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Review

Mesenchymal tumours of the gastrointestinal tract

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Summary

Mesenchymal tumours represent a heterogenous group of neoplasms encopassing benign, intermediate malignancy, and malignant entities. Sarcomas account for approximately 1% of human malignancies. In consideration of their rarity as well as of intrinsic complexity, diagnostic accuracy represents a major challenge. Traditionally, mesenchymal tumours are regarded as lesions the occurrence of which is mostly limited to somatic soft tissues. However, the occurrence of soft tissue tumours at visceral sites represent a well recognized event, and the GI-tract ranks among the most frequently involved visceral location. There exist entities such as gastrointestinal stromal tumours (GIST) and malignant gastointestinal neuroectodermal tumors that exhibit exquisite tropism for the GI-tract. This review will focus also on other relevant clinico-pathologic entities in which occurrence at visceral location is not at all negligible.

Key words: mesenchymal tumours, sarcoma, gastrointestinal tract, GIST, rare tumours

Introduction

Mesenchymal tumours represent a heterogenous group of neoplasm that include malignant, intermediate malignancy, and benign entities. Sarcomas are extremely rare, accounting for only 1% of malignancies in adults and up to 10-15% of malignancies in the paediatric population. They are characterised by a global incidence of 30-50 cases per million person-years and show a wide anatomic distribution. Rarely, mesenchymal lesions may occur in the gastrointestinal (GI) tract. Some of these entities occur almost exclusively in the GI tract whereas other subtypes, when located in the GI tract, may assume distinct morphological features. The majority of sarcomas of the GI tract are represented by gastrointestinal stromal tumours (GISTs), which are the most common mesenchymal tumours in the stomach as well as in the small bowel.

Benign soft tissue neoplasms show an incidence 100-fold higher than malignant ones. This group includes very common entities such as visceral lipomas, leiomyomas and haemangiomas, but also extremely rare entities such as glomus tumour and plexiform fibromyxoma. Importantly, both rarity and heterogeneity contribute to limit diagnostic accuracy. The aim of this review is to describe the clinical and pathologic features of the most common mesenchymal tumours occurring in the GI tract, focusing on the application of immunohistochemistry and, when indicated, of molecular genetics to improve diagnostic accuracy and consequently promote the most appropriate therapeutic approach [1,2].

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Conflict of interest
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Gastrointestinal Stromal Tumours (GIST)

GIST represents a distinctive mesenchymal neoplasm sharing immunomorphologic features with the interstitial cell of Cajal. It exhibits an exclusive tropism for the GI tract. In general GIST shows no sex predilection with a peak incidence between the 5th and 6th decades, although it may occur at any age. The estimated annual incidence ranges from 11 to 15 cases per million people, and approximately 80% of cases harbour activating mutation of *KIT* and *PDGFRA* [3]. Paediatric GISTs represent a clinically as well as a molecularly distinct group, most often featuring succinate dehydrogenase (SDH) genetic aberrations. Interestingly, as demonstrated by both surgical and autoptic series, submillimetric gastric GISTs (so-called microGISTs) are found in approximately 20% of the general population [3]. Notably, the vast majority of these lesions do not progress into clinically meaningful lesions, but undergo instead regressive changes and calcification [4]. Notably, owing to its molecular characteristics GIST represents a still unsurpassed model of molecular targeted therapy of solid tumours.

The most common locations from which GIST may arise are the stomach (50-60%), followed by the small intestine (20-30%), the large bowel (5%) and the oesophagus (5%). More rarely, GISTs primitive of the peritoneum are reported, although most often they represent pedunculated masses detached from the outer visceral wall. Important prognostic factors are tumour size, mitotic activity and anatomic site, which are the basis for the prediction of risk of aggressive biologic behaviour. Moreover, the risk of abdominal dissemination is dramatically increased by intraoperative tumour rupture (up to 90%). Importantly, all the aforementioned features have been incorporated into various risk assessment schemes [5-7].

Localised disease is principally treated surgically, with the addition of imatinib as adjuvant therapy in high-risk patients. Advanced and metastatic disease currently requires a therapy with three consecutive lines of receptor tyrosine kinase (RTK) inhibitors (imatinib, sunitinib, and regorafenib) all directed against the action of mutant *KIT* and *PDGFRA*. Importantly, the mutational status of these genes predicts response to RTK inhibitors and assumes prognostic value [8].

SDH-deficient GIST represents a clinically and pathologically distinct subgroup. It often shows propensity to arise from the stomach, to occur in children and young adults and, outside the context of Carney-Stratakis syndrome, exhbits marked female predominance. Compared to the classic form of GIST, it shows a higher risk of loco-regional lymph nodes spreading, even though the clinical behaviour remains distinctively indolent [9]. On the other hand, NF-1 associated GISTs are typically multicentric, most often arise from the small bowel, and also have a rather indolent course [10].

Grossly, localised GIST presents as a well circumscribed mass of variable size with the cut surface frequently showing foci of haemorrhage. On the other hand, advanced disease often presents as a larger lesion associated with multiple smaller peritoneal nodules.

On histology, based on morphology, GISTs can be categorised into three general groups: spindle cell (70%), epithelioid (20%), and mixed spindle and epithelioid cell type (10%) [3].

Spindle cell GIST is composed of uniformly eosinophilic spindle cells with indistinct cell borders organized in short intersecting fascicles (Fig. 1). The neoplastic cells have light eosinophilic cytoplasm, often with indistinct cell borders. Nuclei tend to be oval and uniform in appearance, often with vesicular chromatin. A peculiar feature, most often observed in gastric neoplasms, is represented by the presence of striking juxtanuclear cytoplasmic vacuoles. The presence of nuclear palisading is seen in a minority of cases and, as it is frequently observed in both smooth muscle and neural tumours, may represent a potentially misleading feature. Microcystic stromal degeneration, fibrosis as well as stromal haemorrhage may represent a prominent finding in some cases.

Epithelioid GIST is composed of cells exhibiting abundant eosinophilic or clear cytoplasm (Fig. 2). Nuclei tend to be round-to-ovoid and uniform. In comparison with spindle cell GIST, tumour cells tend to exhibit a nested pattern of growth. Some cases may exhibit a

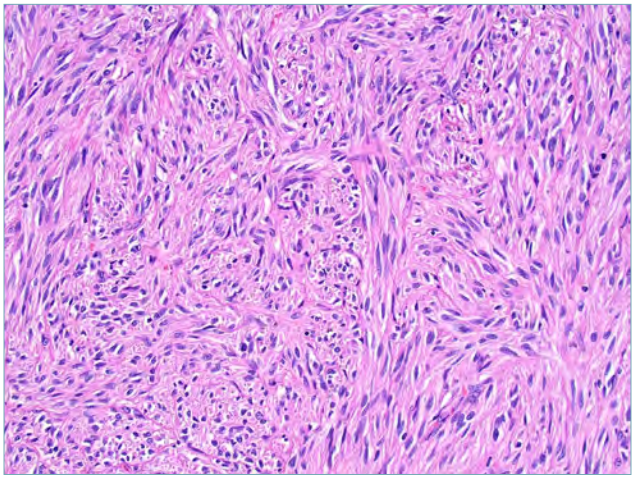

Figure 1. Spindle cell GIST. The neoplasm is composed of short fascicles of uniform spindle cells, with oval nuclei, eosinophilic cytoplasm and poorly circumscribed borders.

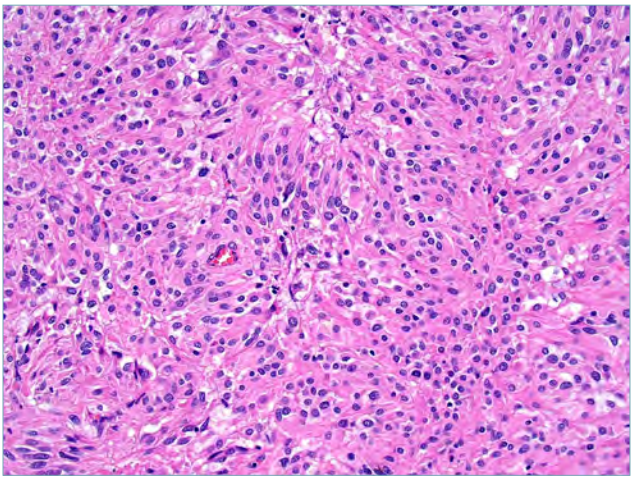

Figure 2. Epithelioid GIST. The neoplasm shows round, epithelioid cells with oval shaped nuclei and eosinophilic to clear cytoplasm. The growth pattern is usually described as nested.

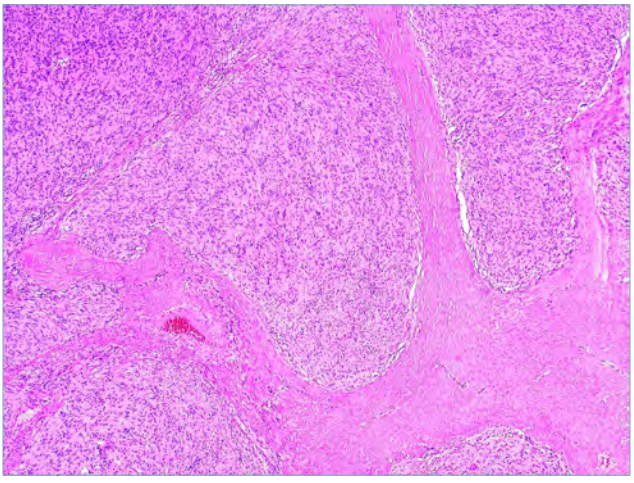

Figure 3. SDH-deficient GIST. This category of GIST shows a typical multinodular pattern of growth.

striking "plasmacytoid" appearance. Epithelioid GIST arises most often in the stomach and are frequently associated with PDGFRA gene mutations [3,11]. Mixed cell type GIST may feature abrupt transition between spindle cell and epithelioid areas or as an alternative the two cell types may be intermingled.

In approximately 10-20% of cases (almost exclusively in the small bowel), hyaline or fibrillary brightly eosinophilic structures known as "skeinoid fibres" can be seen. These structures appear to be composed of nodular tangles of collagen and, typically, exhibit PAS positivity. GIST arising in the small bowel also relatively often may feature a nesting, paraganglioma-like growth pattern. Prominent myxoid change can be seen rarely. Nuclear pleomorphism is not a typical feature of GIST, although it can be observed in approximately 2% of cases. Abrupt morphologic progression to high-grade pleomorphic sarcoma can also be rarely observed (so called dedifferentiated GIST) [12].

SDH-deficient GIST not only represents a clinically distinctive entity, but also shows relatively peculiar morphologic features. A distinctive multinodular pattern of growth is often seen associated with a predominantly epithelioid morphology (Fig. 3) [13].

Even if there are cases in which mitotic activity is remarkably high, in most GIST it tends to be low. In fact, mitotic count (which represents a major prognostic determinant) is assessed on 5 mm^2. The use of mm^2 instead of High-Power Fields (HPF) has the advantage of overcoming inconsistencies due to the use of microscope with variable aperture of the oculars.

Not infrequently pathologists are confronted with biopsies originating from post-treatment GIST. Depending on the level of response to RTKs inhibitors variable amounts of viable cells can be seen and relatively often most of the tissue can be merely represented by diffusely hyalinised fibrotic tissue.

In consideration of the current clinical as well as therapeutic implications immunophenotypic analysis has gained a major diagnostic role. Most cases are KIT (CD117) immunoreactive (Fig. 4A), even if has to be recognized that there are lesions with typical cytoarchitectural features of GIST lacking KIT expression. This phenomenon occurs in 5-7% of cases overall and in up to 18% of gastric GIST. A significant proportion of KIT-negative cases contains mutations of the *PDGFRA* gene and tends to exhibit an epithelioid morphology [11]. In this cases expression of PDGFRA is commonly seen. The pattern of KIT expression is usually cytoplasmic and diffuse, however, up to half of cases will also show a dot-like accentuation of the staining. More rarely a dot-like pattern is seen in the absence of diffuse cytoplasmic staining. Approximately 50% of KIT negative GIST actually express DOG1 (anoctamine-1) (Fig. 4B)[14,15]. In addition to KIT and DOG1, GIST frequently expresses CD34 in 60-70% of cases, smooth muscle actin in 30% of cases. Desmin and cytokeratin can be seen in less than 2% of cases. SDHA and SDHB immunostaining is currently regarded as extremely helpful in recognizing SDH-deficient GIST. In fact, whatever the mutations of *SDH* subunits loss of SDHB expression is seen (Fig. 5) [16]. On the other hand, loss of SDHA predict the presence of mutations in the *SDHA* gene. Following therapy with TRK inhibitors non-canonical immunophenotypes can be observed, such as diffuse

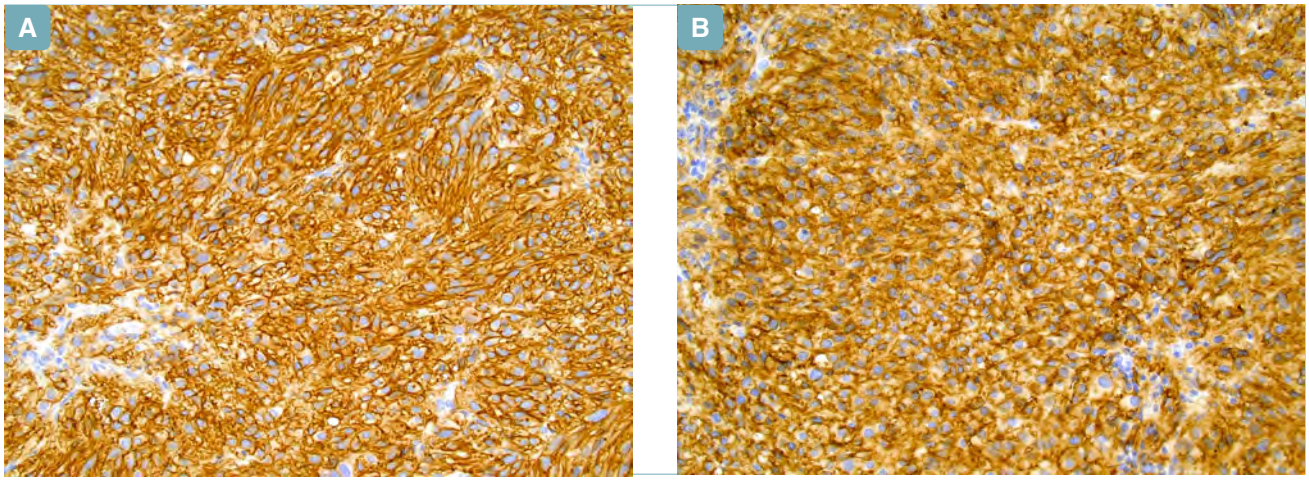

Figure 4. GIST. Diffuse cytoplasmatic immunopositivity for CD117 (A) and DOG1 (B) is usually observed.

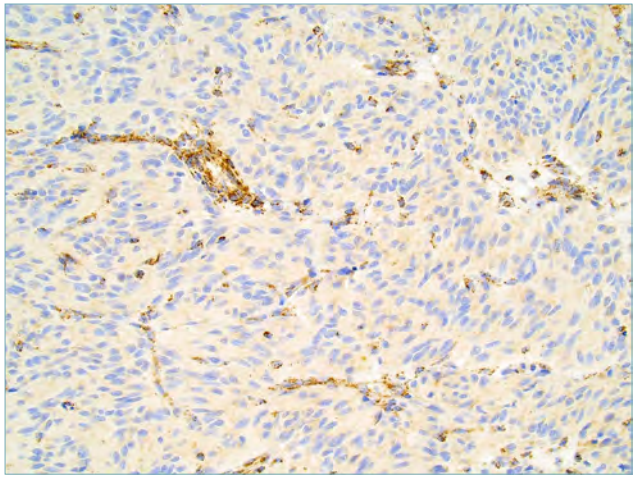

Figure 5. SDH-deficient GIST. In this variant of GIST, the loss of expression of proteins forming the SDH complex (SDHB) is observed. Note the positive built-in control represented by lymphocytes and endothelial cells.

expression of myogenic or epithelial differentiation markers [12].

From a genetic standpoint, GIST represents a relatively heterogeneous and complex group of lesions. Gain-of-function mutations of the oncogenes located on chromosome 4 (4q12) encoding for the type III receptor tyrosine kinases KIT and PDGFRA can be found in approximately 80% of cases. With exceedingly rare exceptions they are mutually exclusive and result in the constitutive activation of either KIT or PDGFRA [17]. Normally, KIT and PDGFRA, are activated by binding of their respective ligands, i.e., stem-cell factor (Steel factor) and platelet-derived growth factor A. Downstream oncogenic signalling for both KIT and PDGFRA involves the RAS/MAPK and the PI3K/AKT/mTOR pathways. Mutations can be deletions, insertions and missense mutations involving exon 11 of the KIT gene (encoding for the juxtamembrane domain of the KIT receptor) in approximately 70% of GIST; exon 9 of *KIT* (encoding for the extracellular domain of the receptor) in less than 10%; exon 13 and 17 of *KIT* (encoding for the intracellular ATP-binding pocket and activation loop domains, respectively) in a small subset of cases. Approximately 10% of GIST harbour *PDGFRA* gene mutations involving exons 12, 14 and 18, with 70% being represented by the exon 18 D842V mutation. The D842V mutation is known for making GIST primarily resistant to available RTK inhibitors. However, the recently approved avapritinib seems to be effective also on this type of mutation.

Approximately 10-15% of GIST is wild type for both *KIT* and *PDGFRA* [18]. They represent a family of tumours with distinctive molecular pathogenesis and, to some extent, different natural histories. Their classification is rapidly evolving as of today, and one may identify: 1) SDH deficient GIST; 2) NF1-related GIST; 3) others, including those with the *BRAF* V600E mutations. Approximately one half of wild type GIST (WT GIST) are marked by alterations involving the SDH complex, which plays a key role in the mitochondrial respiratory cell function [9]. A group of them includes “paediatric” GIST and can be associated with the Carney triad that, when full blown, is characterised by the concomitant occurrence of GIST, pulmonary chondromas and paragangliomas. On the other hand, a group of SDH-deficient GIST carries mutations of the SDHA, SDHB or

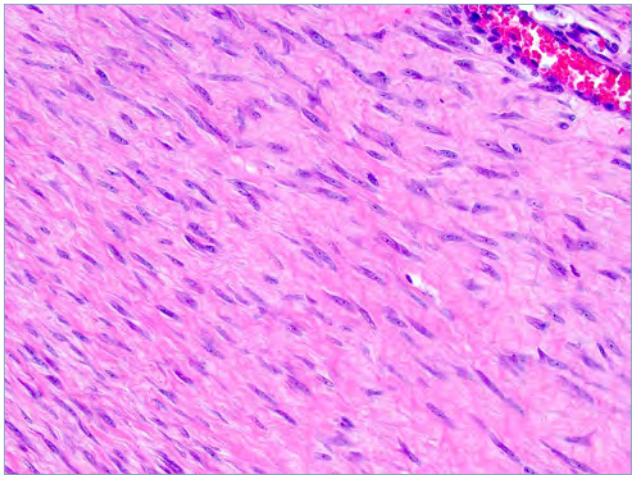

Figure 6. Desmoid fibromatosis. This tumour is composed of long fascicles of uniform, cytologically bland spindle cells, set in a collagenous background.

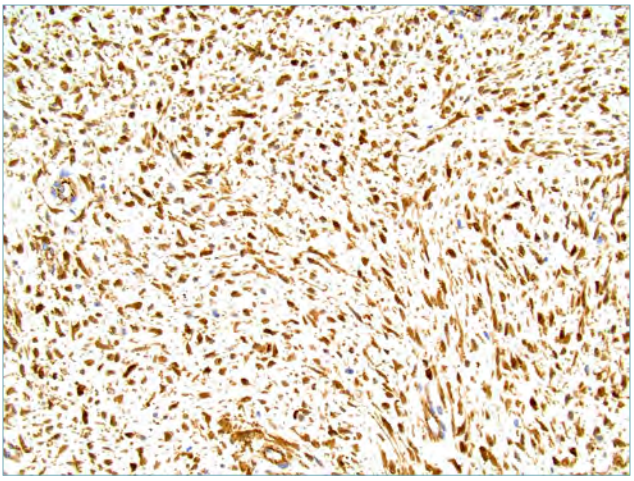

Figure 7. Desmoid fibromatosis. Nuclear expression of beta-catenin is a key diagnostic clue.

SDHC units of the SDH complex, and may be related to the Carney-Stratakis syndrome, a dominant autosomal disorder represented by association of GIST and paragangliomas [13]. WT GIST can occur in the context of NF-1, wherein the mutation of the *NF1* gene leads to loss of neurofibromin, and consequent activation of the RAS pathway [19]. Finally, the remaining SDHB-positive WT GIST are probably a basket of different conditions: some were reported to have the V600E mutation of *BRAF* or, more rarely, of *HRAS*, *NRAS*, *PI3K*. Recent experience would indicate that a significant proportion of so-called "quadruple negative" GIST exhibits *NF1* gene mutations that may be somatic or more frequently germline [10]. As this happens in absence of clinical evidence of Type 1 neurofibromatosis, they possibly represent examples of subclinical forms of the syndrome. Using a Massive Parallel Sequencing approach an *ETV6-NTRK3* gene fusion has been recently detected in a quadruple-negative GIST [20]. As WT GIST tend to be not responsive to tyrosine kinase inhibitors (but keeping in mind that this alteration is very rare) molecular therapy targeting *NTRK* has been successfully applied [21].

Neoplasm with fibroblastic/ myofibroblastic differentiation

Desmoid fibromatosis

Desmoid fibromatosis represents a locally aggressive, non-metastasising myofibroblastic neoplasm that may occur at extra-abdominal (60%), abdominal (25%) and intra-abdominal anatomic sites (15%) [3]. Intra-abdominal lesions are usually located in the pelvis or in the mesentery. Mesenteric desmoids can be sporadic or be associated with a variant of familial adenomatous polyposis syndrome (Gardner's syndrome). This syndrome is defined by the presence of synchronous of metachronous multiple adenomatous polyps, osteomas, epidermic cysts, and desmoid fibromatosis [22]. Intra-abdominal desmoid fibromatosis occur predominantly in young adults.

Macroscopically, tumours appear as a solitary mass with diameter ranging from 5 cm to 10 cm. The cut surface is whitish and hard [3].

Desmoid fibromatosis typically shows poor circumscription often with infiltration of the surrounding soft tissues. Microscopically, the tumour is composed of a monotonous spindle cell proliferation arranged in long sweeping fascicles set in a collagenous background (Fig. 6). A useful diagnostic clue is represented by the fact that neoplastic cells often exhibit a relatively regular distribution without nuclear overlapping. Both cellularity and amount of collagenous stroma can be variable. Nuclear atypia is generally absent and mitotic figures may vary in number but are usually not numerous. Myxoid change of the stroma may occasionally occur. Desmoid fibromatosis exhibits nuclear immunopositivity for beta-catenin (Fig. 7) and multifocal positivity for smooth muscle actin [3]. Nuclear expression of beta-catenin protein represents the consequence of mutations of the *CTNNB1* gene that occurs in approximately 85% of sporadic cases. In Gardner syndrome-associated cases the same phenomenon is determined by the mutation of

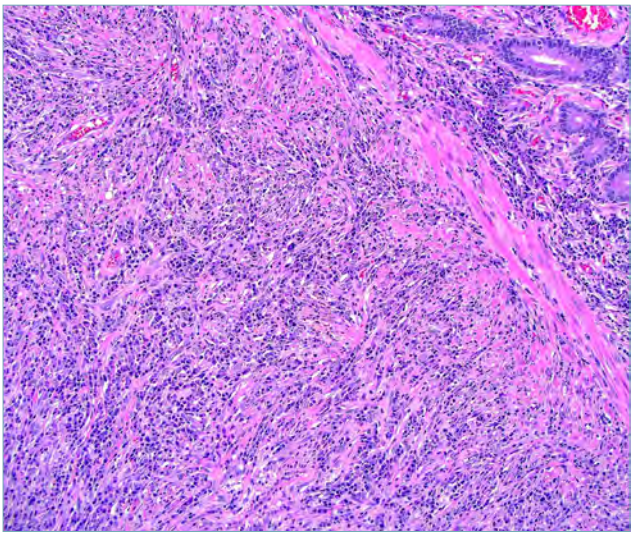

Figure 8. Inflammatory Myofibroblastic Tumour may rarely occur in gastrointestinal tract. In this case neoplastic cells involve the *muscolaris mucosae* of the small bowel.

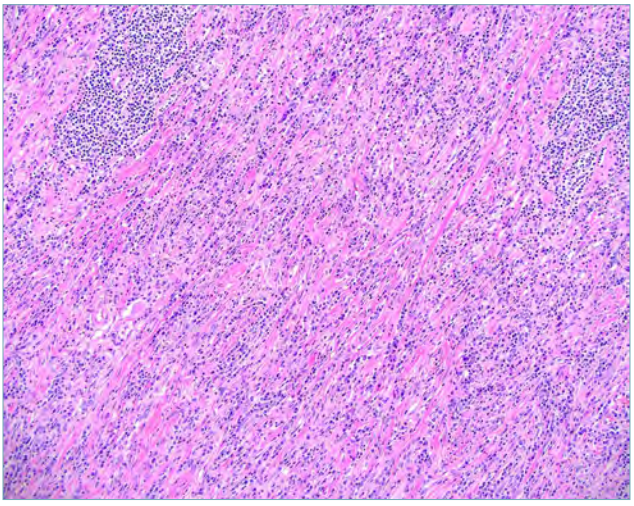

Figure 9. Inflammatory Myofibroblastic Tumour. This tumour is composed of spindle cells, set in a fibrous stroma associated with a prominent inflammatory infiltrate, rich in plasma cells, lymphocytes and eosinophils.

the *APC* gene. A sharp debate surrounds the potential prognostic meaning of *CTNNB1* gene mutations (it has been suggested that the 45F mutation associates with higher rates of local recurrences) that is still unsettled [23]. In the past, the therapeutic approach to desmoid fibromatosis has been mostly represented by surgical excision. The use of radiotherapy as well as of systemic treatments (which include hormone antagonists, tyrosine-kynase inhibitors, low dose cytotoxic chemotherapy) has been suggested for progressive lesion. More recently, in consideration that in a significant subset of patients repeated surgery may lead to increased recurrence rates, whereas spontaneous regression is by contrast observed, a "wait and see" approach has been suggested unless clear clinical progression is observed [24].

Inflammatory Myofibroblastic Tumour

Inflammatory Myofibroblastic Tumour (IMT) is a rare, locally aggressive and rarely metastasising mesenchymal tumour of young adults, composed of myofibroblasts and fibroblasts set in an inflammatory background that includes plasma cells, lymphocytes and/or eosinophils in variable amounts.

IMT is most often observed in the lungs although it may occur anywhere in the body, including the abdominal soft tissue, mesentery, omentum, and the GI tract (Fig. 8) [25].

Three main morphologic patterns are recognised [3]. The "myxoid pattern" is characterized by loosely arranged plump or spindled myofibroblasts embedded in an oedematous myxoid background rich in plasma cells, lymphocytes and eosinophils to the extent that it can mimic granulation tissue (Fig. 9). The "hypercellular pattern" consists of a compact proliferation of spindle cells associated with variable myxoid/collagenous stroma and a rich inflammatory infiltrate. Finally, the "hypocellular fibrous pattern" is characterised by low cellularity, collagenous stroma and sparse inflammatory cells. One or more of these patterns may be identified in a single IMT. Dystrophic calcifications and osseous metaplasia represent rare findings in IMT.

Epithelioid inflammatory myofibroblastic sarcoma (EIMS) is a clinically aggressive form of IMT, characterized by epithelioid tumour cells featuring vesicular nuclei and prominent nucleoli, set in a myxoid stroma; neutrophils are often present [26]. It occurs predominantly intra-abdominally. Immunohistochemically, IMT may show variable positivity for SMA (Fig. 10A), calponin and desmin. Cytokeratins are focally positive in about 30% of cases. More than 50% of IMTs present ALK positivity (Fig. 10B), which is related to *ALK* gene rearrangement. Interestingly, ALK immunohistochemical pattern varies according to *ALK* fusion partner: *RNBP2-ALK* generates a nuclear membrane pattern [27], *RRBP1-ALK* a perinuclear accentuated pattern [28], and *CLTC-ALK* a granular cytoplasmic one [29]. The diffuse cytoplasmic pattern is the most frequent and is associated to many other ALK fusion variants. A subset of IMT present *ROS1* gene rearrangements and are usually associated with immunohistochemical cytoplasmatic expression of ROS1 [30]. Five to 10%

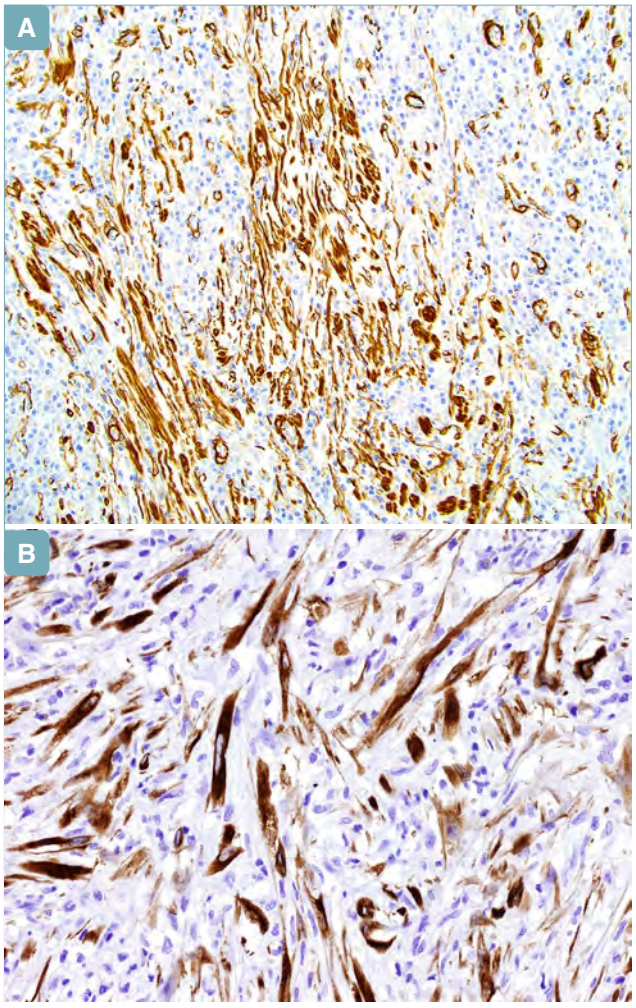

Figure 10. Inflammatory Myofibroblastic Tumour. Neoplastic cells show variable positivity for smooth muscle actin (A) and in half of cases expression of ALK (B).

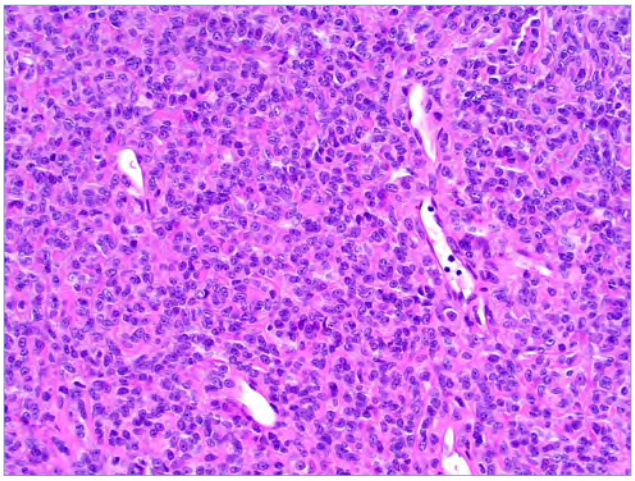

Figure 11. Solitary fibrous tumour. This neoplasm shows spindle cells organised in a "patternless" pattern, set in a collagenous background, and showing thin-walled, haemangiopericytoma--like vessels.

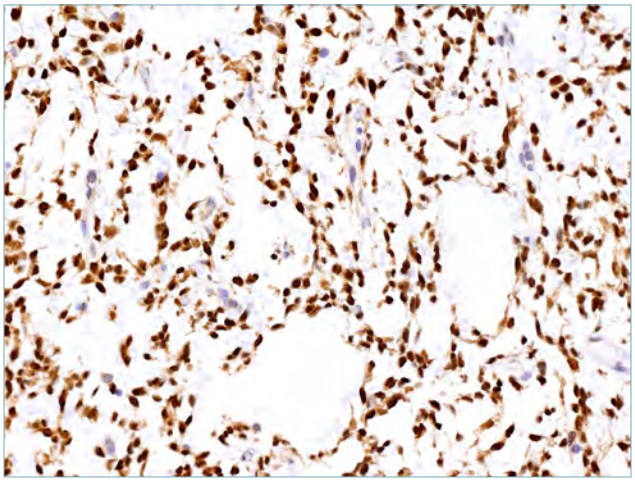

Figure 12. Solitary fibrous tumour. Expression of STAT6 represents the most specific and sensitive diagnostic marker.

of IMT may feature the rearrangement of the *NTRK3* gene [31]. As is the case of ALK and ROS1, *NTRK3* represents a druggable biomarker.
Approximately 25% of extrapulmonary IMT may recur, but metastases are rare (less than 5%). ALK-negative IMTs seem to be related to a higher frequency of metastasis. However, reliable prognostic indicators for IMT have not been validated yet. As mentioned above, epithelioid IMT have a more aggressive clinical behaviour [32].

Solitary Fibrous Tumour

Solitary fibrous tumour (SFT) is a rare neoplasm that even if originally reported as pleural-based tumour, can actually occur at any anatomic site. Approximately 80% of cases are deep-seated [33,34]. SFTs have been described in different parts of the GI tract, liver and pancreas included [35-38].
Microscopically, SFT are composed by a patternless proliferation of spindle cells embedded in a collagenous background featuring distinctive branching, thin-walled blood vessels organized in a "staghorn" configuration (so called haemangiopericytoma-like vascularization) (Fig. 11) [38]. Cellular varation is typically observed in classic examples. Three additional SFT subtypes are recognised: fat-forming SFT is characterised by the presence of mature adipose tissue [39];

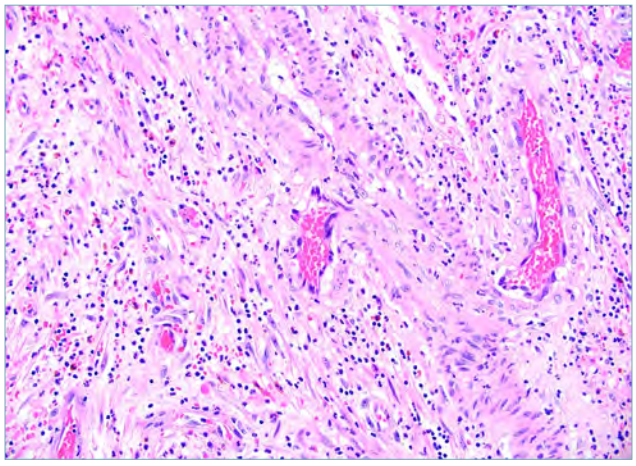

Figure 13. Inflammatory fibroid polyp. The neoplasm is composed of a proliferation of bland, spindle cells, associated with an eosinophilic-rich inflammatory infiltrate.

giant cell-rich SFT features multinucleated giant cells often lining angiectoid spaces [40]; dedifferentiated SFT show transition from classic SFT to a high-grade sarcoma [41].

Immunohistochemically, SFT is strongly positive for CD34, bcl-2 and CD99 (70% of cases). STAT6 is the most specific and sensitive marker (Fig. 12), being expressed in almost all SFTs [42]. STAT6 expression is related to a specific recurrent gene fusion involving *STAT6* and *NAB2* genes [43].

Approximately 12-22% of cases of SFT are malignant. Malignancy-associated features are high cellularity, nuclear pleomorphism, necrosis and more than 4 mitoses per 10 HPF [44,45]. The metastatic risk can be assessed on the basis of mitotic count (2 or more mitoses per mm^2), patient age (55 years or more) and tumour size [46]. However, the absence of these criteria does not exclude a possible aggressive behaviour and no SFT should be regarded as benign [38].

SFT may enter in differential diagnosis with GISTs, schwannomas, benign smooth muscle tumours and monophasic SS. Immunohistochemical analysis for STAT6 is usually sufficient to assess the correct diagnosis.

Inflammatory Fibroid Polyp

Inflammatory fibroid polyp is a benign neoplasm featuring a polypoid configuration, composed of a hypocellular fibroblastic proliferation associated with a variably prominent inflammatory infiltrate, rich in eosinophils. It most often arises in the stomach followed by the ileum [47,48] but may involve the whole digestive tract. The tumour is typically located in the submucosa or restricted to the mucosa that can be ulcerated. Middle-aged adults are typically affected, with a slight female predominance [49].

Small lesions are asymptomatic and most often discovered incidentally. Large masses are associated with abdominal pain and bleeding due to mucosa ulceration. Intussusception is a common presentation for small intestine tumours [49].

Tumours can appear sessile or polypoid, and range in size from few millimetres to large masses. Histologically, inflammatory fibroid polyp is a hypocellular lesion composed short spindled and stellate cells showing fine chromatin, small or indistinct nucleoli, and scant eosinophilic cytoplasm (Fig. 13). The stroma may be myxoid or collagenous, with a prominent mixed inflammatory infiltrate, often rich in eosinophils. Concentric fibrosis (onion-skin) distributed around blood vessels represents a distinctive finding [3].

Immunohistochemically, neoplastic cells express CD34 and rarely smooth muscle actin [50,51]. KIT, DOG1, desmin, S100, SOX10, and keratins are all negative. The differential diagnosis includes IMT, leiomyoma, and plexiform fibromyxoma.

Most cases, particularly when located in the small bowel, harbour *PDGFRA* gene mutation 4 [9,51,52]. Exon 18 mutations, usually c.2525A > T (p.D842V) are associated with a gastric location, whereas exon 12 mutations are almost identified in small intestine tumour [53]. Only rare cases are associated with germline *PDGFRA* gene mutations [54]. Inflammatory fibroid polyp is a benign tumour. Local recurrences and distant metastasis have not been reported.

Plexiform Fibromyxoma

Plexiform fibromyxoma, also referred as plexiform angiomyxoid myofibroblastic tumour, is a benign mesenchymal tumour arising almost exclusively in the stomach. The tumour occurs in the antrum and pyloric region of the stomach, but duodenum may be very rarely involved [3,55]. Age range is rather broad, and include childhood with equal distribution in male and females. Clinically, gastrointestinal bleeding due to mucosal ulceration, weight loss and pyloric obstruction may be observed.

Macroscopically, the tumour appears like as gelatinous or haemorrhagic multinodular mass, ranging in size from few centimetres to large masses. The tumour is typically located in the muscularis propria and protruding into the serosa [55,56]. Histologically, the neoplasm features a distinctive plexiform pattern of growth. The nodules are composed of bland oval to spindled cells with indistinct cytoplasm, set in a myxoid, fibromyxoid or collagenous matrix associated with a rich thin-walled capillary network (Fig. 14). In-

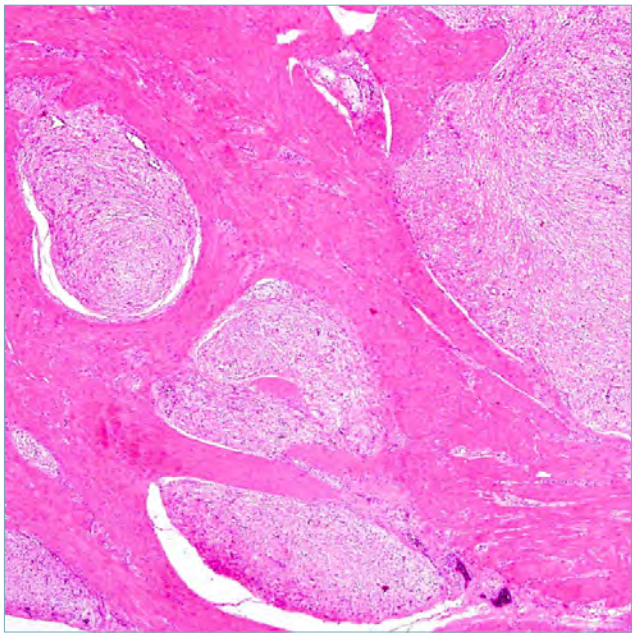

Figure 14. Plexiform fibromyxoma. Proliferation of bland, spindle-shaped cells, set in a fibromyxoid stroma that shows a network of thin-walled capillary-size blood vessels.

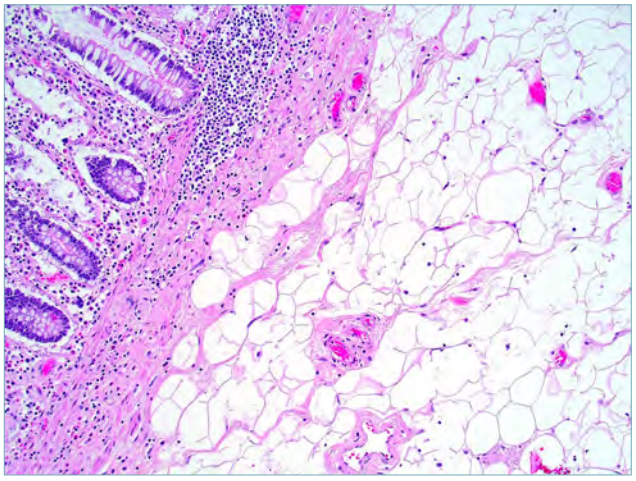

Figure 15. Lipoma. The tumour is composed of mature fat tissue without atypia and variation in size of adipocytic cells. Fibrous septa and histiocytes may be sometime observed.

creased cellularity is observed in those rare tumours occurring in the duodenum. Nuclear atypia is usually absent and mitotic activity is generally low [56]. Neoplastic cells express SMA and occasionally are immunopositive for desmin and h-caldesmon whereas KIT, DOG1, ALK and S100 are consistently negative. Differential diagnosis includes SDH-deficient GIST, plexiform schwannoma and inflammatory myofibroblastic tumour [55,56]. *KIT* and *PDGFRA* mutation have not been reported. Molecularly, *MALAT1-GLI1* fusions and *GLI1* polysomy have been identified in a subset of tumours resulting in GLI1 overexpression [57].

Plexiform fibromyxomas are benign lesions with no reports of recurrence or metastasis [55,56] however in some cases massive gastric bleeding has proved fatal.

Neoplasm with adipocytic differentiation

Lipoma

Lipomas are the most common benign soft tissue tumours, most often arising in the soft tissues of the extremities and trunk [32]. Lipomas more rarely may also occur in the submucosa or subserosa along the whole gastrointestinal tract; the cecum and the ascending colon being the most common sites followed by the ileum, stomach and oesophagus [3]. Rarely, gastrointestinal lipomas may be intramucosal, such cases may rarely be associated with Cowden syndrome [58]. The reported incidence of large bowel lipomas is between 0.2% to 4.4% of endoscopies, with possible slight female predilection and a peak incidence in the 6th decade [59]. Signs and symptoms of GI lipomas are linked to size (highly variable from 2 to > 10 cm) and location. Most patients are asymptomatic, although abdominal pain, and intestinal obstruction have been reported [59]. The histological appearance of lipomas consists in a proliferation of mature adipose tissue, with no cytologic atypia (Fig. 15) [3]. Larger lesions may be accompanied by overlying mucosal ulceration.

Lipoma subtypes, such as angiolipomas have also been described to occur in the GI tract [60]. Molecularly, benign lipomas harbour simple genetic alteration in about 75% of cases, among which the most common is *HMGA2* gene rearrangements [61]. Surgical and endoscopic excision are the treatment of choice for large or symptomatic gastrointestinal lipomas.

Well Differentiated/Dedifferentiated liposarcoma

Liposarcomas are the most common mesenchymal malignancy and are currently classified according to the WHO 2020 as atypical lipomatous tumour (ALT)/well-differentiated liposarcoma (WDLPS), dedifferentiated liposarcoma (DDLPS), myxoid liposarcoma (MLPS), pleomorphic liposarcoma (PLPS) and pleomorphic myxoid liposarcoma [32]. While the primary site of occurrence is usually the soft tissue of the limbs, trunk or retroperitoneum, primary gastrointestinal lipo-

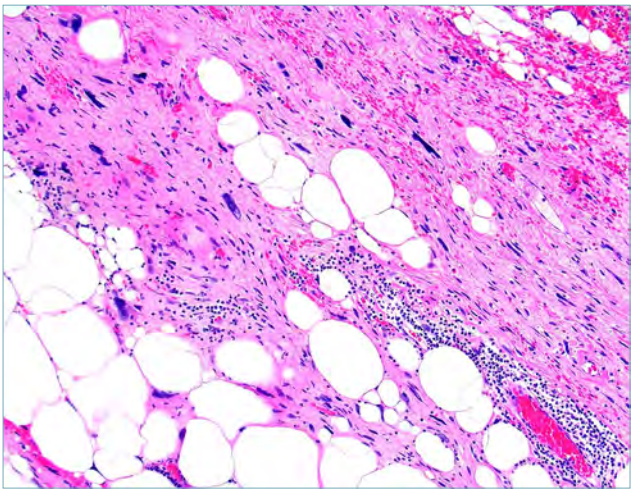

Figure 16. Well Differentiated Liposarcoma. The tumour is composed of atypical lipomatous proliferation with focal nuclear atypia intersected by thick fibrous septa with hyperchromatic atypical stromal spindle cells.

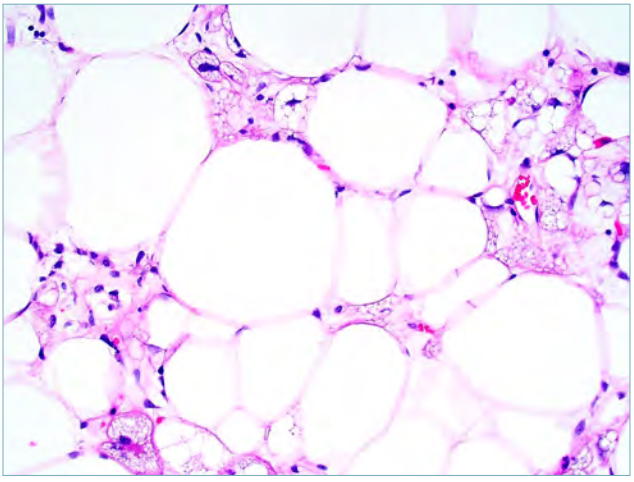

Figure 17. Well Differentiated Liposarcoma. Numerous lipoblasts are rarely observed in WDLPS sometimes they can be completely absent.

sarcomas are much rarer with incidence at autopsy reported to be between 0.1% and 5.8% [62]. Primary gastrointestinal liposarcomas show slight male predominance and tend to occur in middle-aged individuals. Liposarcomas also display a higher tropism for the submucosal layer and muscularis propria of the oesophagus, closely followed by the stomach, small and large intestine [63]. When arising in visceral sites, they usually present as already voluminous polypoid masses with slow growth. Patients usually present with symptoms related to anatomic location, which include dysphagia, cough, vomit, foreign body sensation and weight loss.

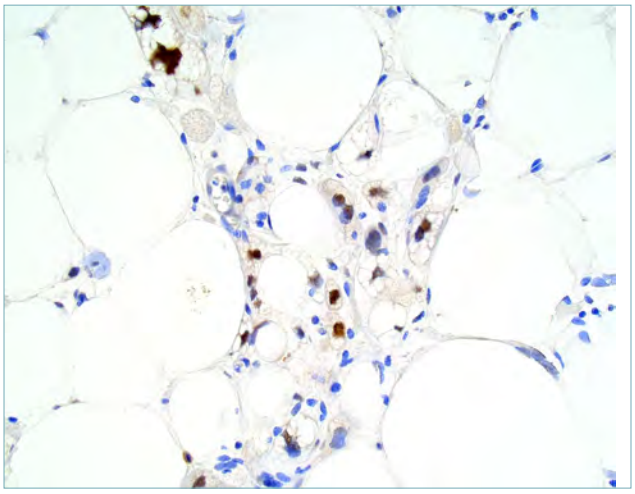

Figure 18. Well Differentiated Liposarcoma. Strong MDM2 nuclear positivity is consistently observed in neoplastic cells including lipoblasts.

Albeit being the most common subtype of liposarcoma, in GI tract WDLPS seems to show a lower incidence than its dedifferentiated counterpart. Both are genetically driven by amplification of *MDM2* and *CDK4* genes that lead to the overexperession of the proteins thereof [64].

Grossly the appearance of WDLPS strongly depends on the proportion of lipomatous and fibrous components and varies from a uniformly yellow mass, similar to a lipoma, to a white-greyish lobulated mass on cut surface.

On histology, WDLS is composed of a mature lipomatous proliferation intersected by thick fibrous septa, with variation in cell size and at least focal nuclear atypia in adipocytic and/or stromal cells (Fig. 16). Mitotic figures are rare. Lipoblasts may be present in variable amounts (from many to none) (Fig. 17); however, this feature is not required for the diagnosis of WDLS. Rarely, foci of heterologous metaplasia may be observed [32]. As mentioned MDM2 overexpression is consistently observed (Fig. 18)

Dedifferentiated liposarcomas (DDLPS) is characterised by a broad morphological spectrum. It is defined by the the presence of abrupt transition from well differentiatiated liposarcoma to high grade non-lipogenic sarcoma (Fig. 19). Most often the dedifferentiated component is pleomorphic however it can be also composed by a monomorphic spindle cell proliferation. Areas of heterologous differentiation (most often

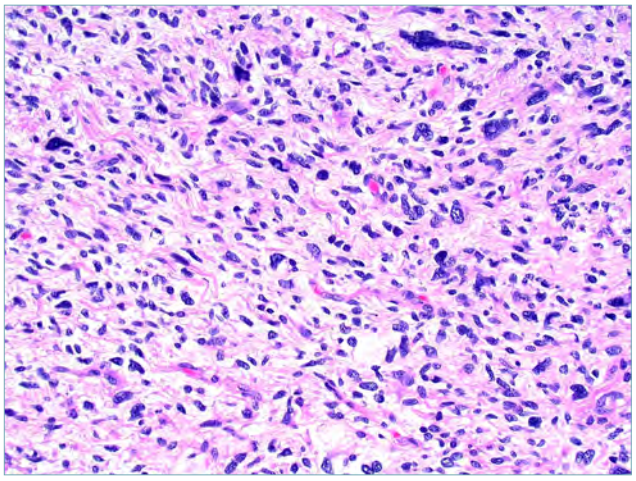

Figure 19. Dedifferentiated liposarcoma. The dedifferentiated component is composed of spindle and pleomorphic cells set in a fibromyxoid stroma.

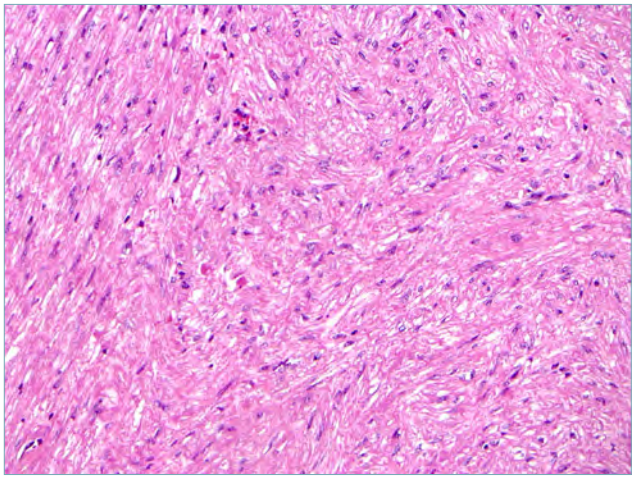

Figure 20. Leiomyoma. The neoplasm is composed of non-atypical, eosinophilic, spindle cells, with blunt ended nuclei.

myogenic) may also be found [32]. Multivisceral surgical resection is the mainstay of treatment.

Although DDPLS and WDLPS are the most common subtypes of liposarcomas described in the GI tract, a few case reports also described the exceptional occurrence of myxoid liposarcomas (MLPS) [65,66]. Myxoid liposarcoma is composed of cytologically bland spindle to ovoid cells associated with monovacuolated lipoblasts, set in a myxoid stroma with prominent plexiform capillary network. Myxoid liposarcoma is MDM2 negative and characterized genetically by a *DDIT3* gene rearrangement that represent a useful diagnostic confirmatory finding.

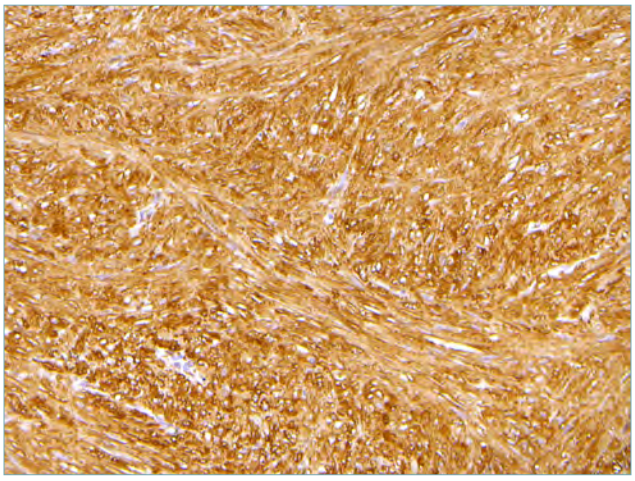

Figure 21. Leiomyoma. Strong and diffuse immunopositivity for desmin is usually observed.

Epithelioid pleomorphic liposarcoma

Epithelioid pleomorphic liposarcoma (EPL) represents a subset of pleomorphic liposarcomas in which an epithelioid morphology predominates [67]. Diagnosis is based on the detection of pleomorphic lipoblasts that unfortunately may be minimally represented. A significant proportion of cases occur in the GI tract of adults. Clinically EPL is a high-grade sarcoma with a dismal prognosis.

Smooth Muscle Neoplasms

Leiomyoma

Leiomyoma is a rare benign mesenchymal tumour showing smooth muscle differentiation and represents approximately one third all mesenchymal neoplasms of the GI tract. Leiomyomas predominantly occur in the oesophagus, colon, and rectum and rarely arise in the stomach and small intestine [68]. Incidental small nodules, less than 7 mm, are recognised in oesophagogastric resections done for other reason [69]. Most cases are sporadic, but exceedingly rare cases occur in association with Alport' syndrome.

Histologically, the tumour is composed of fascicles of spindled cells with blunt-ended nuclei set in eosinophilic fibrillary cytoplasm (Fig. 20) [32]. There may be focal nuclear atypia, but necrosis and mitotic activity are not detected. Detection of any mitotic activity should in fact prompt consideration of malignancy. Neoplastic cells express desmin, SMA, h-caldesmon, and calponin (Fig. 21). The main differential diagnosis is with

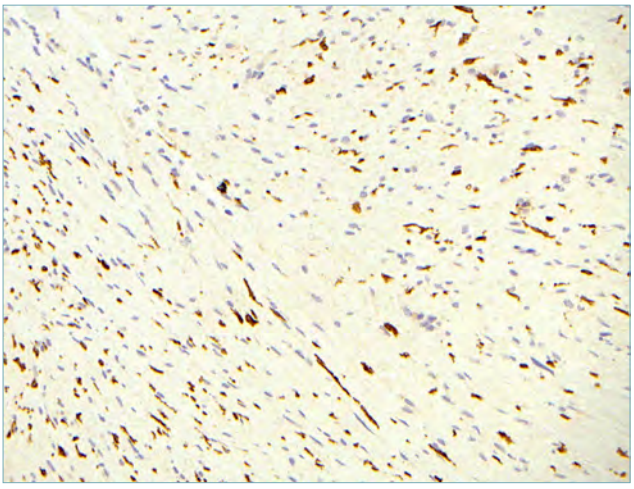

Figure 22. Leiomyoma. KIT immunostaining highlights the hyperplasia of the interstitial cells of Cajal.

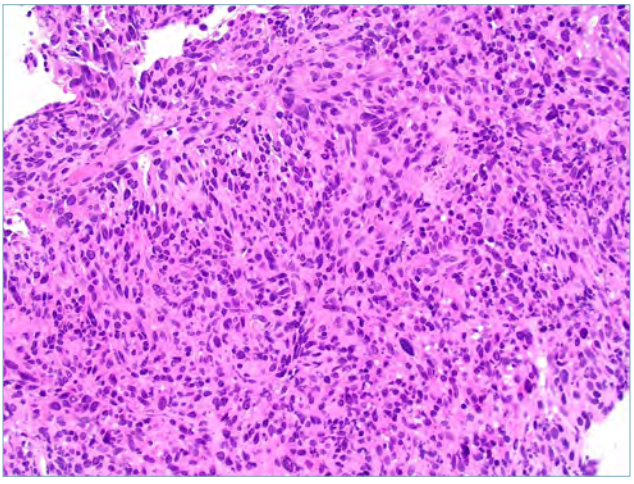

Figure 23. Leiomyosarcoma. The tumour is composed of long fascicles of eosinophilic, spindle cells with blunt ended nuclei.

GIST, which may show similar morphological features. However, KIT (CD117) is consistently negative in leiomyomas. Focal expression of DOG1 can observed in smooth muscle tumours, therefore representing a potential diagnostic pitfall, as is the presence in leiomyomas of hyperplasia of the interstitial cells of Cajal (KIT positive) (Fig. 22). Leiomyomas of GI tract are benign tumours, with no risk of recurrence or distant spread.

Leiomyosarcoma (LMS)

Leiomyosarcoma is an extremely rare malignant neoplasm showing smooth muscle differentiation. In the GI tract it most commonly occurs in the small intestine (40%) and colorectum (40%) and more rarely in the stomach (10%) and oesophagus (10%) [70,71]. In the anorectum and in the oesophagus LMS is relatively more common than GIST. Leiomyosarcoma occur typically in adult patients (peak incidence is in the sixth decade) with the exception of gastric LMS which tends to arise in younger patients (median age: 37 years) [71]. Interestingly visceral LMS, particularly those arising in children, may be related to immunosuppression and aetiologically linked to Epstein-Barr Virus infection [72].
In oesophageal and gastric cases, a slight male prevalence has been described. Leiomyosarcomas may present as polypoid or lobulated intraluminal tumours or as a large solid and necrotic mass [71,73-75].
Microscopically, LMS is composed of long intersecting fascicles of spindle cells featuring abundant eosinophilic cytoplasm and blunt ended nuclei (Fig. 23). Moderate to severe nuclear atypia and in some cases overt pleomorphism are observed. Mitoses tend to be numerous, although rare tumours with low mitotic counts have been reported [71,73]. Necrosis may be present. Immunohistochemically the vast majority express smooth muscle actin, whereas 70-80% of LMS stain with desmin and/or H-caldesmon [70]. Importantly about 30% of LMS may exhibit multifocal positivity for cytokeratin and CD34 [74,76]. The main differential diagnosis is with GIST, the clinicopathologic features of which have already been described.
EBV-associated smooth muscle tumours can show a range of histological appearances, from lesions mimicking leiomyomas to lesions composed entirely of small round to ovoid blue cells. These are positive for SMA, with variable desmin positivity. All show diffuse, strong staining for EBV-encoded small RNA (EBER), which is not seen in conventional leiomyosarcoma. EBV-related LMS should be considered in immunosuppressed patients or in patients with multiple synchronous or metachronous tumours [77]. Schwannoma may also enter the differential diagnosis. In the GI tract, schwannomas tend to be cellular, with peripheral lymphoplasmacytic aggregates, and by immunohistochemistry they are diffusely positive for S100, and negative for SMA and desmin.
Leiomyosarcomas are aggressive neoplasms, with up to 80% local recurrence rate and 55-70% metastatic rate. Tumour size > 5 cm appears to be a negative prognostic factor. Interestingly, in the GI-tract, mitotic counts and nuclear atypia seem not to correlate with outcome [70,71,73]. Different classes of leiomyosarcomas, based on gene expression, have been proposed associated with different outcomes; however, these data are not currently used for clinical decision making [78,79].

Tumours with neural differentiation

Mucosal Schwann Cell Hamartoma

Mucosal hamartoma is a benign neural lesion of the GI tract characterised by an intramucosal Schwann cell proliferation [80,81]. This peculiar lesion of GI typically occur in adults with a median age at diagnosis of 60 years. A slight female predominance has been observed [80]. Most mucosal hamartomas arise in the left colon, and are discovered incidentally at screening colonoscopy. The lesions endoscopically appear as subcentrimetrical polyps. Histologically mucosal hamartoma is composed of intramucosal proliferation of uniform spindle cell with tapering or wavy nuclei (Fig. 24). Mitotic figures and nuclear atypia are absent. The cells immunohistochemically express diffusely S100 protein (Fig. 25) [80]. Mucosal hamartoma is entirely benign and is not associated with syndromes such as NF1 or NF2.

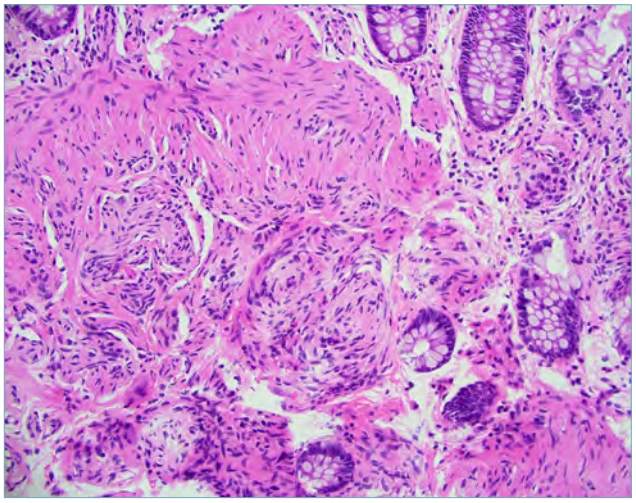

Figure 24. Mucosal hamartoma. The morphological feature is represented by a proliferation of bland spindle cells set in the lamina propria, featuring wavy nuclei.

Schwannoma

Schwannoma is a benign spindle cells neoplasm showing schwannian differentiation, accounting for approximately 3% of all GI mesenchymal tumours, the incidence of GIST being 50 times higher. It can occur anywhere in the GI tract, but it predominates in the stomach with only rare occurrences in the lower oesophagus, colon, and rectum [82]. Schwannoma arises in elderly patients with a female predilection. The tumour is located in submucosa or muscolaris propria bulging into the lumen, sometimes ulcerating the mucosa. It appears as solid mass or polypoid lesions typically lacking intratumoural haemorrhage and necrosis [83]. Small size tumours are discovered incidentally during endoscopic procedures, whereas large masses may cause gastrointestinal bleeding due to mucosal ulceration, or mass-like symptoms.
Microscopically, gastrointestinal schwannomas are well-circumscribed, with a distinctive peripheral lymphoid cuff often containing germinal centres (Fig. 26). Thick-walled or hyalinised blood vessels are less fre-

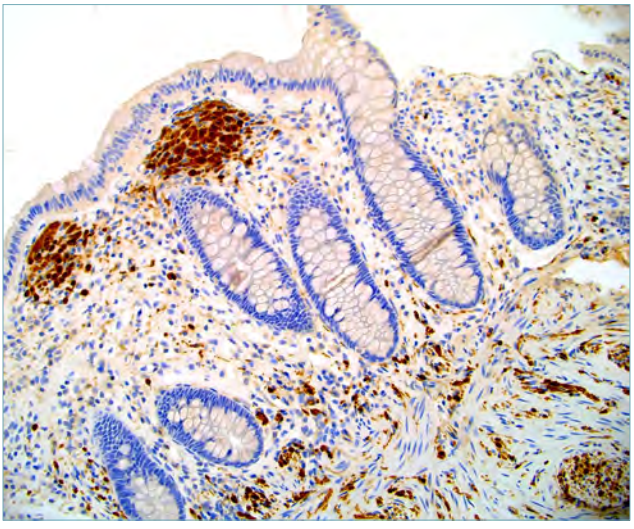

Figure 25. Mucosal hamartoma. S100 immunopositivity is consistently observed.

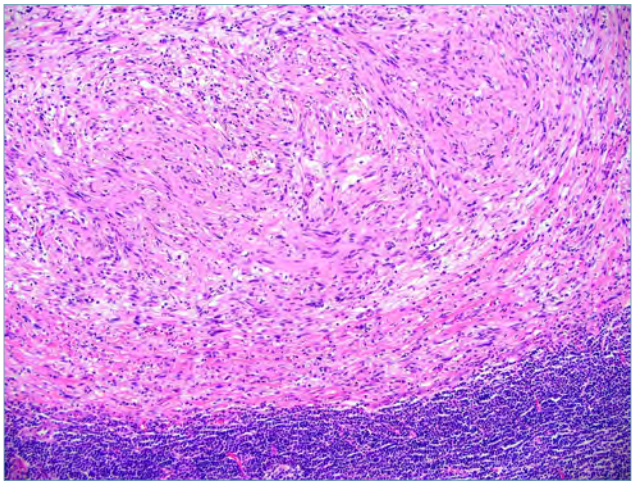

Figure 26. Schwannoma. The tumour is composed of spindle cells organized in short fascicles surrounded by a lymphoid cuff that represents an important diagnostic clue.

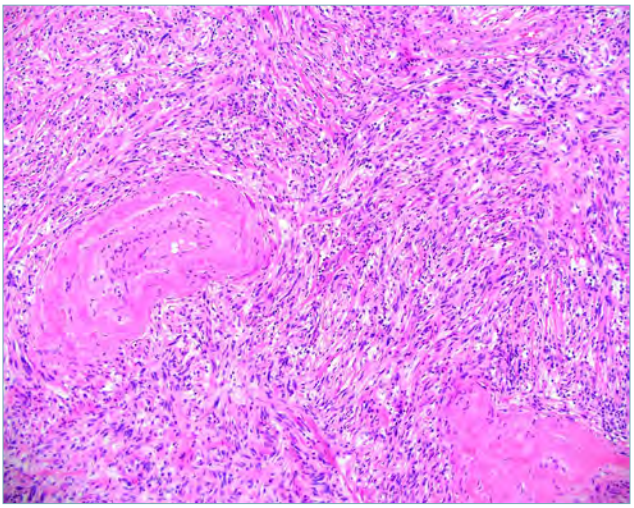

Figure 27. Schwannoma. Thick-walled blood vessels are only occasionally observed in GI-tract schwannomas.

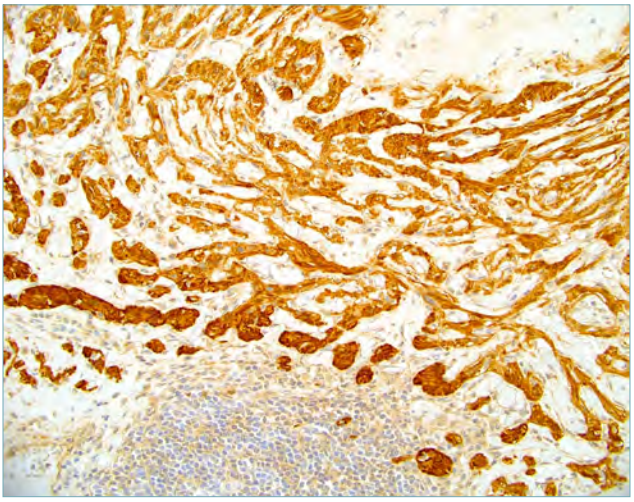

Figure 28. Schwannoma. S100 is diffusely and strongly positive.

quent in GI schwannoma (Fig. 27) that also lacks the typical combination of Antoni A and Antoni B areas generally observed in schwannomas of soft parts [84,85]. The tumour is uniformly cellular and is composed of spindle cell, with tapering nuclei and palely eosinophilic cytoplasm, organised in a fascicular or whorled pattern of growth. Scattered cells with nuclear enlargement and degenerative pleomorphism are common. A low mitotic count is observed, and necrosis is typically absent. The tumour stroma is variable from collagenous to myxoid sometimes contain foci of foamy histiocytes. A subtype of schwannoma relatively often observed in the GI tract is the microcystic/reticular subtype. It appears as an unencapsulated submucosal lesion in the stomach, small bowel, and colon [86]. Microscopically it is characterised by a distinctive reticular pattern of growth associated with formation of microcystic structures.

Neoplastic cells are strongly and diffusely positive for S100 (Fig. 28) and in most cases for GFAP and nestin [87]. Most of conventional schwannoma either sporadic or associated with NF2 syndrome are associated with loss of heterozygosity at *NF2* but most cases of GI schwannoma lack *NF2* gene alterations, suggesting that they may represent a morphologically and genetically distinct group of peripheral nerve sheath tumours [88]. Gastrointestinal schwannomas are benign lesions, long-term follow-up shows no recurrences or metastases.

Perivascular neoplasms

Glomus Tumour

Glomus tumour is a mesenchymal neoplasm composed of perivascular modified smooth muscle cells. Most often the tumour occurs in peripheral soft tissue, although viscera involvement has been reported including the GI tract. In the Gi tract the region of antrum is most often involved followed by oesophageal and intestinal locations [89].

Glomus tumour occurs predominantly in adults, although a broad age distribution is reported, with strong female predilection [89]. Small lesions are usually asymptomatic and represent an incidental finding. In case of larger lesions, upper GI bleeding, abdominal pain, or reflux-type symptoms may occur [90,91]. Glomus tumour of the GI tract is typically a single lesion, although multifocality has been described in approximately 10% of patients. Occurrence of multiple familial glomus tumour is due to inactivating mutations in the glomulin gene (*GLMN*). Most sporadic cases are associated with *NOTCH* family gene rearrangements [92]. *BRAF* gene mutations are reported in 6% of patients [93].

Macroscopically, the tumour appears like as a well circumscribed intramural mass, often multinodular. Extension into the mucosa and the serosa may occur. Histologically the tumour is composed of uniform round cells characterised by sharply defined cell borders, moderate amount of palely eosinophilic cytoplasm and central dark round nuclei with inconspicuous nucleoli (Fig. 29). Foci of oncocytic and epithelioid transformation may be observed [94,95]. The neoplastic cells are organised in nodules, sheets and trabeculae

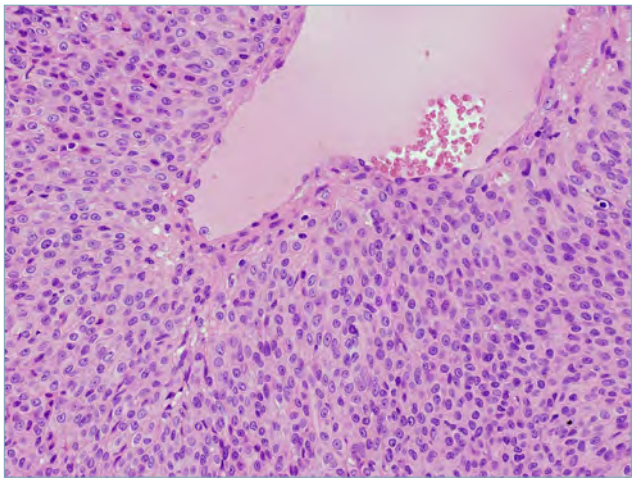

Figura 29. Glomus tumour. This neoplasm is composed of epithelioid cells harbouring round nuclei and showing sharply delineated cytoplasm, arranged around blood vessels.

set in a hyalinised and collagenous stroma presenting a rich vascular network showing a typical hemangiopericytoma-like appearance. Neoplastic cells may occasionally show a spindled morphology. Vascular invasion is observed in one third of cases, a finding that seems to represent a peculiar pattern of growth rather than a predictor of aggressive behaviour. Usually, necrosis and severe atypia are not observed, and the mitotic index is generally low. Malignant glomus tumours exist, although the criteria for malignancy in the GI tract are still poorly defined due to insufficient data. In soft tissue deep locations, increased mitotic activity (> 5 mitoses/10 mm^2) including atypical mitotic figures, and severe nuclear atypia represent criteria used to define malignancy [96].

The majority of cases show a strong and diffuse expression of smooth muscle actin, caldesmon and CD34 in variable conbination. Focal expression of synaptophysin may also be observed, representing a potential pitfall in the differential diagnosis with neuroendocrine tumours, particularly when dealing with small biopsies. Importantly, glomus tumour is negative for keratin. KIT and DOG1 are also typically not reported in glomus tumour allowing excluasion of epithelioid GIST that represents the most common mesenchymal neoplasm in the stomach.

The vast majority of cases are benign and complete resection is curative. However, few cases reported in literature have shown an aggressive clinical behaviour [89,96]. To date criteria to predict aggressive behaviour are not been validated. Based on isolated case reports, large size, presence of spindling and nuclear atypia may represent adverse prognostic factors.

Tumours with uncertain differentiation

Malignant gastrointestinal neuroectodermal tumour/ Clear cell sarcoma of the GI Tract

Malignant gastrointestinal neuroectodermal tumour (M-GNET) represents a highly aggressive mesenchymal tumour closely related to clear cell sarcoma (CCS) of soft parts but with distinctive clinical, molecular and immunomorphological features. Unlike CCS, M-GNET in fact is usually negative for melanocytic markers such as melanA and HMB45 and whereas classic CCS most often harbour *EWSR1-ATF1* gene fusions, M-GNET is more frequently associated with *EWSR1-CREB1* gene translocations. In consideration of these distinctive features, in the GI tract the alternative name of malignant gastrointestinal neuroectodermal tumour has been recently proposed [3]. To date CCS and M-GNET are regarded as two distinct entities and classified separately by WHO classifications of both soft tissue and gastrointestinal tract, and are included in the group of tumours of uncertain differentiation [3,32]. M-GNET occurs most frequently in the small bowel followed by stomach and large bowel but virtually can arise anywhere in GI tract including the oral cavity [97]. The tumour affects predominantly adults, with a peak incidence at 40 years of age. There is no different distribution between male and female patients. Clinical symptoms include anemia, weight loss, pain and, when the tumour occur in small bowel, intestinal obstruction. The M-GNET is a highly aggressive tumour with an overall mortality ranging between 35% and 75%. Recurrences and metastases can occur even after many years from diagnosis. Unlike the vast majority of sarcomas in which lymph node spread is exceedingly rare, in M-GNET shows nodal metastases in approximately 50% of cases [97].

Macroscopically, tumours appear as a well circumscribed firm nodule located into the submucosa of the involved viscera, with a diameter that range from few centimetres to large masses.

Histologically, M-GNET are composed of macronucleolated epithelioid and spindle cells, organised in large nodules demarcated by thick fibrous septa [98]. The neoplastic cells show small amount of eosinophilic cytoplasm and only scattered neoplastic cells show clear cytoplasm (Fig. 30). Multinucleated giant cells are seen in half of the cases (Fig. 31). In M-GNET the most distinctive morphologic feature is represented by the presence of pseudopapillary and/or pseudoalveo-

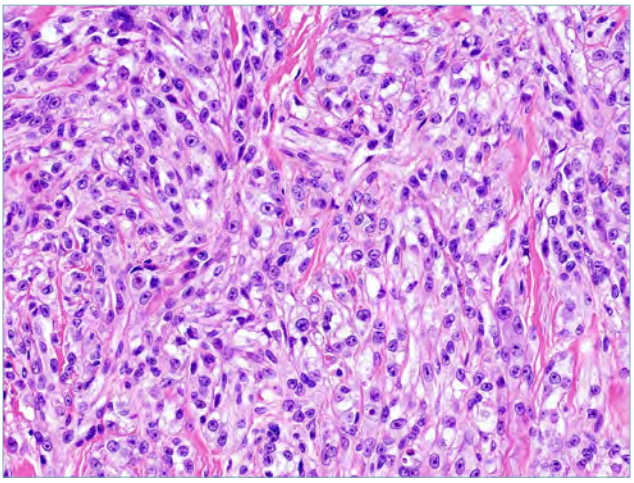

Figure 30. M-GNET. Malignant gastrointestinal neuroectodermal tumour is composed of a combination of neoplastic cells featuring eosinophilic and clear cytoplasm.

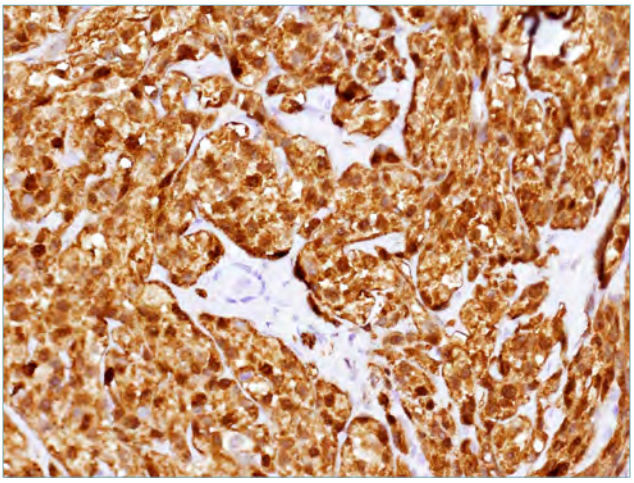

Figure 32. M-GNET. Diffuse S100 immunopositivity is seen.

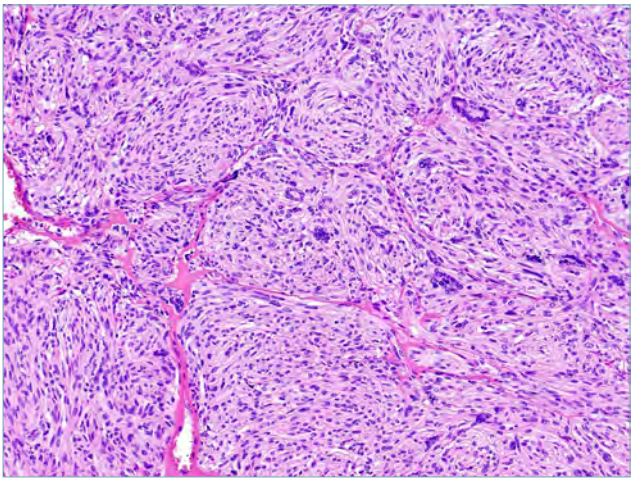

Figure 31. M-GNET. Multinucleated giant cells are relatively often seen.

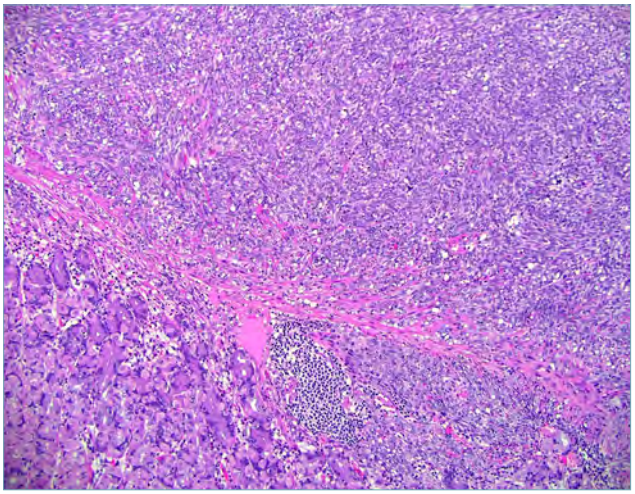

Figure 33. Synovial sarcoma. A primary gastric monophasic synovial sarcoma is seen.

lar pattern of growth [79]. Mitotic activity is variable from scattered mitotic figures to higher mitotic index with also more than 20 mitoses/2 mm^2 [97,98].

The tumour cells are usually positive for S100 and SOX10 (Fig. 32), whereas lack the expression of melanocytic markers such as melanA and HMB45. Furthermore, the tumours are consistently negative for KIT, DOG1, pancytokeratins and for markers of smooth muscle differentiation [98].

The main differential diagnosis includes metastatic malignant melanoma that shares with M-GNET some morphological features such as the nested growth pattern and the diffuse immunoexpression of S100 and SOX10. Of course lack of expression of melanocytic markers in M-GNET can be helpful in the differential diagnosis, even if it is important to highlight that most sarcomatoid melanomas can also loose expression of HMB45 and melan-A. In this context, the identification of molecular alteration, characteristic for M-GNET, may represent the ony way to achieve the correct diagnosis [97].

Synovial sarcoma

Synovial sarcoma is a malignant mesenchymal neoplasm representing 10% of all soft tissue tumours

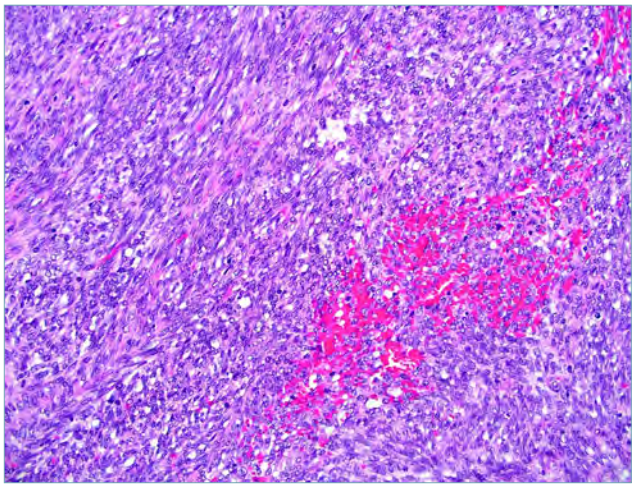

Figure 34. Synovial sarcoma, monophasic. This highly cellular neoplasm is composed of monomorphic, atypical spindle cells.

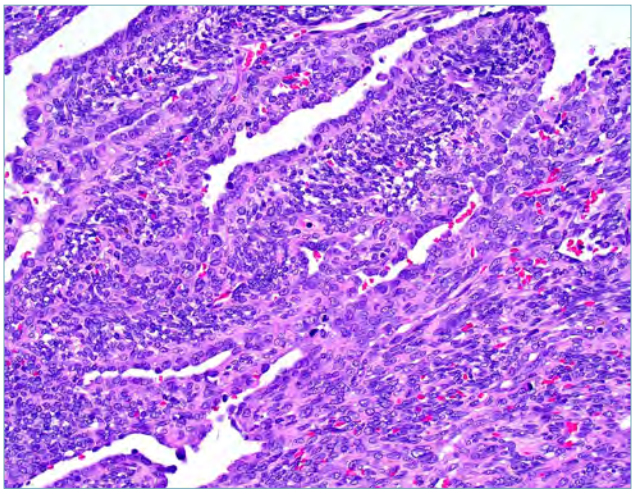

Figure 35. Synovial sarcoma, biphasic. Epithelial component exhibits a glandular configuration.

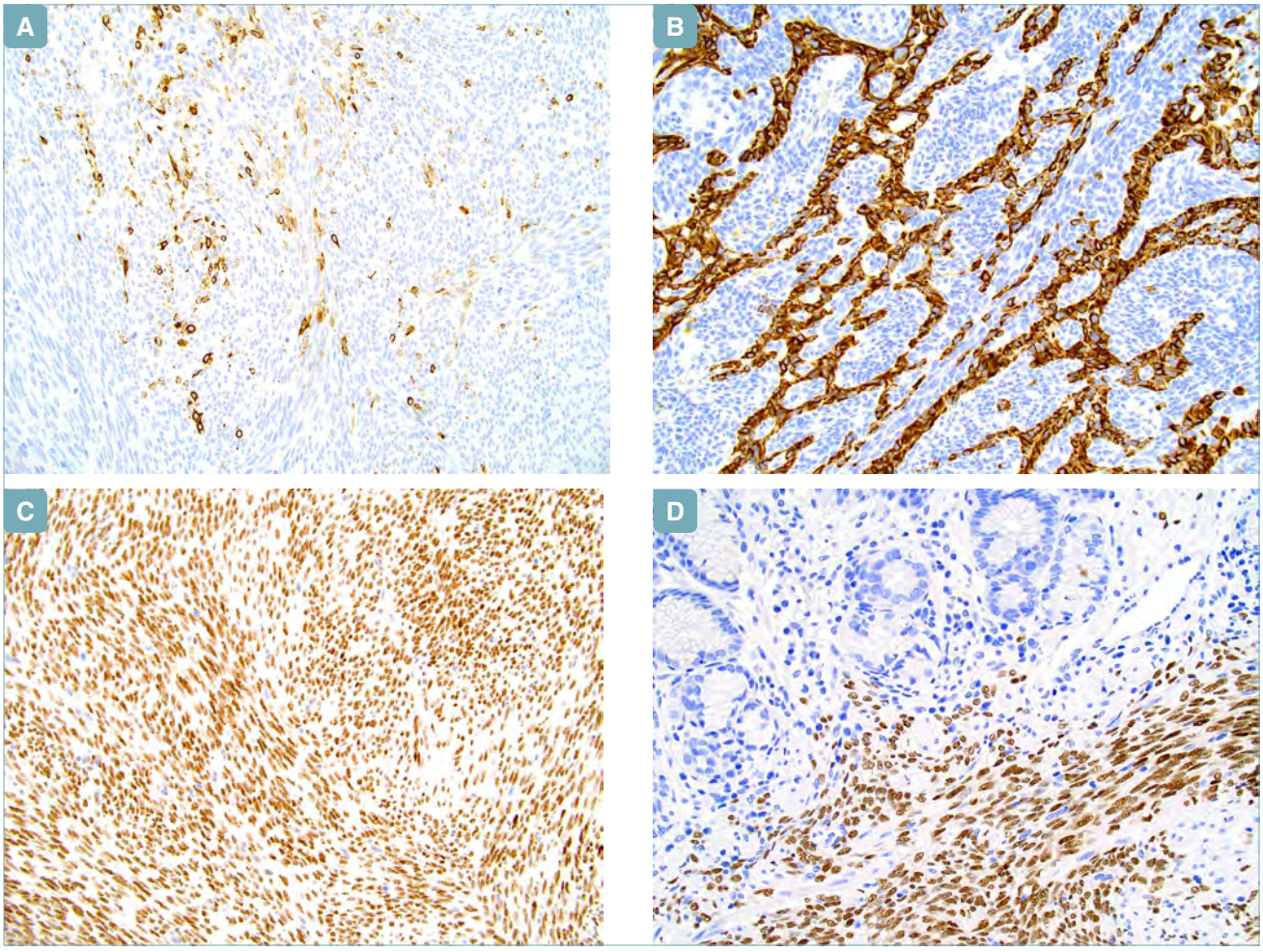

Figure 36. Synovial sarcoma. Pancytokeratins expression in monophasyc SS (A); biphasyc SS (B). Nuclear TLE1 expression is consistently observed but tends to exhibit low specificity (C). Currently the best marker is represented by the expression of SS18-SSX fusion-specific antibody (D).

which typically occurs in lower limbs of children and young adults [99]. Synovial sarcoma of the GI tract are extremely rare: in this context, the stomach is the most common location (Fig. 33), although SS of the oesophagus, small and large bowel and liver have also been reported [99,100].

Synovial sarcoma can be morphologically subdivided in monophasic, biphasic and poorly differentiated variants [99], the monophasic one being most common in the GI tract [3]. Both the monophasic and biphasic variants are characterised by a monomorphic spindle cell population arranged in fascicles (Fig. 34) set in a variablly collagenous matrix, and asscoiated with with an haemangiopericytoma-like vascular pattern [32,99]. Biphasic SS in addition to the spindle cell component, presents an epithelial component, usually organised in nests, cords or featuring overt glandular (Fig. 35), architecture [32,99]. Interestingly, a predominantly monophasic epithelial pattern has also been described [101]. Poorly differentiated SS (PDSS) make up the 20% of SS and it is further subdivided in three groups: i) a round cells subtype with necrosis and high mitotic count, ii) a large epithelioid cell subtype, also associated with rhabdoid features, and iii) a high grade spindle cell subtype [102]. Tumour size greater than 5 cm, presence of neural and vascular invasion, p53 overexpression, and high proliferation index are histological features associated with higher risk of tumour relapse [99].

Immunohistochemically, SS is characterized by the expression of epithelial markers (i.e. EMA, cytokeratins) (Fig. 36A and 36B) together with CD99 and TLE1 (Fig. 36C) [99]. Cytokeratin expression varies among different SS subtypes: while cytokeratins expression is recognisable in the majority of biphasic SSs, it drops to 60-70% in the monophasic subtype [99]. Moreover, PDSS is characterised by cytokeratin expression only in 50% of cases [102]. High molecular weight cytokeratins are more sensitive than low molecular weight cytokeratins, but the most sensitive marker of epithelial differentiation is EMA [102]. S100 positivity is reported between 30-60% of SS, while positivity for CD34 is extremely rare [35,103].

SS is characterised by a translocation involving chromosomes X and 18. This translocation is reported only in SS, and results in three alternative fusion products of the SS18 gene with either SSX1, or SSX2 or SSX4 gene [99]. FISH analysis and amplification of the specific chimeric transcript by RT-PCR are effective techniques to detect translocation t (18; X), representing ancillary tools for diagnosis of SS [99,104].

Very recently a novel SS18-SSX fusion-specific antibody has been developed (Fig. 36D) showing a highly sensitivity and specificity for SS. This specific antibody may replace molecular genetic testing for diagnostic confirmation of SS. The main differential diagnosis of monophasic SS is with GIST. Histological features and positivity for CD117 and DOG1 stainings are usually sufficient to support the diagnosis GIST [15]. Importantly, focal positivity for DOG1 has been reported in SS of the digestive system, representing a possible diagnostic pitfall [105]. Moreover, cytokeratin positivity has been observed in sporadic GISTs [106,107].

S100 positive monophasic SS may enter in differential diagnosis with gastrointestinal clear cell sarcomas (CCS) and CCS-like tumours of the GI tract [68]. Negativity for epithelial markers and *EWSR1* gene rearrangements are distincive features of CCS and CCS-like tumours [68,98,108]. Markers of melanocytic differentiation (e.g. MelanA/MART1, HMB45 and MiTF) are commonly expressed in CCS (but not in CCS-like tumors), helping in the differential diagnosis with SS [68]. Monophasic SSs may also enter in diagnosis with leiomyosarcomas, malignant spindle cell melanomas and spindle cell squamous cell carcinoma. However, a higher degree of pleomorphism is usually observed in all these lesions. Expression of smooth muscle markers and melanocytic markers can easily direct the diagnosis toward leiomyosarcoma and melanoma, respectively. Spindle cell squamous cell carcinoma is usually characterised by a stronger expression of epithelial markers and by the presence of areas of conventional carcinoma [99].

Despite the fact that morphological and immunohistochemical features most often make the diagnosis of biphasic SS relativley easy, the differential diagnosis with gastroblastoma may sometimes be considered. Gastroblastoma is an extremely rare mixed epithelial-mesenchymal neoplasm with just a few cases reported in the literature [109,110]. The mesenchymal component consists of spindle cells with minimal to mild nuclear atypia and variable mitotic activity, while the epithelial one is composed by epithelioid cells organised in sheets, nests, or cords with no or mild nuclear atypia [109,110]. Immunohistochemistry is helpful in the assessment of the correct diagnosis, since gastroblastomas are negative for SSX-SYT, EMA and TLE1; moreover, gastroblastoma lacks SYT gene rearrangements.

Conclusions

Mesenchymal tumours represent an extremely heterogeneous group of lesions. Visceral locations are increasingly recognised due to refinement of diagnostic criteria. Even if GIST represent by far the commonest lesion (at least in the stomach), actually mesenchymal neoplasms may occur in the GI-tract. Accurate diagno-

sis can be challenging, but representsthe cornerstone of accurate therapeutic planning. The combination of morphologic, immunophenotypic and molecular findings represents the best strategy to allow accurate classification.

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