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Gastric Solid Glomus Tumor and Multiple Glomangiomyomas of the Large Bowel with Intravascular Spread, Multifocal Perivascular Proliferations and Liver Involvement

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The authors present a case of multiple glomus tumors (GTs) of the gastrointestinal tract, representing the type of a gastric glomus tumor proper and large bowel glomangiomyomas with myopericytoma-like features, observed in a 46-year old female, with multifocal perivascular proliferations of primitive cells and hepatic involvement. Histologically, the multilobular gastric tumor and hepatic lesions corresponded to a typical glomus tumor, while the tumor situated in the transverse colon, up to 7 cm in diameter, presented as a glomangiomyoma infiltrative (with myopericytoma-like foci), and satellite tumors in the large bowel mucosa, 0.5-0.7 cm in diameter, represented small glomangiomyomas. In addition, the patient demonstrated two types of concomitant vascular lesions: 1/ intravascular spread in the form of neoplastic plugs that obliterated the lumen of medium-size veins, and 2/ microscopic perivascular proliferation of primitive, small cells seen in the vicinity of the main tumor and in the adjacent adipose tissue. The patient has been ill for 2.5 years; she has been subjected to a partial colectomy with a resection of the small intestinal loop, greater omentum and the right ovary, followed by chemotherapy. At present, she is stable, and the infiltration – especially in the epigastric region – has decreased.

The picture may confirm the theory that multiple GTs develop in association with multifocal proliferation of perivascular stem cells, as well as that their ability to penetrate into the lumen of large vessels gives origin to satellite tumors, which are not necessarily metastatic. It seems that at present, the group of perivascular SMA+ tumors may include infantile-type myofibromatosis in adults, myopericytoma, glomangio(myo)pericytoma, glomangiomyoma, glomus tumor proper, and glomangioma. Most likely, also some tumors previously classi-

fied as hemangiopericytomas belong to this group. The distinctive feature present in at least some of the above listed perivascular tumors is their synchronous or metachronous growth in a particular region and their ability to occupy intravascular space as nodules or solid bands, which in turn may give origin to satellite tumors. Multifocal lesions associated with a short survival in a given patient will obviously support the presence of metastatic disease. In the remaining cases, determination whether the patient has metastatic disease requires deep consideration and caution, also while deciding on treatment to be employed.

Introduction

Glomus tumors (GTs) are uncommon mesenchymal perivascular tumors. They comprise about 1.6% of all soft tissue tumors [49]. The lesion was probably first clinically described in 1912 and subsequently, a histological description was provided by Mason in 1924 [25]. Glomus tumors are composed of cells histogenetically resembling the modified smooth muscle cells forming part of the specialized Socquet-Hoyer canal, an intrinsic anatomical component of the glomus body, and vascular spaces. Vascular channels, comprising an integral part of the tumor, are of a capillary size or are dilated, as in the cavernous angiomas. Tumor cells may be more rounded, like normal glomus cells, or spindle, like smooth muscle cells. GTs have been divided into three groups, according to the proportion of the three main components of these neoplasms: glomus tumor proper (solid glomus tumor), glomangioma (like haemangioma cavernosum with islands of glomus cells) and glomangiomyoma. The least common glomangiomyoma consists

predominantly of closely packed smooth muscle cells and capillary-size vessels.

GTs are usually benign, solitary, non-heritable and painful lesions. The vast majority of GTs are located in the skin and subcutis of the distal parts of the extremities and subungual region, but other – visceral – locations have been also described.

Multiple GTs account for approximately 10% of all cases of this tumor [49]. As solitary and sporadic lesions, multiple GTs mainly involve the peripheral sites, but are asymptomatic [6, 8, 13]. Multiple GTs situated in peripheral locations are much more common in children and adolescents as compared to adults [2, 6, 12]. Some, but not all of them are familial, with an autosomal dominant mode of inheritance with incomplete penetrance and variable expressivity [25, 18]. Histologically, they present as glomangiomas [46].

Multiple GTs in adulthood with the visceral location involving two different parts of the body and presenting as a glomangiomyoma variant of GT are very rare.

A Case Presentation

A 45-year old female was operated on for the first time in 2004 due to a tumor, 7 cm in diameter, involving the transverse colon. Multiple nodular lesions in the liver were noted intraoperatively and recognized as metastatic disease. The involved segment of the large bowel, omentum, the loop of the small intestine and the right ovary were resected. The primary histological diagnosis was a gastrointestinal stromal tumor (GIST) of the large bowel, metastasizing into the greater omentum and liver. Imatinib was introduced, initially at the dose of 400 mg/24h, with a subsequent increase of the dose of imatinib and additional introduction of celebrex at the dose of 100mg/24h. In view of the patient's failure to respond to the therapy and further progression of the disease as manifested by imaging studies, the treatment was discontinued after 12 months. In 2005, the patient was qualified for Sutent treatment. After two months, the medication was discontinued due to severe adverse effects. In February 2006, the patient was admitted to Second Chair of General Surgery, Collegium Medicum, Jagiellonian University, Cracow, where imatinib therapy was continued, employing the dose of 800mg/24h. CT demonstrated multiple hepatic foci, up to 11 cm in diameter. An irregular infiltration was noted in the hilus of the liver that extended to involve the wall of the stomach, duodenal loop, pancreatic head and the adjacent fragment of the hepatic lobe. Within the lumen of the right branch of the portal vein and in the veins situated in the confluence

of the mesenteric vein, lesions were seen that might be compatible with tumor plugs. A polycyclic, partially solid and partially cystic mass was seen in the minor pelvis that corresponded to a recurrent tumor (no histological confirmation). The patient was subsequently subjected to endoscopy, which revealed a multilobular, grape-like, submucosal tumor in the antrum of the stomach, several centimeters in diameter. Endoscopic tumor sections were collected for histopathology. Follow-up CT, ultrasonography and gastroscopy performed 6 and 12 months later demonstrated the lesion to have stabilized. Nodular hepatic lesions showed signs of disintegration, with the largest lesion being 12.5 cm in diameter. The infiltrate regressed in the region of the hilus of the liver, pancreas, duodenum and stomach. The gastric wall was irregularly thickened. In the vein draining into the superior mesenteric vein confluence, a tumor plug, 2.7 cm in diameter, persisted. The tumor situated in the pelvis minor decreased in size.

Material and Methods

The endoscopic specimens (case No. 1580729) and the core biopsy of the liver (case No. 1583752) were fixed in 10% buffered formalin, routinely processed, embedded in paraffin, and sectioned and stained with hematoxylin and eosin, alcian blue+PAS (pH 2.5) and for reticulin fibers (silver preparations).

Histological sections and paraffin blocks of tissue fixed in formalin were submitted to us for evaluation from the Department of Pathology, Wrocław. The sections originated from surgical material (No. 6104–6120/04), resected in 2004.

Immunohistochemical studies were performed on formalin-fixed, paraffin-embedded tissue using a DAKO immunostainer (DAKO, Denmark) and primary antibodies: VIM (1:50, DAKO, Envision), SMA (1:50, DAKO, Envision), DES (1:50, DAKO, Envision), CD117 (1:25, DAKO, Envision), CD34 (1:25, DAKO, Labvision), CD31 (1:20, DAKO, Envision), MIB-1 (1:50, DAKO, Labvision), PDGFR β (1:50, SantaCruz, Envision), ER (1:50, Novocastra, Labvision), PR (1:50, Novocastra, Labvision).

Microscopic findings

Endoscopic sections of the gastric tumor showed solid sheets composed of small, uniform, oval and polyhedral cells arranged around numerous, thin-walled, small blood vessels, either of capillary size or of small venules type. In one of the slides the cells formed a minute subepithelial

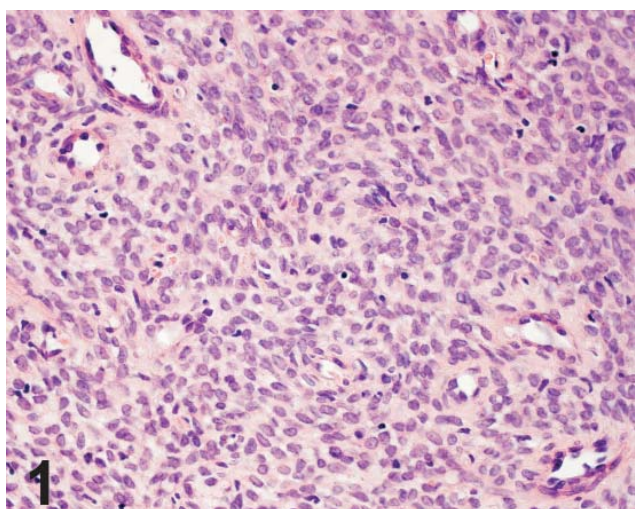


Fig. 1. Endoscopic biopsy of the gastric tumor: uniform cells are arranged around small vascular spaces.

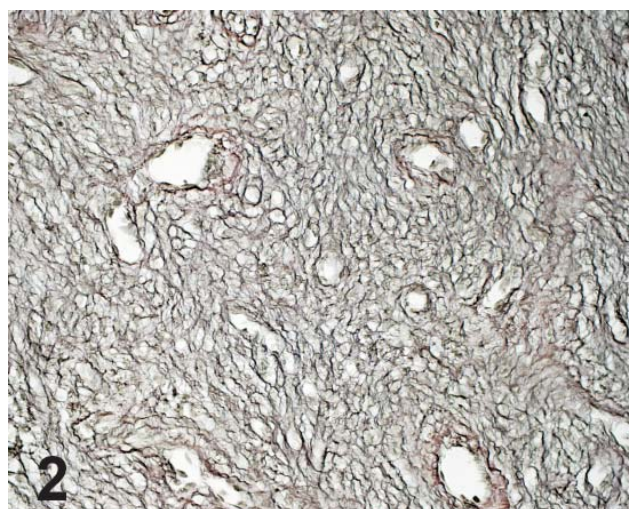


Fig.2. Endoscopic biopsy of the gastric tumor: a rich network of reticulin fibers encircling single tumor cells.

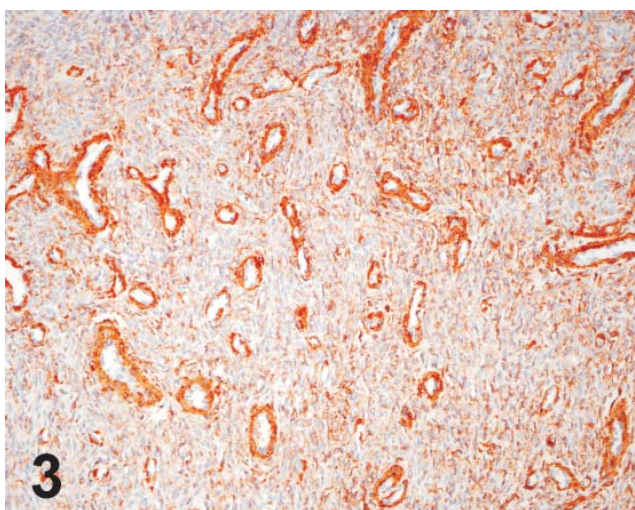


Fig.3. Immunoreactivity for SMA seen in almost all glomus cells.

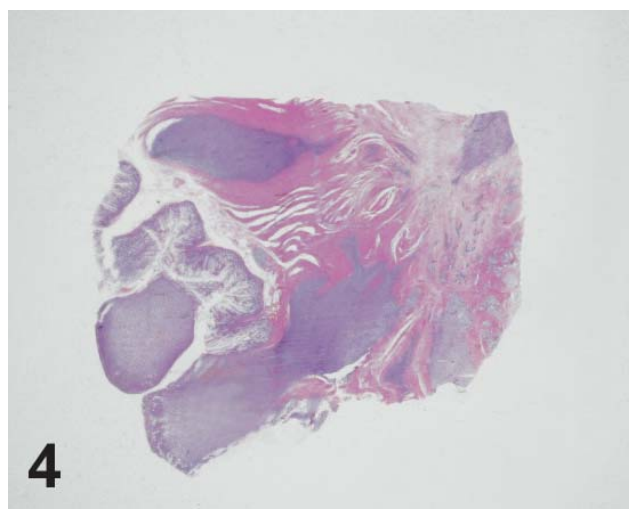


Fig. 4. Multiple satellite tumors in the large bowel developing underneath the surface epithelium.

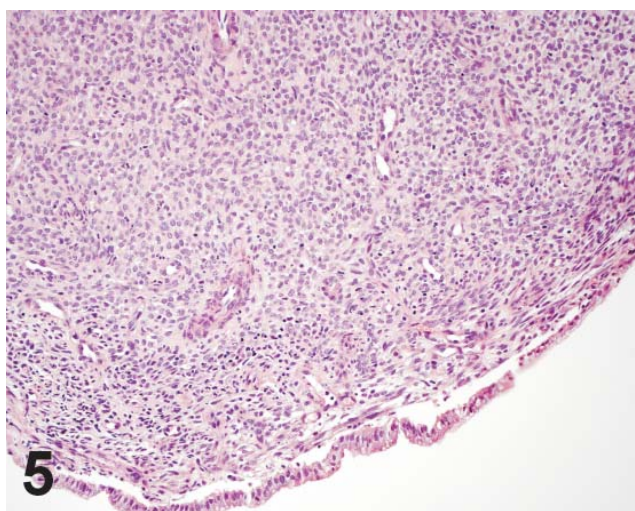


Fig. 5. One of the small multiple polypoid satellite tumors of the large bowel – here with a typical glomus tumor pattern.

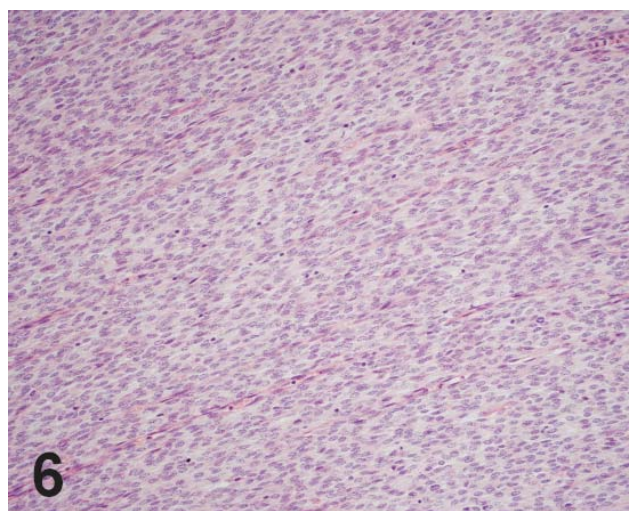


Fig. 6. The majority of the large bowel lesions consisted of uniform spindle cells arranged in bands.

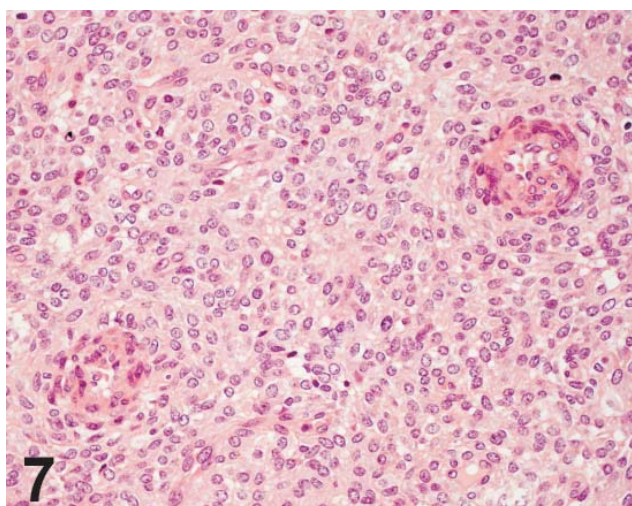


Fig. 7. One of infrequent myopericytoma-type fields in the large bowel tumor with a whirl-like arrangement of cells around vascular spaces.

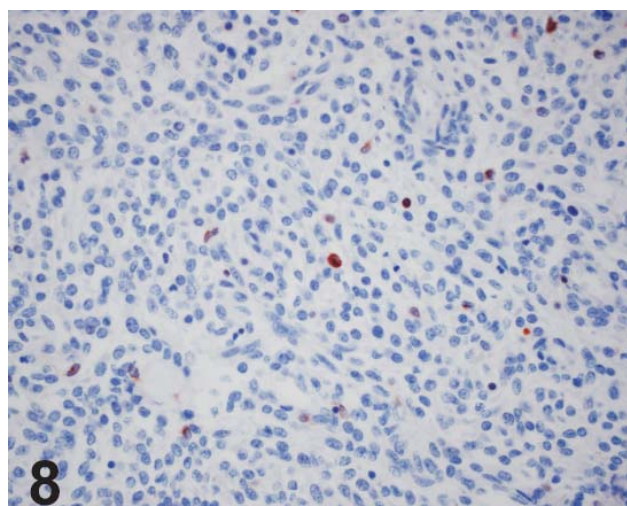


Fig. 8. One of only several fields showing single cells with proliferative activity (MIB-1).

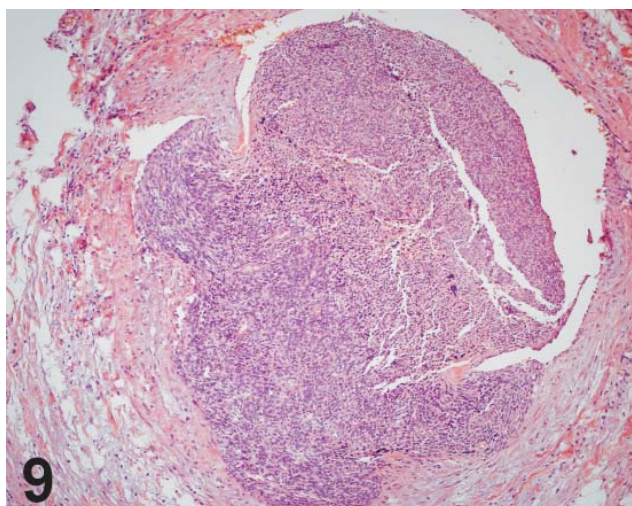


Fig. 9. A medium-size vein obliterated by a tumor plug with cytologically benign glomus-type cells.

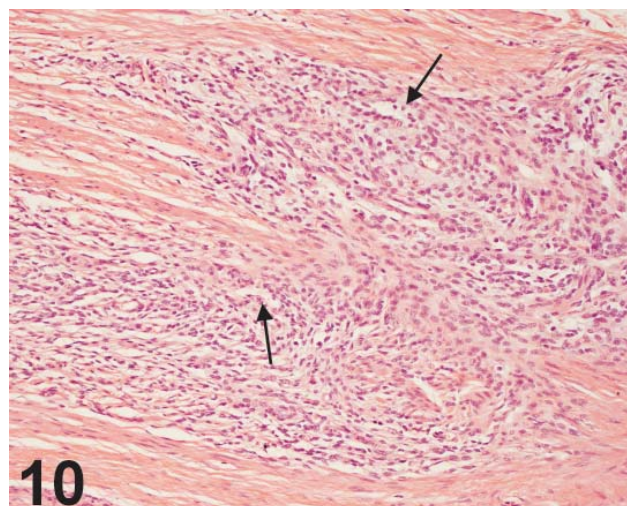


Fig. 10. Perivascular proliferations of primitive small spindle cells with scant cytoplasm; slit-like vascular spaces are visible (↑).

polyp. Tumor cells were characterized by faintly eosinophilic cytoplasm, round, centrally situated, slightly polymorphic nuclei, with inconspicuous nucleoli (Fig. 1). A dense network of reticulin fibers enveloped single cells and small groups of cells (Fig. 2). Immunohistochemically, the tumor cells were positive for SMA (Fig. 3) and VIM, and negative for CD117, DES and S-100 protein. Positive reactions to CD34 and CD31 were observed solely in vascular walls. The diagnosis was solid glomus tumor of the stomach. The same tumor properties were found in a core biopsy of the liver. In both cases, mitoses were absent and no proliferative activity was observed in reaction with MIB-1.

The specimens of the large bowel tumor, adjacent

adipose tissue and greater omentum showed tumor structures similar to those characteristic of gastric and hepatic lesions, but also displaying some variations: 1/ the uniformity of the cells was even more pronounced, 2/ fairly large areas of spindle cells were present (Fig. 6), 3/ occasionally, the cells were arranged circumferentially around vascular channels, forming concentric whorls (myopericytoma-like fields) (Fig. 7), 4/ thin-walled vessels were less numerous, 5/ the network of argentophilic fibers was abundant, but in some areas it enveloped single cells only, close to the vessels, being entwined around small groups and cords of cells in other locations. In addition to the main tumor mass, the preparations showed small, well-circumscribed nod-

ules, 0.5-0.7cm in diameter that grew in polypoid fashion in the lamina propria of the mucosa (Fig. 4, 5). Band-like tumor infiltrations involved the entire thickness of the large bowel wall and the adjacent adipose tissue. Tumor plugs obstructed the lumen of several medium-size veins (Fig. 9). In all the preparations, only single mitoses were noted, and only in one tumor section, a scarce number of MIB-1 positive cells were observed in several neighbouring fields (Fig. 8). Immunohistochemical reactions to SMA, DES, VIM, S-100 protein, CD117, CD34 and CD31 were identical as in the case of sections originating from the gastric and hepatic tumors. In addition, almost all tumor cells showed progesterone receptors. Reactions to estrogen receptors and PDGFRA were negative. Additionally, the neoplastic infiltration was accompanied by microscopic perivascular proliferations of very small, elongated, more primitive cells with hyperchromatic nuclei and with scant cytoplasm, showing no mitotic and proliferative activity in reaction with MIB-1 (Fig.10). The final diagnosis was a glomus tumor infiltrative characterized by a complex histological pattern.

Discussion

GTs involving the internal organs are most often situated in the gastrointestinal tract. Tumors of the respiratory tract are rare; isolated cases were described in the mediastinum, kidney, renal pelvis, pancreas, peritoneal cavity, female genital tract or the periurethral region [7, 14, 16, 22, 28, 30, 39, 42, 43, 44, 51]. A patient with a synchronous GT involving the esophagus (a single tumor) and the lungs (four nodules) was an exception to the rule [3].

In the gastrointestinal tract, GTs usually involve the stomach [10, 27, 33, 38, 47]. Up to 2002, close to 120 cases of gastric GTs were reported [38]. To this number, several score of GTs cases presented in Japanese literature should be also added [47]. The majority of gastric GTs were situated in the antrum; usually these were benign tumors, below 4 cm in diameter, but large (e.g. 8.5 cm), and even giant lesions – up to 12 kg - were also described [14, 21, 33].

A small number of GTs were detected in the esophagus, tongue and mesentery [3, 25, 40].

Intestinal GTs are much less frequent than gastric tumors. Since 1975, Russian authors have reported eight cases of single GTs situated in the small intestine, including two duodenal tumors. Unfortunately, only two abstracts are available that describe a giant (up to 17 cm in diameter) duodenal tumor growing into the bile duct wall and showing a cellular polymorphism, mitoses and necrotic foci [31], as well as a malignant GT of the jejunum with numerous metastases [41]. British literature reports merely several cases of GTs in the small intestine [15, 20, 26]. A duodenal GT

described by Jundi constituted a single lesion up to 23 mm in diameter that involved the mucosa causing superficial mucosal ulceration, and the submucosa; in HE staining and immunohistochemistry, the tumor demonstrated features typical for GT proper [26]. In addition, four cases of single GTs involving the large bowel were presented [4, 23, 38, 45]. The patients were adults, with the exception of a 10-year old girl with a lesion situated in the transverse mesocolon [23].

Multiple GTs account for a very small percentage of this type of tumors situated in the gastrointestinal tract. Several such lesions were identified in the stomach: in 1992, Haque found two tumors in the antrum and several concomitant satellite nodules in the gastric wall and the adjacent fatty tissue [21]. Chernekhovskaia presented a description of a multiple gastric GT in a 19-year old female, with no recurrence after two years [11]. In both the above quoted cases, the tumors corresponded histologically to GT proper.

Glomangiomyoma is the least common variant of GT (10%) [49]. Similarly as the other two histological variants, it may occasionally form multifocal lesions in the skin (glomangiomyomatosis) [9, 13, 32, 48, 49]. Single glomangiomyoma type tumors were observed in the internal organs [7, 28, 30, 39, 43, 44]. Two separate GT types developing in a single patient are also possible, as well as two histological patterns within a single tumor [9, 33, 46].

Multifocal GT-type lesions in women were tender in the course of menstrual cycle and during pregnancy, what might have been related to estrogen sensitivity [25]. In the present material, the tumors showed solely progesterone receptors.

And thus, in the presented adult female patient, exceptional circumstances cumulated: a multiple GT of the gastrointestinal tract with the involvement of the large bowel, two different histological GT types, a multifocal growth of glomangiomyoma type nodules, with glomangio(myo)pericytoma-like areas, as well as two variants of vessel-associated proliferation, i.e. tumor cells growing into the lumen of blood vessels and perivascular proliferation of small, undifferentiated cells.

Undoubtedly, the clinical course of the disease looked unfavorable, but histopathology alone did not allow for diagnosing glomangiosarcoma. In fact, only a single feature seen in the preparations, namely the infiltrating growth of the largest tumor situated in the large bowel, indicated a tendency to aggressive course, thus the diagnosis might have been „an infiltrative glomus tumor”. As to the presence of tumor cells within blood vessels, in the case of GTs such a phenomenon does not necessarily point to a malignant behavior of the disease. As it follows from the reports published to date, GTs are accompanied by two types of vascular involvement. One of them, more commonly seen,

is the intravascular spread [21, 37]. In a patient with multiple gastric GTs, Haque observed multifocal intravascular growth – band-like underneath the endothelium, and nodular, seen as polypous lesions that protruded into the vessels; in that case, perivascular proliferation was slight. The author favored the hypothesis that initially, the patient developed a single (two?) GT in the stomach, while the remaining lesions represented intravascular, non-destructive proliferation, analogous to that observed in an intravenous leiomyomatosis [21]. A cytologically benign glomangiomyoma of the bronchus was also described; the lesion invaded blood vessels [28]. Sometimes such a pattern was termed “vascular invasion”, but usually with a reservation that a pattern of local spread may be involved [38]. Miettinen found proliferation of this type in 11 of 31 GTs of the stomach, with only one metastasizing case. The presence of the glomus type cells in the lumen of blood vessels and beneath the endothelium was also cautiously termed „vascular space involvement”, without prejudgement about the biology of these cells [14]. Finally, isolated cases were reported describing solely intravascular tumor growth, as the pedunculated GT, 0.7 cm in size, situated within the vein and presented by Beham, and a giant tumor, 14 cm in diameter, encountered by Acebo [1, 5]. In addition to GTs, other myoid perivascular tumors, such as myopericytoma or myofibromatosis-type perivascular myoma also demonstrated ability to form intravascular nodules in some cases [19, 34, 35, 36].

Another type of vascular involvement is perivascular proliferation, which is more commonly seen around normal vessels in the close vicinity of a GT, and less frequently at a distance from the main tumor mass; it may provide a background for multifocal growth [18]. There is also a unique description of a malignant GT, which relapsed after primary excision, and the recurrence was accompanied by focal proliferation of mature structures resembling normal glomus bodies, which, nevertheless, lacked communication with the recurrent tumor [8].

The majority of GTs are benign tumors or at worst locally infiltrating lesions. Metastasizing GTs are rare. Some authors distinguish the following forms of malignant GTs: locally infiltrative, but cytologically bland GT, glomangiosarcoma arising in a benign glomus tumor, and glomangiosarcoma *de novo* [17]. Only in exceptional cases are purely histological properties indicating malignant character detected, which allow for an immediate diagnosis of glomangiosarcoma [14, 29]. Folpe studied 52 atypical tumors, eight of which gave histologically confirmed metastases. He proposed the following histological criteria for malignancy in glomus tumors: 1/ malignant glomus tumor is a lesion with a deep location and a size of more than 2 cm *or* atypical mitotic figures *or* moderate to high grade nuclear

grade and ≥ 5 mitoses/50 HPF, and 2/ a glomus tumor of uncertain malignant potential has only high mitotic activity and superficial location *or* large size only *or* deep location only. In his study, 38% glomus tumors which fulfilled the criteria of malignancy developed metastases. GTs of uncertain malignant potential did not metastasize [14]. Khoury described malignant glomus tumors and established that out of 45 malignant GTs of the skin and soft tissues, 25 cases metastasized [29]. In the series investigated by Miettinen, of 32 gastric and intestinal GTs, only one gastric tumor, 6.5 cm in diameter, metastasized and that tumor showed no histological features of glomangiosarcoma. The author suggested that the size of 5 cm might be a more appropriate indicator of risk of malignancy for deep located glomus tumors [38]. Folpe recognized that metastases might have constituted multifocal proliferation in the cases he described, but short survival in his patients indicated rather the tumor spread [14].

According to the above presented criteria, the GTs described in this paper, both involving the stomach and the large bowel, should be immediately classified as malignant (“deep” location and diameter above 2 cm).

On the other hand, GTs were described that were characterized by a large size and located in the internal organs, but did not metastasize [50]. Be it as it may, the category of “glomus tumor of uncertain malignant potential” seems to be definitely needed.

The group of perivascular neoplasms used to include glomus tumors and hemangiopericytoma. It has been established, however, that there are several kinds of tumors that partially manifest histological features of classic hemangiopericytoma, but share the property of perivascular proliferation of SMA+ myoid cells. These tumors, i.e. infantile-type myofibromatosis in adults, myopericytoma and glomangiopericytoma were combined by Granter to form a common group constituting „a histological continuum of lesions showing cytoarchitectural features of perivascular myoid differentiation”. Granter favored the idea that the tumors he described were arising from a pluripotent periendothelial cell with differentiation to the smooth muscle cells, pericytes and glomus cells [19]. Clusters of glomus cells are found not only in the glomangiopericytoma. Areas corresponding to typical glomus cells were also present in myopericytomas, tumors that sometime develop multifocally and have the potential for intravascular growth [34, 35, 36].

Thus, the group of SMA+ perivascular tumors arising from perivascular stem cells would include: infantile-type myofibromatosis in adults, myopericytoma, glomangiomyoma, glomangiopericytoma, glomus tumor proper, glomangioma and possibly the classic form of hemangiopericytoma. The majority of tumors formerly

regarded as hemangiopericytoma are presently classified as solitary fibrous tumors (CD34+), with not fully established histogenesis. Ultrastructural studies carried out by Ide et al. demonstrated the heterogeneous structure of solitary fibrous tumors (SFT). In addition to the undifferentiated perivascular mesenchymal cells and pericytes; the neoplasms constantly demonstrated the presence of endothelial cells and fibroblasts, and in one tumor, light microscopy demonstrated the presence of glomoid-type foci, whose ultrastructure corresponded to myopericytes. Myofibroblasts constituted a small minority, contrary to former theories on histogenesis. Based predominantly on their results of ultrastructural studies, the authors suggested that SFTs arise from perivascular pluripotent mesenchyma, differentiating into pericytes, fibroblasts and endothelial cells and – in the glomus-type areas – also into myopericytes (in immunohistochemistry, these fields were SMA +). Obviously, intermediate forms were also seen in the SFTs, such as fibroblast/pericyte or pericyte/endothelial cell [24]. Thus, cells that are candidates for primary neoplastic proliferation would be undifferentiated mesenchymal cells - perivascular stem cells – that undergo concentric perivascular proliferation, similarly as it was suggested by Granter in the case of perivascular myomas.

A distinctive feature of at least some of the above mentioned perivascular myoid neoplasms is synchronous or metachronous multifocal growth in a given region of the body, as well as the ability to occupy intravascular space as nodules or solid, subendothelial bands, which in turn may provide the background for satellite tumors developing in the vicinity. Multifocal lesions with short survival in a particular patient will, of course, indicate neoplastic spread. In the remaining cases, establishing whether we deal with a metastasis requires a thorough analysis and caution, also when selecting appropriate treatment.

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