascites	A wide variation in morphology, from a well-formed network of vessels to sheets of epithelioid and spindle atypical cells without a clear formation of vessels, with necrosis	CD31, CD34, ERG, D2-40
Glomus tumor	Equal predominance, with a paper showing female predominance	Stomach	Upper GI bleeding	Cells with a round and uniform shape and sharply defined borders organized in sheets and nests surrounding vascular spaces	SMA, calponin, TLE1, caldesmon. Variable desmin. S100 and c-kit are absent.
Schwannoma	Marked female predominance	Stomach	Mass-like symptoms	Spindle cells distributed in hypo and hypercellular areas; older lesions may show cystic changes, hemorrhage, and hyaline thick- walled blood vessels	S100, SOX-10
Granular cell tumor	Sixth decade of life	Esophagus	Asymptomatic	Monotonous and epithelioid cells with abundant eosinophilic and granular cytoplasm	S100 and calretinin
Perineurioma	Female predominance and appear in middle-aged adults	Rectosigmoid colon	Asymptomatic, GI bleeding	Show expansion of the *lamina propria* by uniform and bland spindle cells, entrapping colonic cripts	EMA, claudin-1, and GLUT1
Ganglioneuroma	Wide age range	Large intestine, with a predilection for the left side and rectum	They present in colorectal cancer screening as small polypoid lesions (inferior to 2 cm) and can be solitary, multiple, or diffuse; however symptms are not specific	Expansion of the *lamina propria* by ganglion and schwan cells, accompanied by eosinophils, sometimes with cystic colonic glands	S100, SOX10
PEComa	Rare	Colon and small intestine	Symptoms are not specific	Nested, trabecular, and alveolar architecture, surrounded by a delicate vasculature; the cells are usually epithelioid with round to oval nuclei with a granular eosinophilic cytoplasm, but a minority of spindle cells can be seen	α-SMA, desmin, HMB-45 Melan-A, MiTF
***NUTM1*-rearranged colorectal sarcoma**	Teens and young adults; more common in females	Colorectal	Symptoms are not specific	Three distinctive patterns: intersecting fascicles with uniform cells pattern, a hyalinized/nested pattern, and an epithelioid and rhabdoid pattern	nuclear expression of NUT, variable keratin expression and expression of CD117 and DOG1, retained expression of SMARCB1 and SMARCA4

Table 1. *Cont.*

Entity	Demographics	Site	Clinical Presentation	Histology	Immunohistochemistry
Mesenchymal tumors associated with *NTRK* rearrangements	-	-	Symptoms are not specific	Spindle cells tumors	CD34, S100, NTRK
Synovial sarcoma	Middle-aged to older adults	Stomach	Polypoid or an ulcerated lesion	Monophasic with uniform spindle cells with scarce matrix or biphasic with glandular elements	SS18/SSX positivity. Focal positivity for keratins and EMA in monophasic lesions and strong staining in the biphasic version
Gastrointestinal clear cell sarcoma/malignant gastrointestinal neuroectodermal tumor	Young adults	More common in the small intestine, stomach, and colon	Polypoid or mural in appearance, with ulceration resembling carcinomas	Nested or pseudopapillary pattern and sometimes a spindle phenotype	S100, SOX-10, Melan-A, HMB45, MiTF

24. Conclusions

Gastrointestinal sarcomas exhibit significant diversity in their characteristics and morphology. While GIST is the most common mesenchymal tumor of the GI tract, it is crucial to recognize the broader spectrum of entities. Awareness of the various entities and diagnostic options is challenging.

Although morphology remains fundamental, the considerable morphological similarities make it challenging to achieve precise diagnoses based solely on morphology. Acknowledging this, incorporating an updated immunohistochemical panel, and considering molecular markers have become essential components of the diagnosis.

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Abbreviations

a-SMA	Alpha-smooth muscle actin
APC	Adenomatous polyposis coli
FISH	Fluorescence In Situ Hybridization
GI	Gastro intestinal
GIST	Gastrointestinal stromal tumor
IMT	inflammatory myofibroblastic tumor
LMS	Leiomyosarcoma
MEN	Multiple endocrine neoplasia
PEComas	Perivascular epithelioid cell tumors
VM	Vascular Malformations

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