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About Two Rare Neoplasms of the Gastrointestinal Tract: Multicentric Epitheliod Angiosarcoma of Small Bowel and Symplastic PeComa of Colon - A Case Report and Literature Review

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Abstract

Two cases of rare gastrointestinal pathology are presented. The first concerns a 66-year-old man hospitalized for severe intestinal hemorrhage and hemoperitoneum. He presents multiple nodular lesions involving the jejunum and ileum. The histological and immunohistochemical findings lead to the diagnosis of Multicentric Epithelioid Angiosarcoma. Variant of angiosarcoma peculiar to the gastrointestinal tract, with particular clinical-pathological characteristics

The second concerns a 66-year-old man was admitted to hospital with symptoms of intestinal obstruction. The endoscopic examination revealed a large polypoid neoformation obstructing the lumen of the right colon. The combination of histological and immunophenotypic data of the intraluminal polypoid neoformation leads to the conclusion that the diagnosis of PeComa is consistent. The neoplasm presents some particular characteristics represented by the presence of bizarre, nucleolated and multinucleated elements with sometimes rhabdomoblastic-like aspects which has led to an in-depth differential diagnostic evaluation. The current literature at the moment does not offer concrete data for the nosographic and prognostic positioning of these morphological features.

INTRODUCTION

It is not unusual to encounter rare and difficult to interpret pathological entities in daily routine. Therefore, the Pathologist is obliged to be not only informed of their existence but also to provide the clinician with the elements for a correct prognosis and effective treatment. The cases covered by this study are an example of a rare pathology and challenging diagnostic difficulty

CASE 1

A 64 year old man was admitted to the emergency room for profuse enterorrhage. At laparotomy, abundant hemoperitoneum and numerous nodular formations were found scattered on the visceral serosa of of the jejunoileal loops. The section of the intestine where these neoformations were located was resected. The patient died a few days after surgery

MATERIAL AND METHODS

The surgical material consists of a section of the ileal loop and a jejunal segment. The ileal fragment measures 120 cm. At about 40 cm from one of the resection margins, whitish nodular formations are present on the serous surface. At the opening of the viscus, similar neoformations can be found on the internal surface (Fig.1a). The jejunal segment, 33 cm long, also presents similar whitish formations on the serous surface. Its lumen is almost completely obstructed by whitish nodular neoformations. Numerous fragments of the nodular neoformations are taken, fixed in buffered formalin and included in paraffin. Sections are prepared stained with Hematoxylin and Eosin, others are tested with a large panel of antibodies for immunohistochemistry

Table 1

KAE1-AE3	VIM	CDX2	CD56	CHRGR	NSE	SYN	DOG1	CD117	CD31	CD34	FLY1	WT1

HISTOPATHOLOGY

This is an apparently solid neoplastic proliferation (Fig.1b), consisting of cellular elements of globose appearance (Fig.1c), epithelioid (Fig.1d) with amphophilic cytoplasm and a voluminous, rounded, hyperchromatic nucleus (2a), sometimes strongly atypical (Fig.2b). Very lively mitotic activity. There are areas of labyrinthine appearance (Fig.2c) in which elements of hobnail appearance project (Fig2d.)

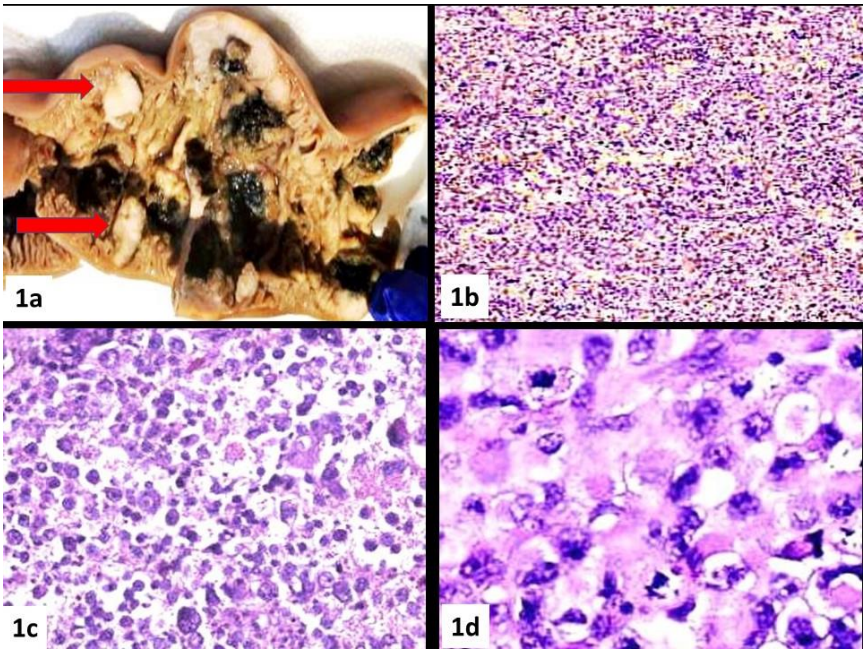

Fig 1. a) *Interior of a small intestine section. Whitish nodules are visible* **(arrow; b,c,d)** *Epitheliod Cells(HE 75,125,175 X)*

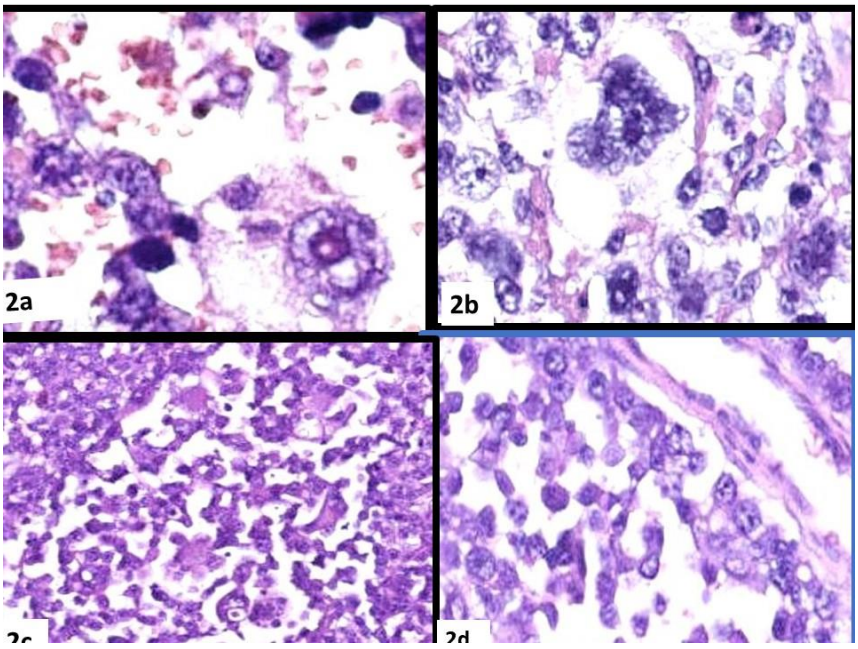

Fig 2. a-b) *Anaplastic Cells (HE 500X);* **c)** *Area of small labyrinthine cavities(He 125X);* **d)** *Pseudopapillary vegetations with hobnail elements(HE175X)*

IMMUNOHISTOCHEMISTRY

The results of the immunohistochemical investigation are summarized in Table 2.

KAE1-AE3	VIM	CDX2	CD56	CHRGR	NSE	SYN	DOG1	CD117	CD31	CD34	FLY1	WT1
+	+	-	-	-	-	-	-	90%	$+_f$	$-+_f$	$+_f$	$+_{fc}$

f=focal, c=cytoplasmic

In particular, an intense and diffuse expression of Keratin (Fig 3a) and Vimentin (Fig.3b) is detected. The endothelial makers, CD 31 (Figs3c-d) and Fl1 (Figs 4a-b) are expressed focally but with intense positivity. The same can be said for WT1 with cytoplasmic expression (Figs.4c-d). CD34 it is to be considered negative.

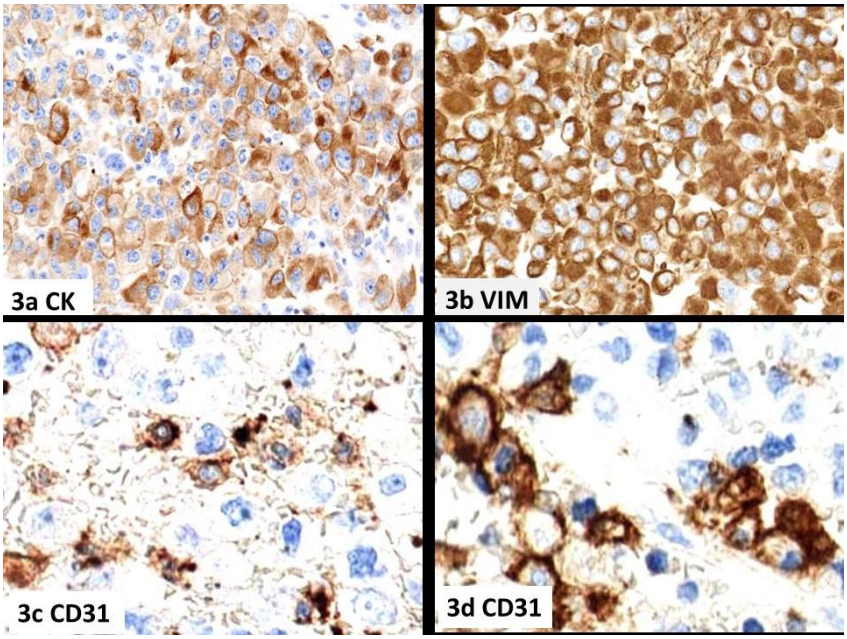

Fig 3. a) *Citokeratin AE1-AE3*; **b)** *Vimentin; c-d) CD31*

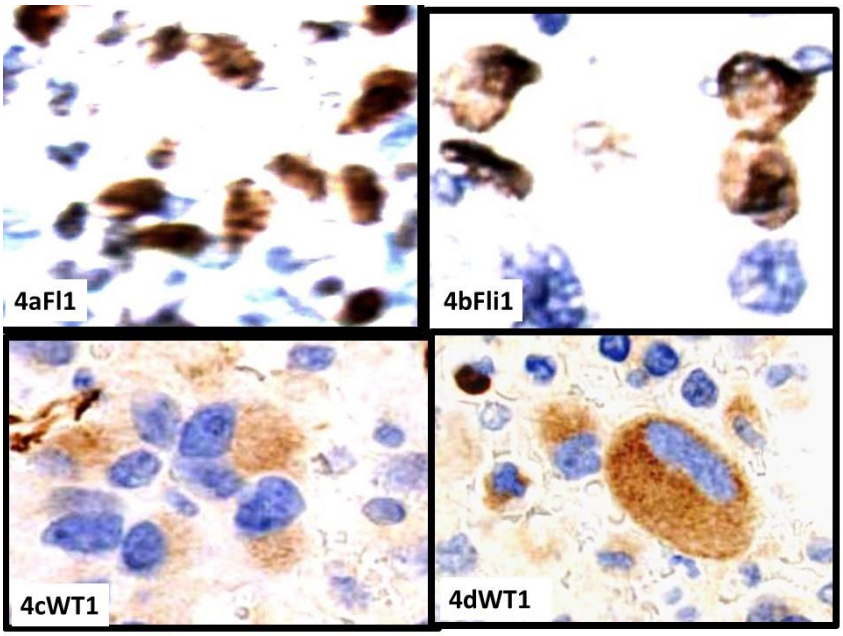

Fig 4. a-b) *FLI1*; **c-d** *WT1 Ccytoplasmic positivity*

DIAGNOSIS: Multicentric Epthelioid Angiosarcoma of the small bowel

DISCUSSION

A review updated to 2020 reports 98 articles dedicated to angiosarcoma of the gastrointestinal tract. For a total of 112 patients.

This indicates that the majority of these are reports of single cases. 45% involved the small intestine, 35.5% the large intestine. Esophagus and stomach respectively 2.7% and 3.5%.Of which 60% were male and 40% female. With an average age of 62 years. Restricting the analysis to cases relating to the small intestine, 70% were represented by males and 30% by females - with an average age of 63 years. 12% of patients had multiple lesions, ,7 cases (50.0%) involved the small and large intestine, 5 cases (35.7%) the stomach and small bowel, 1 case (7.1%) the esophagus and large intestine and 1 case (7.1%)

the stomach, small and large intestine.Bleeding of lower GI tract (melena or rectal bleeding) was present at 57.2% of cases, while 42.8% of patients experienced abdominal pain and 22.4% abdominal distention.[1]

In the well-differentiated forms of Angiosarcomas, well-defined vascular channels are recognized, whose lumens are lined with abnormal endothelial cells. As the aggressiveness increases, the architecture tends to change with cellular polystratification and papillary vegetations. In poorly differentiated tumors, the histological identification of an angiosarcoma can be challenging [2]. The one that presents the greatest diagnostic difficulties is the one defined as "epithelioid" fully described by Fletcher in a study of eight cases: "*Cardinal morphologic features were the diffuse, sheetlike growth pattern, with only focally apparent vascular differentiation, and epithelioid tumor cells with a degree of intracytoplasmic vacuolation/lumen formation. Immunohistochemically, all eight cases coexpressed keratin as well as endothelial markers*."[3]

This neoplasm must be differentially diagnosed with other epithelioid neoplasms: Carcinoma, Malignant Peripheral Nerve Sheath Tumor, Epithelioid Sarcoma,Melanoma, Maignantl Mesothelioma ,Anaplastic Large cell lymphoma, Epihelioid Hemangioendthelioma. The immunophenotypic profile of epithelioid angiosarcoma, in addition to diffuse and intense expressivity for Cytokeratins and Vimentin, is characterized by the expression of endothelial markers [4-5] as in Table 3.

Table 3

Marker	Sensitivity	Specificity
CD31	71-100%	High
CD34	40-100%	Low
vWF	50-84%	Hig
UEA1	70-87%	Low
FLi1	94%	High
ERG	100%	High

[4-5]

Scrolling through the literature, twenty items relating to epithelioid angiosarcoma of the gastrointestinal tract were found. In sixteen it was possible to identify the site: Duodenum #2, Jejunum #2, Colon #2, Stomac#2, Stomach+ileum #1.

A peculiar characteristic of angiosarcoma of the gastrointestinal tract is multifocality. So much so that it is considered a very distinct variant with particular clinical-pathological characteristics. Twelve items related to this condition are reported in the literature: in 3 cases the lesions are localized in the Stomach and Duodenum, in 2 in the Duodenum and Colon, in 1 in the Jejunum, in 4 in the Ileum, in 2 it is not specified

CONCLUSION

The case we studied falls fully within the framework of Multicentric Epithelioid Angiosarcoma of the gastrointestinal tract.

The clinical presentation dominated by haemorrhagic phenomena (enterorrhagia. hemoperitoneum) is classic for this type of neoplasia. As is characteristic the rapid fatal outcome followed after a few days by surgery.

Macroscopic examination of the surgical specimen highlights the presence of multiple nodules at the mucosal level, multifocality (Fig.1a)

On the microscopic level the epithelioid aspect is very evident, usually compact (Figs.1b-c-d). The malignant nature of the neoplasm is indicated by the presence of anaplastic elements and by the accentuated mitotic activity (figs 2a-b) A careful search is able to highlight areas of labyrinthine (Fig.2c) and papillary (Fig.d) appearance indicating the angiogenic aptitude of the tumor. Differentiation from other epithelioid neoplasms is, however, possible only at the level of immunophenotypic profile with the expression of endothelial markers, CD31, Fli1. CD 34 is often reported as very weak or even negative, as in our case [6,7] . WT1, tested for possible mesothelial primitiveness, was found to be expressed at the cytoplasmic level, as expected in vascular neoplasms [8-9]

CASE 2

A 66-year-old man was admitted to hospital with symptoms of intestinal obstruction. The endoscopic examination revealed a large polypoid neoformation obstructing the lumen of the right colon. The patient underwent surgery and was followed by right colectomy with resection of a portion of the terminal ileum.

MATERIAL AND METHODS

The surgical specimen includes a short segment of ileum, cecum and segment of right colon, with a total length of 22 cm. At approximately 4 cm from the distal resection margin, a large polypoid formation is found stenosing the lumen (4x3.4 cm). From the polypoid neoformation some fragments are taken, including also a section of the overlying mucosa. The material is fixed in buffered formalin and embedded in paraffin. Sections are stained with Hematoxylin and Eosin and tested with a panel of antibodies.

Table 4

VIM	ACTSM	MYO	MYOG	DESM	HMB45	MELA	SOX10	CKAE1-AE3	CK7	CK20	S100	CD117	Ki67

MYO=Myosin Smooth Muscle (SMMS-1),Myog= Myogenin

HISTOLOGY

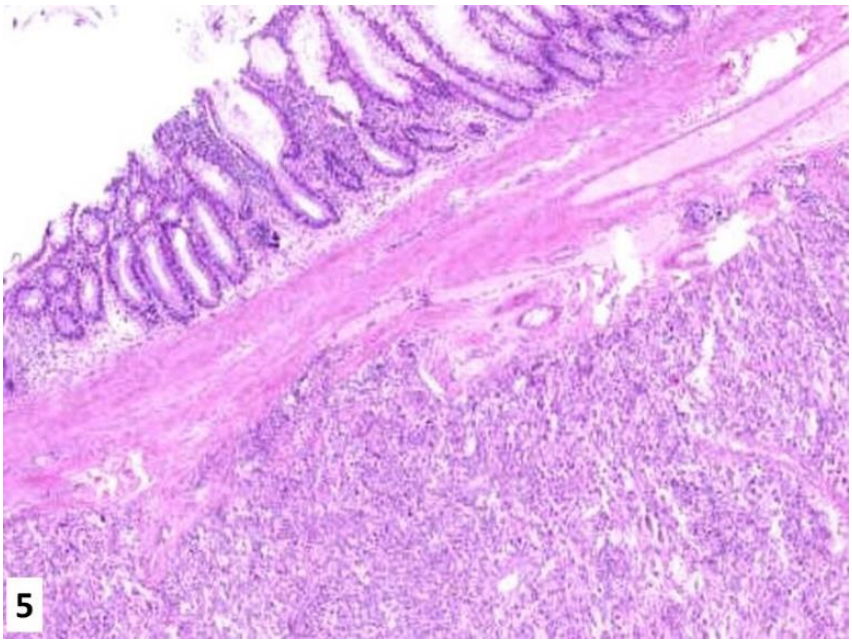

Fig 5. *Pushing behavior of the neoplastic proliferation located below an intact mucularis muosae(HE 175X)*

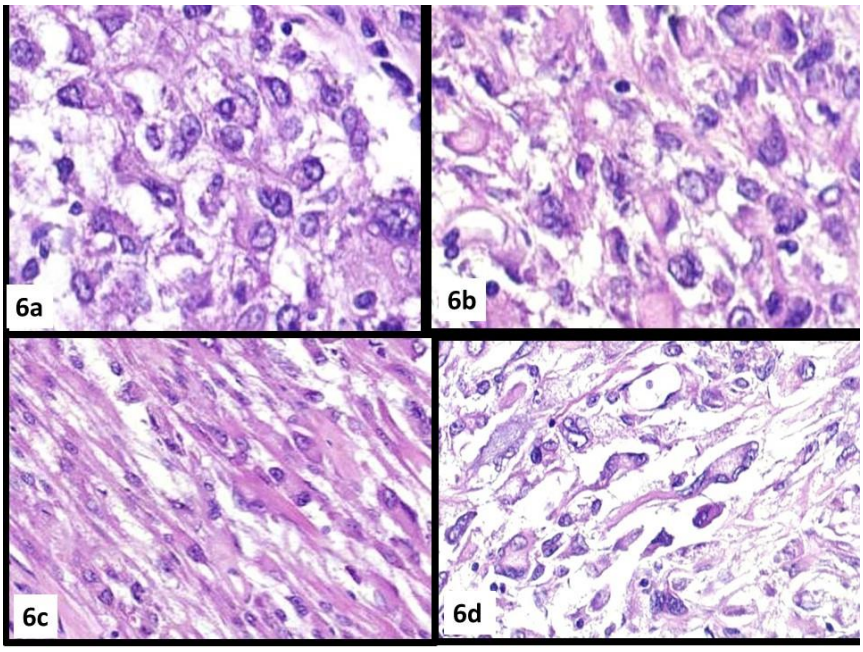

Fig 6. *Various aspects of neoplastic proliferation* **-a)** *clear cells;* **b)** *epithelioid cells;* **c)** *spindle cells; tadpole cells (HE 175X)*

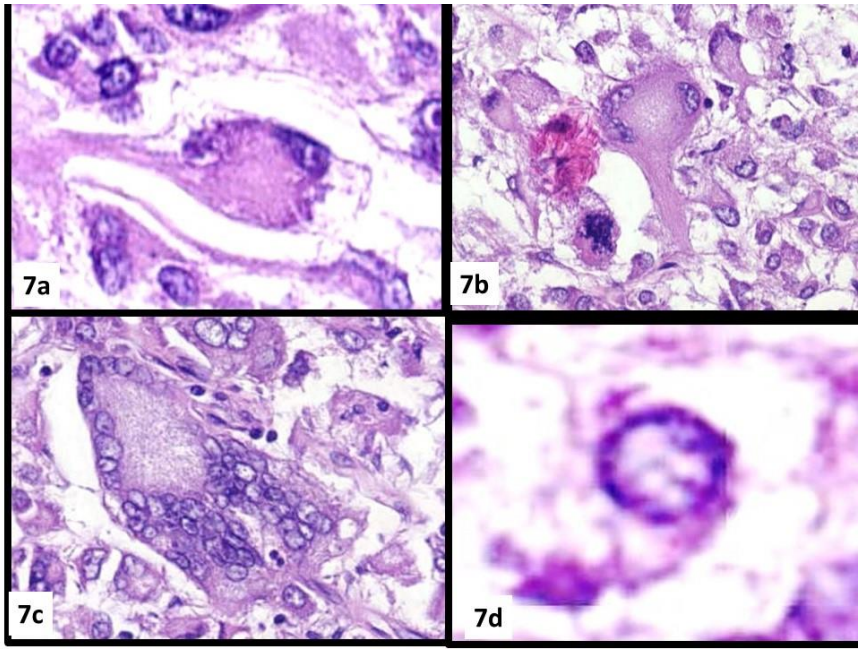

Fig 7. a) *multinucleated tadpole cell (HE175X);* **b)** *racket cell (there is a mitosis adjacent to it)(HE175X);* **c)** *Plurinuleated gisnt cell(HE 175X):* **d)** *nuclear pseudo inclusionHE 500X)*

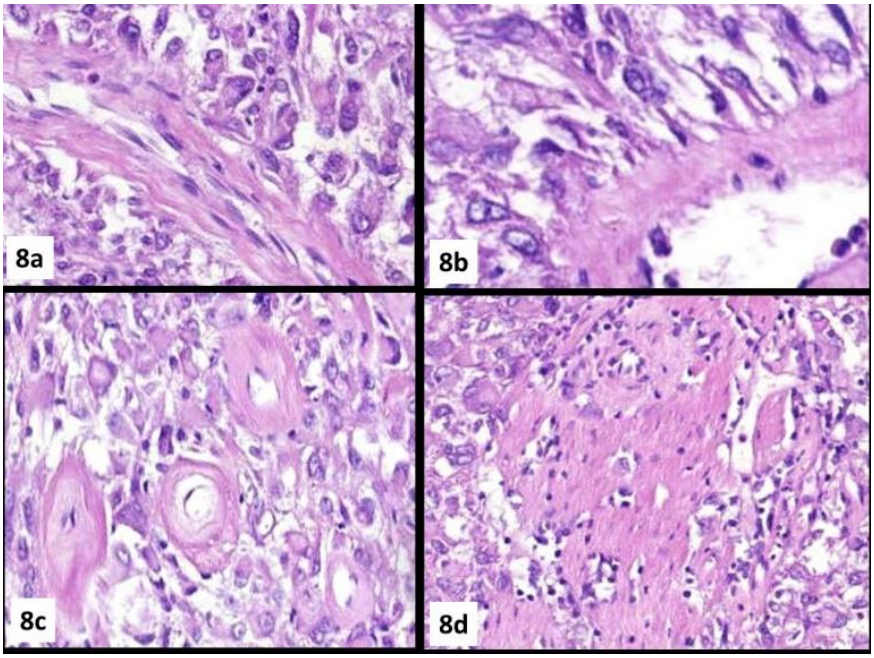

Fig 8. a-b) *Radial anchoring of epithelioid cells to a vessel wall(HE 175X);* **c)** *hyalinous thickening of the vessel walls(HE 175X);* **d)** *Fibrojaline band in which the lumens of some small vessels can be recognized(HE 125X)*

The neoplastic proliferation is located in the submucosa up to the muscular mucosae under which it expands in a pushing manner (Fig.5). It is a solid proliferation made up of elements of the most varied shapes and sizes. From Clear Cells with optically empty cytoplasm (Fig.6a), to Epithelioid with acidophilic cytoplasm (Fig.6b), to Spindle (Fig.6c) to Tadpole (Figs.6d-7a), to Racket (Fig.7b). The cells are often very atypical, sometimes monstrous, multinucleated with hyperchromatic and nucleolate nuclei (Fig.7c). Endonuclear pseudoinclusions are quite frequent (Fig.7d). Mitotic activity 2/50HP., it is possible to recognize neoplastic elements in close perivascular connection (Figs.8a-b), The muscular tunic of medium-sized vessels appears replaced and thickened by acidophilic hyaline material deposition (Fig.8c).

Thick accumulation of hyaline material intersect the neoplastic tissue, they seem to derive from the growth and fusion of the hyaline vascular walls. It is not uncommon, in fact, to recognize small vascular lumens within these bands. (Fig.8d).

IMMUNOHISTOCHEMISTRY

The results of the immunohistochemical investigation are summarized in TABLE 6 .

VIM	SMACT	MYO	MYOG	DESM	HMB45	MELA	SOX10	CKAE1-AE3	CK7	CK20	S100	CD117	Ki67
+	+	+	-	-	+	$+_f$	-	-	-	-	-	-	3%

SMACT = Smooth Muscle Actin, MYO=Myosin Smooth Muscle (SMMS-1), Myog = Myogenin, f=Focal

Smact is diffusely and intensely expressed in the spindle cell-predominant areas (Figs.9a-b), while Myosin is uniformly expressed in all elements (Figs 9c-d.). HMB45 is diffusely and intensely expressed (Figs.10 a-b), while MelA t shows scattered but intensely positive elements (Figs.10c-d.)

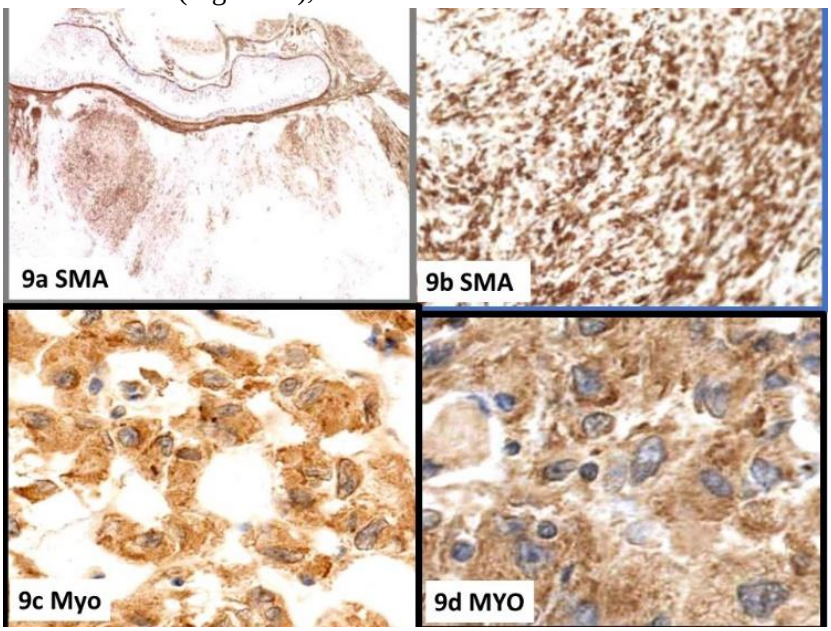

Fig 9. a) *At low magnification, the area of greatest positivity for SMACT can be recognized, which corresponds to b) the area in which the spindle cell component prevails;* **c-d)** *positivity for Myogenin is uniformly expressed. in* **c)** *the trabecular aspect is particularly evident. The trabecular cords delimit small vascular spaces*

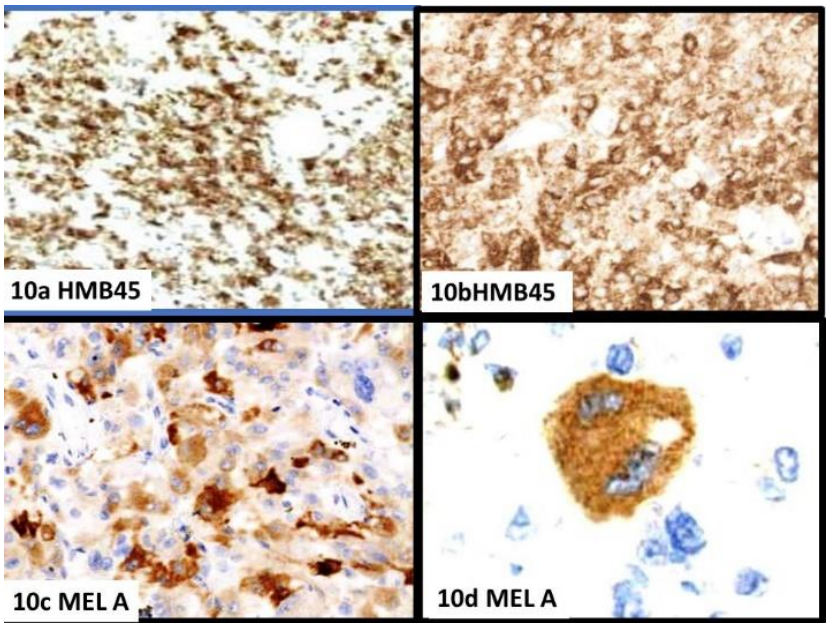

Fig 10. a-b) *HMB45 Intensely and uniformly expressed;* **c-d)** *MEL A with patchy expressiveness and variable intensity*

Diagnosis

Pleomorphic neoplasia with immunophenotypic expression leiomuscular and melanocytic consistent for PeComa

DISCUSSION

"PEComas are mesenchymal neoplasms composed of perivascular epithelioid cells (PECs) — distinctive epithelioid cells that are often closely associated with blood vessel walls and that express both melanocytic and smooth muscle markers"(WHO2020)[10] The nature of these cells is, however, conjectural because no normal counterpart has been described.[11] The term PeComa is an umbrella term that groups together a group of tumor entities that differ in morphology and anatomical location but have in common the simultaneous expression of leiomuscular and melanocytic markers. The first entity of this family is the so-called *Angiomyolipoma (AML)* whose classic location is the kidney. In 1991 the Verona group (Bonetti, Martignoni et al.) first demonstrated the expressivity of HMB45 by angiomyolipoma cells [12]. This same group demonstrated in 1994 that Clear cell ("Sugar") tumor of the lung is a lesion strictly related to angiomyolipoma [13]

The PeComa family actually includes in addition to the angiomyolipoma (AML), Clear cell "Sugar" Tumor of the lung(CCST) .Lymphangioleiomyomatosis (LAM),Clear Cell Myomelanocytic Tumor (CCMMT) of the falciform ligament / ligamentum teres,. And other tumors with similar features at various sites that are simply termed PEComa. May arise in almost any site; Retroperitoneum, abdomen, pelvis, Uterus, GI tract, Kidney, liver (AML), Lung (CCST, LAM) , uncommon in extremities, bone, skin.

Renal AML and LAM occur at increased frequency in patients with Tuberous Sclerosis Complex (TSC). Approximately 10% of all PeComas occur in people with the genetic tuberous sclerosis syndrome.

The morphological patterns of AML, CCST, LAML are quite characteristic, and, therefore, quite easy to diagnose. Instead in PeComas NOS, the morphological picture is completely anonymous which makes the diagnosis very difficult.

These tumors appear to be formed by by nests, trabeculae, or sheets of epithelioid cells, with cytoplasm sometimes predominantly acidophilic, sometimes predominantly clear, sometimes multinucleated. Often in perivascular radial position. Others are formed by spindle cells of myoid appearance. Very frequently with a mixed composition. Rare nuclear pseudoinclusion are sometimes detected. Scattered multinucleated and polymorphic cells were found in 54 and 77%, respectively. Sclerohyalinosis phenomena of the vascular walls and accumulations of interstitial fibrohyalin material are variously present. When predominant they give rise to the so-called *Fibrous Variant*. The literature reports TFE3, Hmb45, Melan A, Smooth Muscle Actin, Caldesmon, Miosin Smooth Muscle, Desmin as immunophenotypic markers of Pecoma. HMB45, Melan A, and SMA are expressed in almost 100% of cases. The others are present in variable percentages. Desmin staining of the tumor cells also revealed either focal, scattered, or weak to moderate results, but was completely negative within the thickened vessel walls [14 -15]

By inserting the entry Gastrointestinal PeComa into Pubmed (eliminating those relating to liver, pancreas, peritoneum and retroperitoneum) 42 items reporting lesions affecting the gastrointestinal tract from the esophagus to the rectum are obtained.

A study on 35 cases of PeComa in the gastrointestinal tract gave the following results:

Table 7

SITE	N°	%
Colon	19/35	54
Small Int	12/35	35
Stomach	2/35	6
Gall Bladd.	1/35	3
Omentum	!/35	3

A median of 45 years. A F/M ratio = 1.7:1. Pure epiheliod pattern was found in 20/35 (57%), pure spindled in 2/35 (6%), mixed spindle cell and epithelioid in 13/35 (37%). Patients with metastatic disease were 13/35 (37%) [16].

The Case under study offers the opportunity for some considerations regarding its nosographic location and its prognosis. First of all, the diagnosis of PeComa was not feasible at glance. The extremely polymorphic and atypical proliferation oriented towards other hypotheses of a sarcomatous nature with aspects very suggestive of a rhabdomyoblastic histogenesis. Therefore, the myogenin antibody was tested, which gave a completely negative result. On the contrary, smooth muscle antibodies (SMACT, Myosin) showed diffuse expressivity. The possible negativity for Desmin is, moreover, already reported in above mentioned literature. The expressivity for SMACT it is particularly intense and widespread in the areas where spindle elements prevail, while in those with a prevalence of epithelioid elements the expressivity is weak and sparse. Myosin is uniformly expressed in all elements. These data are widely reported in the literature. The data we observed regarding the greater expressivity of HMB45 towards Mel A is in agreement with what has been reported in the literature. Also significant is the deposition of hyaline material on the vascular walls whose growth gives rise to the formation of fibro-hyaline accumulatins inside which very often small compressed vascular lumens are recognizable. A peculiar aspect of this neoplasm for which we have not found evidence in the literature is the presence and significance of rhabdomyoblast-like elements and multinucleated monstrous cells. However, they are very different from those of the so-called Rhabdoid PeComas (17-18).

For PeComas NOS the histological prognostic criteria are currently codified as follows. *Benign*: <5 cm, noninfiltrative, non–high nuclear grade and cellularity, mitotic rate ≤1/ 50 HPF, no necrosis no vascular invasion; *Uncertain malignant potential*: Nuclear pleomorphism/ multinucleated giant cells only ("Symplastic" PEComa— or Size >5 cm only ("*Although PEComas with nuclear atypia/ multinucleated giant cells alone are probably benign, it is probably best to classify them as having "uncertain malignant potential," given the rarity of these tumors. It is more difficult to precisely classify PEComas showing only a single worrisome feature other than nuclear pleomorphism/ giant cells, in part owing to the rarity of such cases, and these cases should also be labeled as having "uncertain malignant potential," with the hope that this label will ensure long-term clinical follow-up")* ; *Malignant* : Two or more worrisome features >5 cm, infiltrative, high nuclear grade and cellularity, mitotic rate ≥1/ 50 HPF, necrosis, vascular invasion)(Folpe).[19]

CONCLUSION

The literature indicates that the intestinal localization of PeComa, although rare, is not extremely rare with a prevalence in the colic area (as in our case). The case we studied from an immunophernotypic point of view is compatible with the diagnosis *of Intestinal PeComa NOS with Symplastic morphological features*, with the following specific characteristics: Dimensions 4x3.4 cm, pushing expansion, diffuse presence of "Symplastic" elements, mitotic index 2/50HPF, proliferation index 3%, no necrosis, no vascular invasion. According to the parameters indicated above, it should be placed among the lesions with *Uncertain Malignant Potential* (UMP). Whether the finding of Symplastic elements in a PeComa is the expression of an autonomous variant or is a simple accident is not yet known, therefore the attribution of UMP is justified.

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