

Mezenchymal (Non-epithelial) “Non-GIST” Tumors of the Digestive Tract

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Rezumat

Tumori mezenchimale (nonepiteliale) “non-GIST” ale tubului digestiv

Deosebiri morfologice, imunohistochimice și ultrastructurale ca și cele clinice sau prognostice între multiplele varietăți de tumori mezenchimale (nonepiteliale, stromale) ale tubului digestiv au determinat rememorarea unei serii “anecdote” de 16 observații de leziuni “non-GIST” întâlnite în peste patru decenii de practică chirurgicală. Diagnosticul a fost stabilit pe baza elementelor clinice (acuze dispeptice și dureroase, hemoragii digestive, fenomene ocluzive sau chiar tumoră palpabilă) – unele leziuni fiind descoperite incidental – și confirmat de investigațiile radiologice și endoscopice și în principal de explorarea intraoperatorie și examenul anatomo-patologic la parafină. Au fost astfel înregistrate 9 schwanoame, trei leiomioame, două lipoame și câte un caz de fibrom și respectiv mixom, localizate majoritar pe stomac (n=12), ileon (n=1) și colonul drept (n=30). Toate cazurile au fost operate practicându-se îndepărtarea leziunilor cu coleretă mucoasă sau parietală, exereze atipice, conservatoare sau rezecții viscerale standard, segmentare sau sectoriale. În seria noastră nu am înregistrat morbiditate sau mortalitate postoperatorie. Urmărirea observațiilor pe o perioadă medie de 24 (limite 6-60) luni nu a evidențiat recidive sau metastaze. Chiar dacă interesul actual este prioritar îndreptat către tumorile GIST, studiul leziunilor

non-GIST merită de asemenea continuat fiind util practicienilor care se pot confrunta cu aceasta patologie, permițându-le o evaluare și terapie optimă.

Cuvinte cheie: tumori mezenchimale, non-GIST, leiomioame, schwanoame, diagnostic, tratament

Abstract

Morphological, immunohistochemical and ultrastructural but also clinical and prognostic differences between multiple types of mesenchymal (stromal, nonepithelial) tumors of the gastrointestinal tract prompted us the remembrance of an anecdotic series of sixteen observations of mesenchymal “non-stromal” gastrointestinal tumors (MNSGIT) encountered in four decades of surgical practice. The diagnosis was mainly established on clinical grounds (dyspepsia, pains, digestive hemorrhage or obstruction, palpable tumor) – some lesions being incidentally discovered - and confirmed by radiology, endoscopy, intraoperative exploration and microscopic pathology examination which revealed 9 schwannomas, three leiomyomas, two lipomas, fibroma and “mixoma” one case each. Our cases were located on the stomach (n=12), small bowel (n=1) and right colon (n=3). All the cases were operated on being practiced tumor exeresis with mucous or parietal ruff excision, atypical, conservative and standard (segmentar or sectorial) visceral resection. There was no postoperative morbidity or mortality in our series. Median follow-up for our cases was 24 (range 6 – 60) months and there are not evidence of recurrences or metastatic disease. Even if the actual concerns are priority oriented towards the study of GIST, the current nosology of the tiny subgroup of mesenchymal (non-epithelial) “non-GIST” lesions of the

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digestive tract must be reloaded helping the practitioner which can be confronted with this pathology to a better evaluation and optimal therapy.

Key words: mesenchymal, non-GIST tumors, leiomyoma, schwannoma, diagnosis, treatment

Introduction

Mesenchymal (non-epithelial, stromal) non-GIST tumors of the digestive tract (MNGTDT), both benign and malignant, outnumbered by epithelial neoplasias and even lymphomas, are a lesional group which, for a long period of time, has been characterized by confusions and controversies related to its histogenesis, pathogenesis, anatomical and clinical features and biological behavior.

The traditional stage concerning histopathologic descriptions, with isolated observations or small case series was succeeded by the redefinition of these "bizarre" lesions in the studies initiated by Martin (1960), Stout (1962), Mazur and Clark (1983), the immunohistochemical and ultrastructural researches identifying their phenotype and biologic behaviour and clarifying their taxonomy by separating two main lesional subcategories (1,2,3,4,5,6,7,8).

The first one is constituted by the somewhat recently described GIST, which are believed to originate from the mesenchymal, pluripotent interstitial cells of Cajal (ICC), pacemaker cells destined for the initiation and coordination of gastrointestinal motility. The main role of the mutations is found at proto-oncogene c-kit gene level, codifying a tyrosin kinase transmembraneous receptor CD 117 (c-kit protein) which is a specific marker for these tumors and in a smaller proportion expresses the antigen CD 34. The unpredictable evolution of these lesions imposed the replacement of the "antinomy" benign – malignant with the term of stratifying risk of malignancy depending on the size and number of mitoses. Finally, the discovery of a highly selective tyrosin kinase inhibitor opened new promising perspectives in case of metastasis, recurrences or inoperability (9,10,11,12,13,14,15, 16,17,18,19,20,21). The second less numerous subgroup, but with a wide lesional spectrum, includes tumoral lesions composed of mesodermal tissues similar to those found in the soft parts of the body, i.e. smooth muscle and nervous tissue, as well as fat, fibrous and vascular cellular elements. Lesions associating two mesenchymal components or a combination with an epithelial structure are also described. Unlike the GISTs, the majority of these tumors have a benign behaviour, but rare malignant cases or ones with sarcomatous evolution are described as well.

The extremely low incidence of these true medical curiosities with which a surgeon can (by chance) be confronted in his career, determined the reconsideration of such cases treated in more than four decades of professional practice (22,23,24,25,26,27,28,29,30).

Patients and method

The retrospective series presents the experience accumulated relating to this pathology at the Ist and IVth Surgical Clinics of the "Gr.T. Popa" University of Medicine and Pharmacy Iași between 1970-2009, including 16 cases of MNGTDT, 9 males and 7 females with an average age of 53 (range 30-72) years*.

The medical files, imaging documents, pathology and operative protocols were reviewed. The final diagnosis was formulated by two brilliant pathologists: prof. Lorică Gavrilă and prof. Gioconda Dobrescu. We recorded 9 schwannomas – 8 gastric and one colic, three leiomyomas – gastric, ileal and colic, one case of each, two lipomas – gastric and colic, one case of each, and finally one fibroma and one "myxoma", both of the stomach. All these tumors were operated on and underwent case - adapted conservative or standard extended operations. There were no postoperative morbidity and mortality in our series. Average follow-up for our patients was performed at periods of 24 (6-60) months and there were no indicators of recurrences or metastasis.

Results

The majority of cases (12) were localized in the stomach (Table 1).

The gastric MNGTDT was represented by 8 schwannomas and leiomyomas, fibromas, lipomas and myxomas respectively, one case of each of the four latter. The majority of tumors was disposed on the antrum, a "sore" zone in terms of peristaltic, gastric secretions, and rich in histiocytic reticular elements. Two of the nervous tumors and the fibroma had an exophytic growth, the leiomyoma was interstitially developed and the remaining lesions protruded within the lumen.

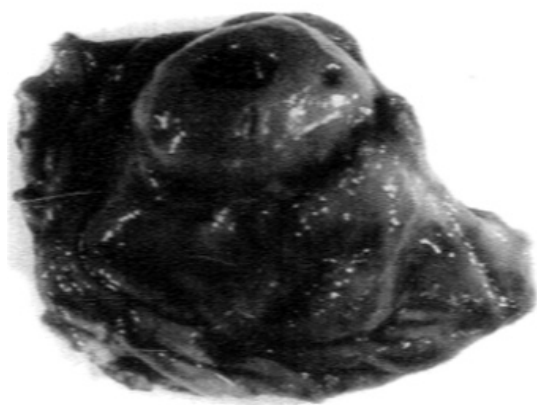
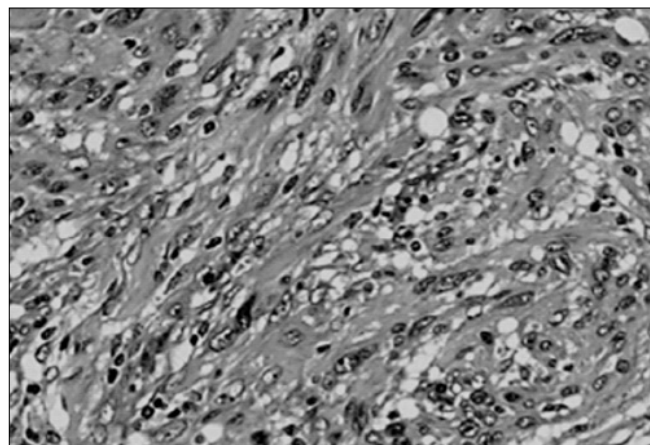
The clinical signs and symptoms of gastric MNGTDT were nonspecific, determining diagnosis delays and even errors. The main features can be classified in three categories:

- different dyspeptic complaints i.e. anorexia, satiety, digestive discomfort, pyrosis, ulcerous symptoms, gastric stasis, post-prandial fullness, bloating, nausea, vomiting - which were present in ten of our patients, in rare situations dominating the clinical scene, but having a guiding character;
- digestive bleedings - hematemesis and/or melaena, usually intermittent or occult, rarely with a life threatening character, all of them imposing however an active diagnosis policy in which the conventional radiology (Fig. 1, 2) gives way to emergency routine endoscopy.
- presence of a palpable, firm-elastic, regular, mobile, generally painless tumor, which can sometimes reach extreme dimensions if observed with exophytic development (two cases);

* In four cases the first author was a member of the operative team lead by professors Vl. Butureanu, M. Chifan, V. Strat and L. Vexler, the remaining ones being personally operated on, some becoming the subjects of publications (27,28,29,30).

Table 1. Demographic, clinical and radiological data, topography, size, operations and pathology in gastric MNGTDT

Case	Age	Sex	Clinical features	Radiology	Endoscopy	Topography	0 cm	Operation	Pathology	
1	BM	58	♂	melena, anemia	lacuna (menisc)	-	lesser curvature	5	tumorectomy	schwannoma
2	BG	61	♂	tumor, ascites	normal !	-	antrum ant face	15	tumorectomy+ruff	schwannoma
3	CI	54	♀	dyspepsia	lacuna	-	subcardial	3	tumor+parietal res	schwannoma
4	CG	72	♀	digestive bleeding	lacuna	-	fundus	6	fundus resection	schwannoma
5	RO	54	♂	dyspepsia	lacuna	-	antrum	4	antrectomy	schwannoma
6	SI	48	♂	ulcer-like	retraction, rigidity	-	lesser curvature	8	2/3 gastrectomy	leiomyoma
7	CM	56	♀	occult bleedings	lacuna	+	antrum	4	antrectomy	schwannoma
8	LB	56	♀	tumor, pain	normal !	-	antrum ant face	6	hemigastrectomy	fibroma
9	AN	48	♂	ulcer-like	lacuna + niche	+	antrum	3	antrectomy	lipoma
10	BI	50	♂	occult bleedings	lacuna	+	antrum	3	antrectomy	schwannoma
11	SG	53	♂	acute bleeding	"cockarde" image	?	great curvature	4	hemigastrectomy	myxoma
12	AN	57	♀	biliary colic	cholelithiasis	-	antrum ant face	2	tumor+parietal res	schwannoma

**Figure 1.** Rounded lacunae of the gastric fundus determined by a bleeding schwannoma**Figure 2.** Antral "cockarde" image of a bleeding myxoma with severe secondary anemia**Figure 3.** Gastric ulcerated schwannoma**Figure 4.** Gastric schwannoma; microscopy

- the symptomless or atypical evolution as in a recent case incidentally discovered in the course of a cholecystectomy for lithiasis must also be remembered.

In the case of gastric lesions we noticed the outstanding disproportion between the nervous tumor and the other ones from different tissues, contrary to the medical literature series which related the predominance of leiomyomas.

Five cases of schwannoma underwent a tumoral resection with mucous or parietal ruff (including also the huge extraphytic pediculated lesion with ascites). A fundusectomy with “tactic splenectomy” was performed on the patient with tumor located in the gastric fundus. Conservative standard exeresis (antrectomies, hemigastrectomies) were practiced in all the other cases. Gastric leiomyoma was found in only one 45 years old man, diagnosed and treated ten years for a peptic ulcer syndrome with capricious pains and high digestive stasis. An upper GI tract X-ray revealed retraction and rigidity of the lesser curvature and thick mucosal folds. Endoscopy was not supported by our patient. The surgical exploration confirmed the radiological accounts of infiltration, thickness and loss of elasticity in the last 8 cm of the vertical portion of the lesser curvature, process extended on 3-4 cm of both gastric faces. A “high” subtotal gastrectomy was performed. The gastric wall appeared thickened (1 cm), mainly due to the muscular layer, white-grey coloured flesh-like infiltration. Histology specified the diagnosis of gastric leiomyoma. (Fig. 5, 6)

In addition to this, a gastric lipoma, fibroma (with extrinsic development) (Fig. 7) and myxoma (Fig. 2, 8) respectively were also recorded. The lipoma was symptomless (and cade) the fibroma presented as a palpable tumor, but the myxoma determined acute, important, repeated hematemesis and melena leading to severe anemia and prompting intensive care measures, emergency upper GI tract x-ray (which revealed an antral cockarde – Fig. 2) – endoscopy not being available (?) and surgical exploration. A clear contured, mobile endogastric lesion with elastic consistence of 3 cm ϕ was located near the great curvature of the antrum, presenting a central active ulceration (Fig. 8). A generous hemigastrectomy was performed and microscopic examination ascertained the diagnosis of myxoma. Our case was cited by Miettinen in 2009 (31).

We report only one MNGTDT of the ileum in a 30 years old man urgently operated on for an acute obstructive syndrome. An ileal intraluminal tumor of 5 cm ϕ determining a small bowell intussusception was discovered and a segmentary enterectomy was performed. Microscopy showed leiomyoma with spindle cells disposed in palisade. The immuno-histochemistry was negative for CD 117 and CD 34 (Fig. 9, 10).

All three cases of colic mesenchymal non-GISTs tumors were right-sided: under the right angle, at the middle of the ascending colon and on the cecum, respectively.

The first one (LV, 32 year old ♂), was operated on elsewhere for a suspicion of acute apendicitis and diagnosed as a “cecal tumor” and referred to us. During relaparotomy a firm, sessil tumor of 5-6 cm ϕ , fixed to the posterior wall of the cecum with paracolic nodes was identified and a standard hemicolectomy was performed. Pathology confirmed the diagnosis of schwannoma (Fig. 11).



Figure 5. Gastric leiomyoma; operative specimen

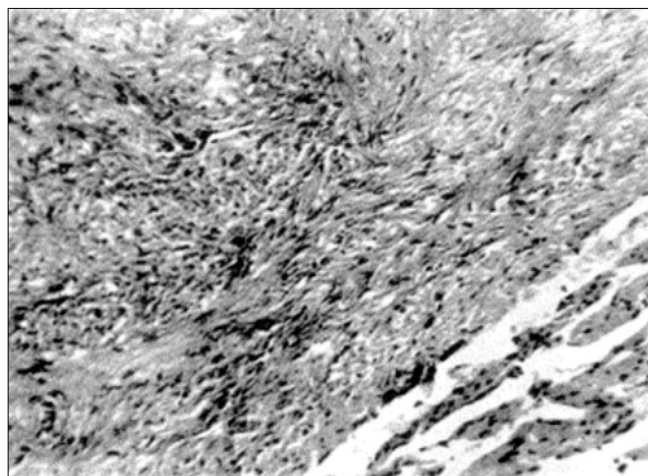


Figure 6. Gastric leiomyoma; microscopic aspects

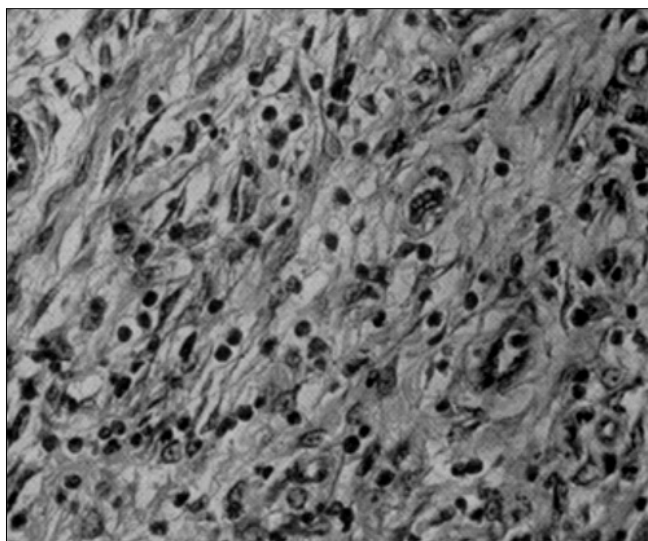


Figure 7. Gastric fibroma (microscopy)

The second patient, also a young (30 year-old) man, is hospitalised with pain in the right hypochondrium and flank, where a firm, regular tumor of about 5 cm in ϕ , seeming to

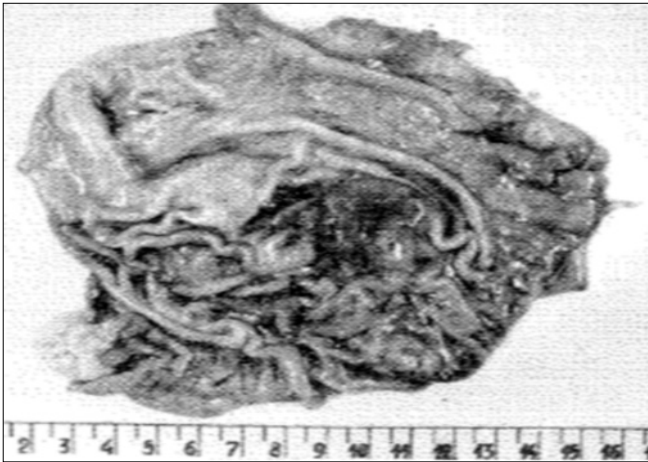


Figure 8. Gastric myxoma; operative specimen



Figure 9. Leiomyoma of the small bowel

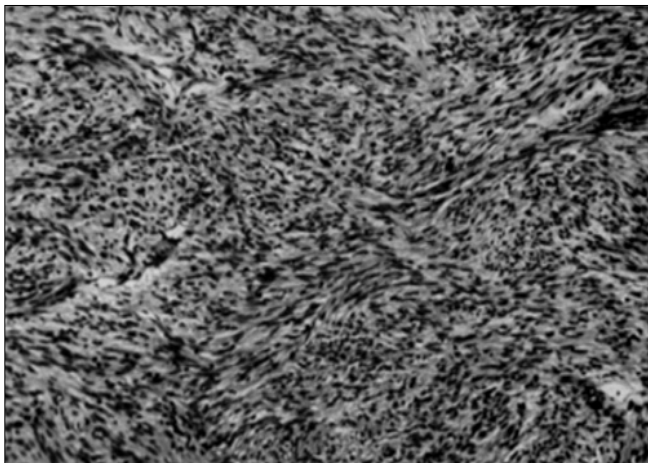


Figure 10. Ileal leiomyoma with fusiform cells

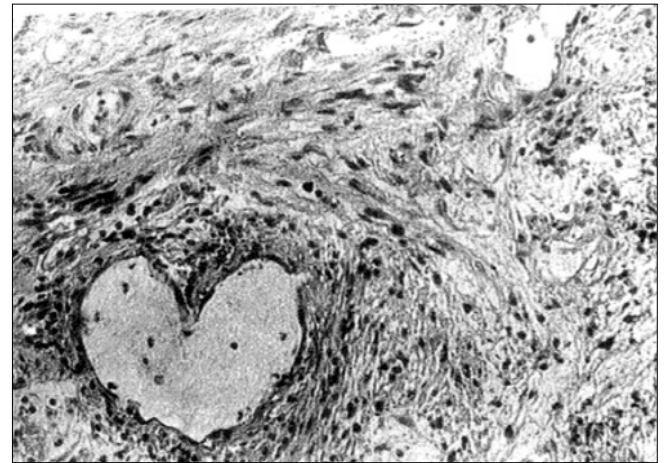


Figure 11. Colic schwannoma, microscopic aspect

joint the liver but without any digestive complaints is found. Calcifications in the area of the tumor on the plain abdominal radiography together with positive Cassoni reaction suggested the diagnostic of echinococcosis and no more investigations were recommended (!?). During surgery a firm, relative mobile, well conturated tumor that had developed on the medial side of the ascending colon, encountered by normal bowell wall and without adenopathy was identified. An exeresis of the tumor with parietal ruff was performed. (Fig. 12)

Histopathology showed a colic leiomyoma with central necrosis and calcifications.

Finally, the third observation of colic MNGTDT was a 68 year old woman complaining of pain in the right hipochondrium, alternance of diarrhea and constipation, bloating, weight loss and discrete anemia. Irigography highlighted an ovoid, radiolucent, supple lacuna, 5-6 cm in ϕ , on the ascending colon and colonoscopy a sessile, well-contoured polyllobated, brown-yellowish tumor (Fig. 13, 14). Clinical features, age and lack of pathological diagnosis were the arguments pleading for a standard right hemicolectomy. Pathology: the

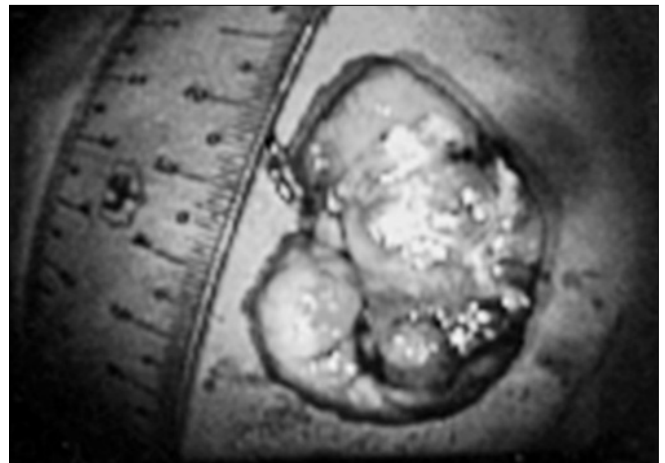


Figure 12. Colic leiomyoma; operative specimen

tumor was composed of mature adipocytes structured in lobules.

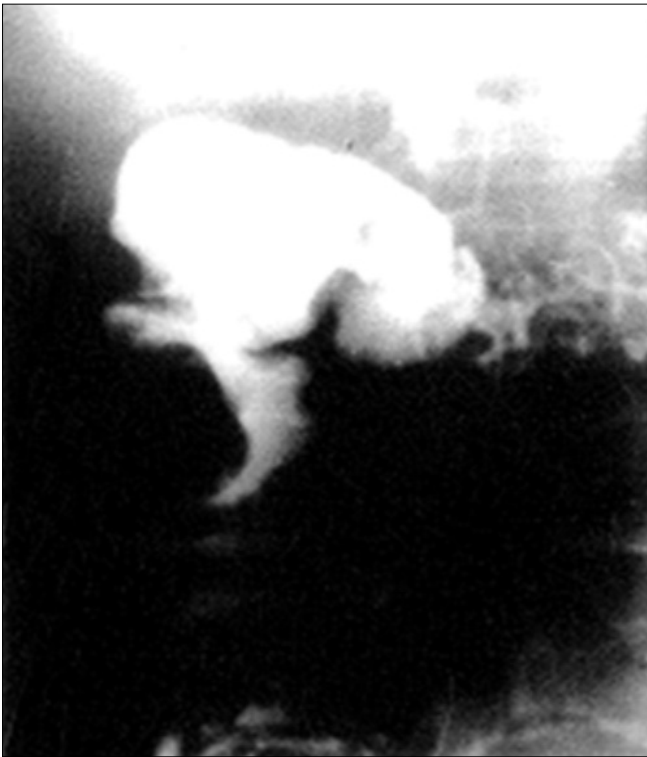


Figure 13. Ovoid lacuna of the ascending colon



Figure 14. Colonoscopy: colic lipoma

Discussions

Complex mesenchymal structure of the digestive tract determined a great diversity of the tumoral lesions, each tissue component having the potential of representing the origin of a neoplasia. This also contributed to numerous confusions in the definition, taxonomy, pathogeny and risk stratification, and particularly in the therapy of this pathology.

Aided by traditional foreign and also autochthonous mentions of cases of mesenchymal digestive tract tumors, modern researches were allowed to identify the majority group of GIST, all publications high lighting the immunohistochemical and ultrastructural characteristics, antigenic expression and biological behaviour of these lesions dominated by malignant propension.

Overwhelming numerical predominance of the GISTs inevitably lead to the minimization and even ignorance of the “genuine” digestive mesenchymal tumors composed of cellular elements identical with those from the soft body tissues, but with a benign evolutive statute and different prognostic. The long list of the MNGTDT – not closed by our cases – includes in a more or less aleatory order, smooth muscle and nervous sheath lesions but also tumors from the areolar submucous (subepithelial) tissues: fibrous, adipous, vascular and finally, different variants: glomic, desmoid or inflammatory fibroplastic tumours, mesenchymomas, hamartomas, clear cell or synovial sarcomas ... all of them illustrating the tisular richness of this wide anatomic territory. We briefly render from our experience the main morphoclinical features of these neoplasias.

Leiomyomas, only three cases in own experience, are the more frequent MNGTDT, originating from smooth muscle, muscularis mucosae and even from the musculature of the small vessels of the digestive wall. They are usually infiltrative lesions, also taking the form of polypoid protuberances and rarely of exophytic tumors. Microscopic features showed a paucicellular eosinophilic appearance with well-differentiated spindle-shaped cells and bland-looking ovoid nuclei without atypia. However in rare cases leiomyomas present large hyperchromatic synplastic nuclei with high mitotic rate and malignant behaviour. On immunohistochemistry they are positive for actine and smoothelene and negative for CD 117 (6,9,28,32,33,34).

Leiomyoblastomas, the old “bizarre” tumors of the smooth muscle, revealed themselves as intermediate structures between leiomyomas and leiomyosarcomas (7,35).

Schwannomas (neurolemmomas, neurinomas) are majority in our series, especially on the stomach. They derived from the nerve sheath of the Schwann cells and rarely from the cells of the peripheric sympathetic nervous system, differing however from their homologous lesions of the soft tissues. Usually they appeared as solitary, compact, round or oval shaped, circumscribed but not encapsulated tumors, with submucosal, interstitial, subserosal or sandglass development and variable volume from 1-2 to 3000 g. In terms of microscopy the lesions are composed of bundles of spindle cells with eosinophil, granular cytoplasm and focal significant pleomorphism, rare mitoses and a characteristic peripheral lymphocyte cuff. Schwannomas presented a strongly reactivity for S-100 protein. Their clinical course is slow and benign,

with hemorrhagic and mechanical complications due to the tumoral volume, but they present the possibility of malignant degeneration when not removed. Ultrastructural variants are autonomous nervous tumors (ancient plexosarcomas), granular tumors and hybriide, epithelial-stromal lesions (27,36,37,38,39,40).

Lipomas (adipocytic tumors) occur most commonly in the right colon and rarely in the stomach or other sites, as polypoid, unique, submucous, well delimited lesions of variable dimensions, sometimes determining obstructive phenomena. They are composed of uniform, mature, well-differentiated adipocytes without atypia. Even if rare sarcomatous changes are described, digestive tract lipomas have a solide reputation of benignity (30,41,42,43). The majoritary collagen componence of the mesenchymally tissues can determine the development of solitary fibrous tumors of the digestive canal, described by Vanekas originating from the muscular layers.

These lesions with generally firm consistency, are sessile, polypoid or pediculated, have different dimensions with possibility of subserous extension and are structured from mature fibroblasts, anarchically disposed in a dense, extracellular, collagen matrix. The positivity for CD 34 confirmed their fibrohistiocytic and dendritic nature however different from the ICC of GISTs' one. In the same family there are included inflammatory fibroid polyps, elastofibromas and plexiform or with eosinophil infiltration fibromas (44,45,46).

Finally, "myxoma" appeared as an intramural etalated process, with semitransparent aspect containing numerous irregular nodules composed from myxoid elements reproducing the mucoid tissue structure of the umbilical cord (Wharton's jelly). It consists of star shaped cells situated in a stroma holding muscle fibriles with scanty vascularisation. Miettinen described a fibromyxoma with capillary plexiform pattern, similar with the mixoid GISTs while Takahashi observed a plexiform angio-mixoid myofibroblastic tumor (29,31,47).

The rarity, nonspecific symptomatology and slow course of the MNGTDT, all of them persisting until an incidental or complication occasioned discovery, underlined the importance of diagnostic efforts in view of screening, defining their feature-precisely, planning and putting in practicethe therapy of these tumors.

Conventionally radiologic barium studies, which have been diminishing in importance lately, can still reveal the presence of lesions greater than 0,5 cm, asses their orgin, dimensions, number, limits and ulcerations, infiltration or rigidity of the digestive wall and stenosis or compressions from exophytic masses, but are unconvincing in terms of early or subtle aspects. Well-known images of these lesions are represented by rounded, solitary, regularly outlined lacunes or the objectification of a niche in the center of the tumor, achieving the "cockarde image". Calcifications in cases of leiomyomas and phlebolits in angiomas can be occasionally distinguished (48,49).

Modern imaging procedures bring diagnosis and topographic details, defining relations with adiacent structures. CT objectived homogeneous, hypodense with enhanced contrast structures and MRI allows lesions to be precisely localised,

monitoring the neighbouring structures' displacements. The examination presents hyposignal or moderate signal in T1 and hypersignal in T2. Postgadolinium sequences showed a slow and uniform lesion contrast intensification. Both last mentioned investigations, together with FGA-PET, are useful in post-therapy follow-up of these tumors (50).

Standard endoscopy and its modernisations becomes the first-line exploration in the diagnosis of MNGTDT (51,52). Wireless capsule endoscopy offering access to the entire small intestine, push and pull, double balloon and especially (tri-dimensional) endoscopic ultrasound are useful in obiectivization of these lesions and confirmation of the origin of an active or recent bleeding and also for some diagnostic or therapeutic purposes. Biopsies are considered of limited value but excisional biopsies of less than 2 cm lesions are valuables. Anyway, both provide specimens for immunohistochemical and ultrastructural examinations with KIT and PDGFRA identification trying to segregate the differences between GIST and non-GIST and benign and malignant lesions respectively, endeavours which are not always achieved, promoting surgery as the gold standard therapy of these lesions (53,54,55,56).

The indications, extension (enucleation, conservative excision, atypical, limited or segmentary visceral resection) and also the procedures of the surgical treatment (open, laparoscopic, endoscopic, robotic or combined) must be adapted to the lesion, the degree of certainty of the diagnosis, the intuition and the expertise of the surgeon (57,58,59,60,61).

Our work has some limitation that need to be adressed. First, it is a retrospective study with a small number of cases and few inclusion criteria: histopathology and prolonged survival without recurrences or metastasis.

Also, the majority of our patients benefited at the timeonly of reduced diagnosis possibilities: clinical examination, radiology and endoscopy, the CT scan, MRI or echoendoscopy being performed later or not at all.

Finally the absence of immunochemical and structural determinations of the specific tumoral markers may rise doubts about the non-GIST status of some of our observations.

Conclusions

In the pathology of the mesenchymal (submucosal, non-epithelial) tumors of the digestive tract, apart from well contured GISTs neoplasms, the existence of the non-GISTs lesions must be recognisedas well. Clinical rarity, nonspecific symptomatology, slow evolution, late or fortuit diagnosis and rare malignization yelds confusions or lack of a correct framing of these lesions with suboptimal therapeutical solutions (insufficient or mutilant operations). These difficulties increase proportionally in the absence of adequate investigations, in cases of emergency operations and lack of experience on behalf of the medical practitioners. A surgeon faced with clinical and paraclinical data which suggests such situations must also take into consideration the possibility of non-GIST tumors, exhausting the exploratory options, in order to prepare a well-adapted, efficient surgical act. Long-term postsurgical follow-up of these cases is mandatory.

Author's contributions

MRD – conceived the study and performed surgery
SD: drafted the paper, critical literature review

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