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Complex treatment after pathohistological and immunohistochemical analysis in synchronous neoplasms - anorectal achromatic malignant melanoma and gastric extrapleural solitary fibrous tumor

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Abstract

A 76-year-old woman diagnosed with extremely rarelysynchronous neoplasms - rectal malignant melanoma (RMM) and a benign variant of gastric extrapleural solitary fibrous tumor (GESFT) is presented. Against the background of a literature review, the pathomorphological characteristic, the necessary immunohistochemical panel and the difficult differential diagnosis with the wide range of benign and malignant mesenchymal tumors are discussed. The necessary complex oncological treatment, directly depending on the prognostic risk factors for each of these synchronous tumors is analyzed.

For the first time in the English medical literature, a clinical case with synchronous tumors - rectal achromatic malignant melanoma and gastric solitary fibrous tumor is presented.

After complex treatment, including surgery and adjuvant radiotherapy of the RMM and surgery of the gastric tumor, we report a one-year disease-free survival with a good quality of life.

Introduction

Anorectal malignant melanoma (ARMM) is an extremely rare and very aggressive disease with a very poor prognosis [1-5]. This highly malignant entity constitutes only 0.5-4% of all anorectal malignancies and less than 1% of all melanomas [6,7]. The first description of ARMM in the literature dates from 1897, by Moore [8]. Amelanotic lesions are frequent in mucosal melanoma [9]. The incidence is difficult to calculate because several authors indicate amelanotic melanomas those only partially devoid pigment at visual inspection [10,11]. Solitary fibrous tumor (SFT) is a rare neoplasm, first described as a pleural formation in 1931 by Klemperer *et al.* [12]. Subsequently, it was found that SFT is localized not only in the intrathoracic organs and structures, but also in extrapleural areas, involving soft tissues and parenchymal organs [13]. SFTs make up <2% of all soft tissue tumors [14,15]. Gastric localization of SFTs is a very rare disease, which by 2018 was published in seven patients, one of whom with pronounced pathohistological dedifferentiation [15]. For the first time in the English medical literature, a clinical case with synchronous tumors - rectal achromatic malignant melanoma and gastric solitary fibrous tumor is presented.

Clinical case

We present a 76-year-old patient with symptoms including diarrheal syndrome and periodic rectorrhea with anal pain. The diagnosis was made in October 2019 after rectocolonoscopy with biopsy. In January 2020, after immunohistochemical analysis of the biopsy material, an operation, including extirpation of the rectum a modo Miles with simultaneous partial resection of the stomach was performed.

From the examinations: Rectocolonoscopy: Approx. 4 cm from the anorectal line, a tumor process on the posterior wall, ulcerated and easily bleeding to the touch was found. A biopsy for histological verification was taken.

CT of the thorax and abdomen: Lung, mediastinum, liver, gallbladder, pancreas, spleen, adrenal glands, kidneys - without pathology observations; There are no pathologically enlarged paraaortic, pelvic and inguinal lymph nodes. Small pelvis:

Rectum - Near the sphincter along the lateromedial contour on the left, there is a reinforcing intraluminal formation. Free perirectal adipose tissue, no visible changes.

Stomach- In the middle third, along the greater curvature, there is an intramural lesion measuring 35/24 mm, with calcification on

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the upper surface, a solid component in the lateral part, as well as a hypokinetic area near the mucosa. Macroscopically, the gastric tumor resembles GIST.

Intraoperatively: After mid-xyphopubic laparotomy, in the distal part of the large curvature of the stomach, an intramural tumor 4 cm in diameter with a macroscopic GIST was found. Partial resection of the stomach with removal of 2 cm of healthy tissue surrounding the tumor was performed. Liver metastases and enlarged paraaortic lymph nodes were not detected. On the posterior wall of the rectum, 3 cm proximal to the anus, a tumor formation was found. Sigma and rectum were dissected and total mesorectal excision with abdomino-perineal extirpation of the rectum modo Miles was performed.

Histological diagnosis: Macroscopic description: 1) **Resect of the colon (recto-anal area)** with a length of 35 cm. In the area of the rectum at the level of the anorectal line a nodular tumor 6 cm in diameter is found, with lobulated surface, inhomogeneous brown color and hemorrhage. When cut macroscopically, the tumor does not pass into the surrounding soft tissues. The tumor is 3.5 cm from the outside of the anus. ; 2) **Part of the stomach** 6/4.5 cm. A submucosal incision reveals a nodule with a gelatinous consistency with a diameter of 2.5 cm. Areas with calcifications and cartilage density are established.

Microscopic description

The tumor of the rectum is represented by solid nodules of the same type of cells with sparse cytoplasm and large round nuclei with mostly peripherally located chromatin and large nucleoli. The cells are closely spaced, with no distinct stroma between them, only the presence of capillaries in places. In some areas there are hemorrhages and intercellular edema, giving discohesion to the cells. No pigment is found. Cell growth is reported among the colon glands, enclosing them without destroying them, thus some of the glands are atrophic and others are dilated and filled with mucus. There is mitotic activity. The tumor engages the mucosa and submucosa with ulceration (Figures 1A and 1B); **Resection line** - free of tumor cells; Anus - acanthosis and papillomatosis of the epidermis; free of tumor cells; Regional lymph nodes/12 pieces/without metastases, with sinus histiocytosis.

Soft tissue tumor of the stomach, located submucosally with the involvement of the tunica muscularis. It consists of randomly arranged cells of different types: those with round nuclei, others with small elongated nuclei and others with morphology of single and multilocular lipoblasts with low mitotic activity (Figures 2A , 2B and 3).

Immunohistochemistry (IHC)

From the rectal tumor: Diffuse positive IHC expression in tumor cells for HMB 45; S100 protein; Melan A (Figure 4).

From a gastric tumor: Diffuse positive CD34 reaction in tumor cells and tumor blood vessels and adjacent gastric wall (Figure 5A and 5B) and focal positive S100 protein expression in part of tumor cells (Figure 5C).

Negative reaction for CK AE1-AE3 in tumor cells, but positive expression in normal gastric epithelium adjacent (Figure 6A); Negative reaction for SMA and Desmin in tumor cells, but positive in blood vessels (Figure 6B and 6C); Negative reaction for Myogenin (Figure 6D).

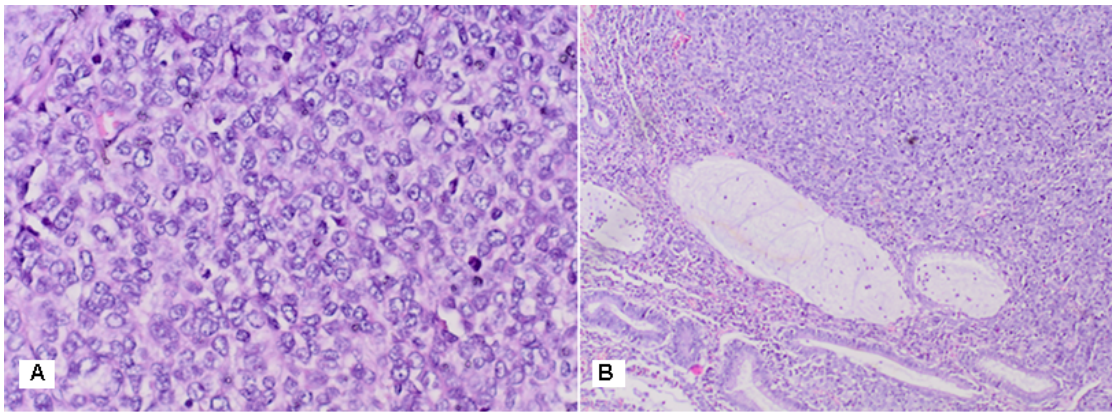

Figure 1. Pathohistological characteristics of rectal achromatic malignant melanoma: A) H & E x 40; B) H & E x 20

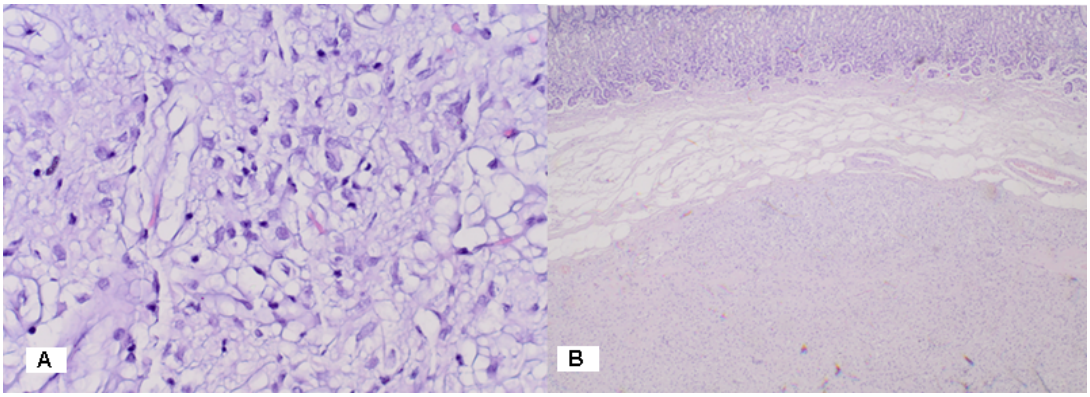

Figure 2. Pathohistological characteristics of gastric solitary fibrous tumor: **A)** H & E x 40; **B)** H & E x 4

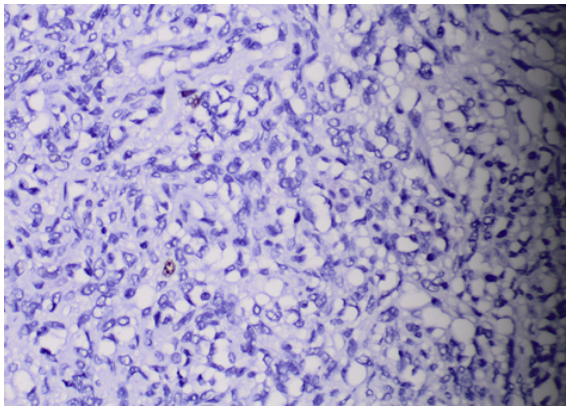

Figure 3. Photomicrography of Ki 67 IHC expression: Low mitotic activity 1% -2% x40

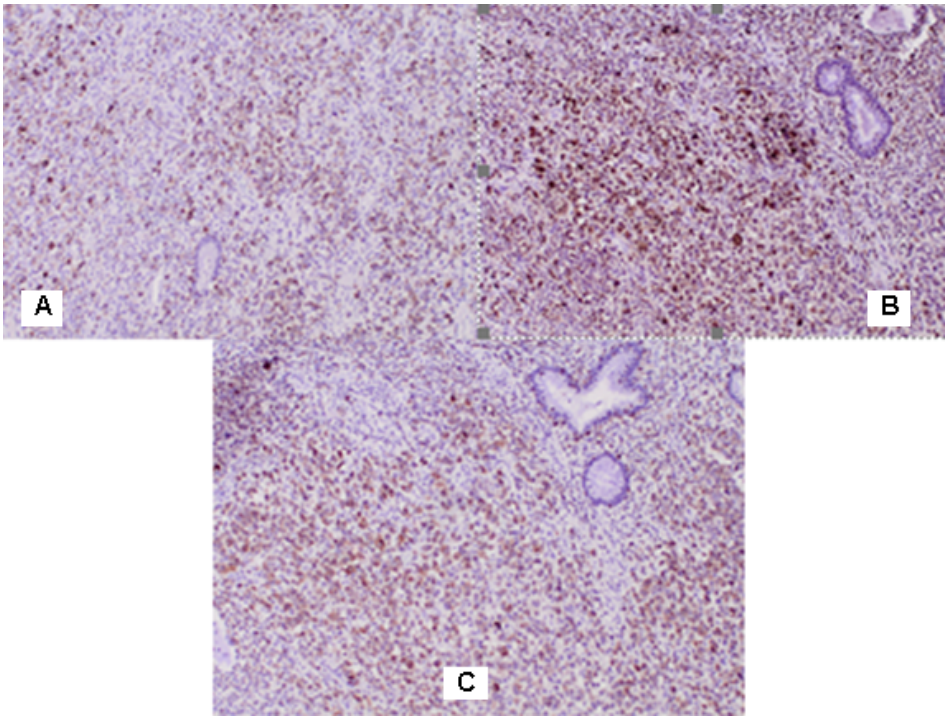

Figure 4. Photomicrography of positive diffuse IHC expression in tumour cells in anorectal malignant melanoma: **A**) HMB 45 x 20; **B**) S100 protein x 20; **C**) Melan A x 20

Histological diagnosis

1) After IHC**: Achromatic malignant melanoma of the rectum - small cell variant pT3pN0Mx G3/ Stage II; 2)** After IHC**: Benign variant of gastric solitary fibrous tumor**

Postoperatively, adjuvant intensively modulated radiotherapy (IMRT) with VMAT technique in the anorectal tumor bed up to total dose (TD) 56 Gy and in the pelvic lymph nodes bilaterally up to TD 54 Gy with a daily dose (DD) 2Gy was performed (Figure 7).

To assess the need for therapy with BRAF inhibitors or MEK inhibitors, a molecular biological analysis for mutations in codon 600 BRAF, that were missing was performed. The patient was assessed for dispensary observation. During September 2020, on the control CT examination with intravenous contrast of the thorax, abdominal organs and small pelvis - no pathological changes are found. After one year from the diagnosis of synchronous tumors, the patient is without local recurrence and distant metastases, in good quality of life.

Discussion

All melanomas, whether cutaneous or mucosal in origin, originate from melanocytes, which are cells derived from the embryological neural crest [1]. The rectum has a typically glandular epithelium. On the other hand, the anal canal, below the pectineal line, is covered by a squamous epithelium [16]. Right above the pectineal line is the transition zone, where both glandular and squamous cells are present. Melanocytes may appear in the three regions (rectum, anal canal and transition zone), although the occurrence of melanoma is more frequent in the transition zone and squamous epithelium [17-24]. A timely diagnosis of anal melanoma is made even more difficult by the fact that up to 80% of lesions lack obvious pigmentation and up

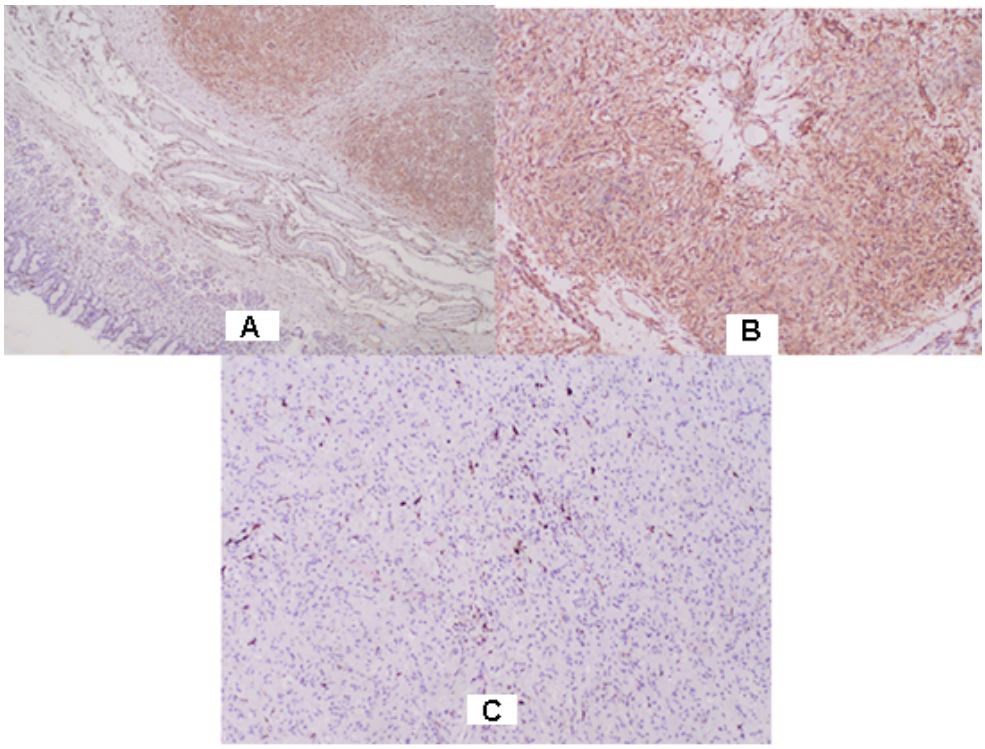

Figure 5. Photomicrography of positive IHC expression in gastric solitary fibrous tumor: **A**) CD 34 x 4; **B**) CD 34 x 20; **C**) S100 protein x 20

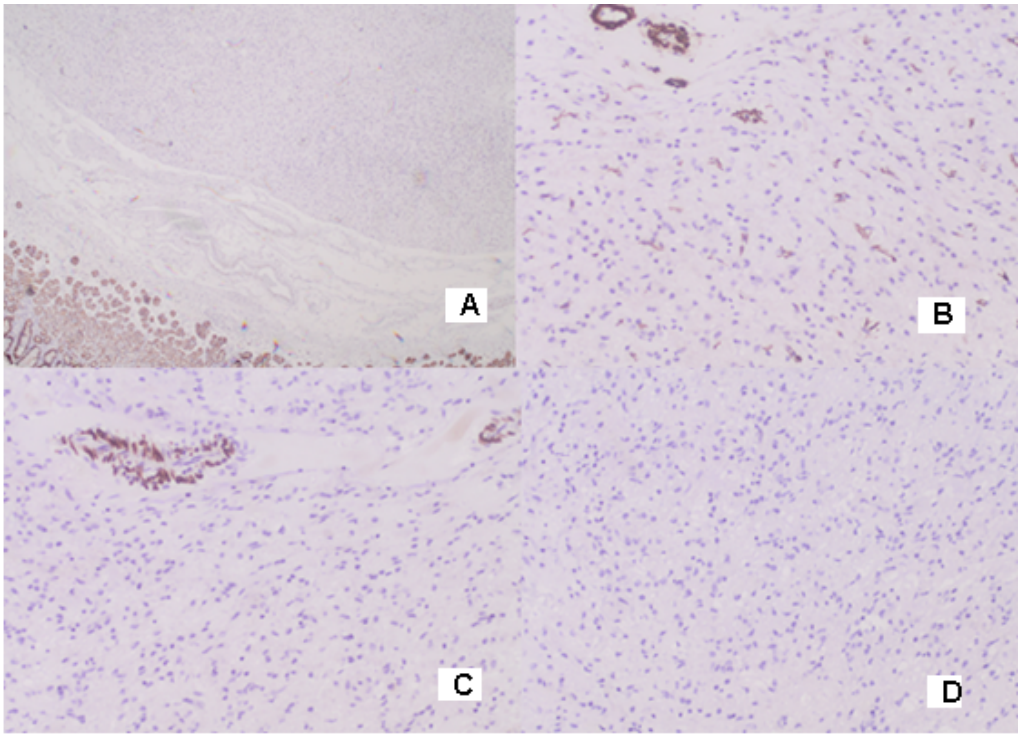

Figure 6. Photomicrography of IHC expression in gastric solitary fibrous tumor: **A**) Negative reaction for CK AE1-AE3 in tumor cells, but positive expression in normal gastric epithelium adjacent x4, **B**) Negative reaction for SMA in tumor cells, but positive in blood vessels x 20; **C**) Negative reaction for Desmin in tumor cells, but positive in blood vessels x20; **D**) Negative reaction for Myogenin x 20

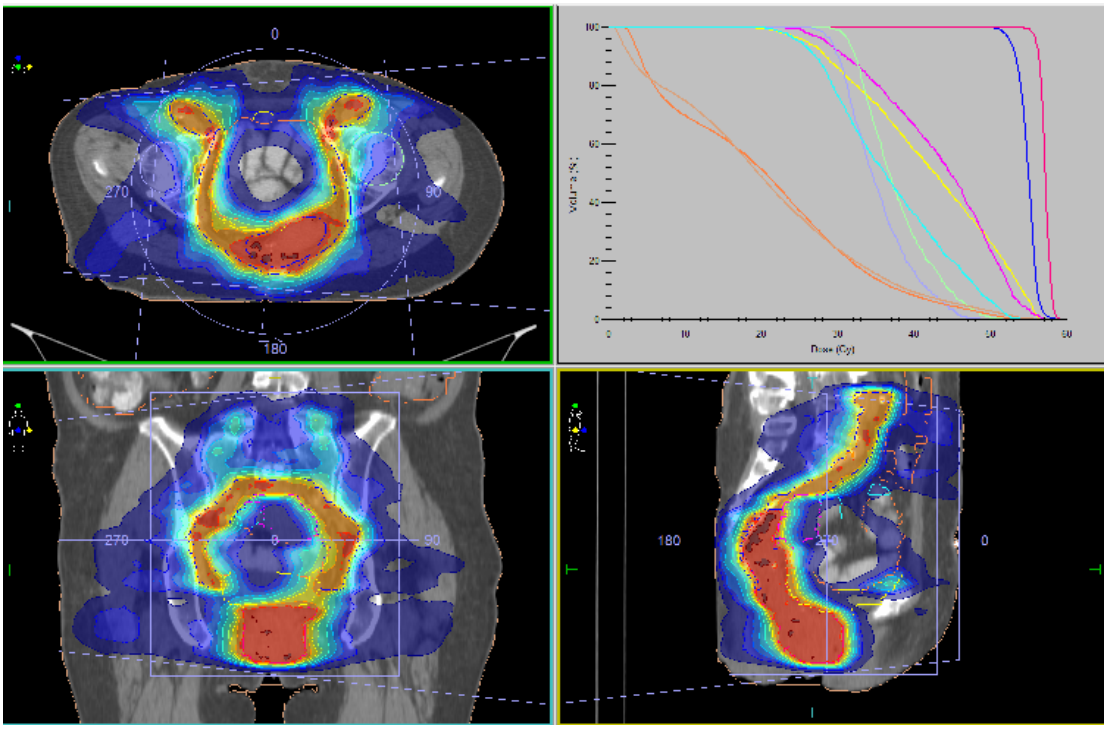

Figure 7. Adjuvant IMRT with VMAT technique in the anorectal tumor bed up to TD 56 Gy and in the bilaterally pelvic lymph nodes up to TD 54 Gy with DD 2Gy

to 20% of tumors are even histologically amelanotic [25,26]. ARMM is often misdiagnosed in about two thirds of patients and most often as haemorrhoids, adenocarcinoma polyps and rectal cancer [27]. Anal melanoma is staged on a clinical basis, focusing on loco-regional and distant spread. Stage I is local disease only, Stage II is a local disease with increased thickness and ulcerations, Stage III is local disease with involvement of regional lymph nodes, and Stage IV shows distant metastatic disease [6,28].

Pathohistological characteristics

Macroscopically observed single or multiple, large polypoid mass, 80% pigmented, grows near dentate line [29]. The pathohistological microscopic characteristic is identical to cutaneous melanomas with the following cellular patterns: epithelioid; spindle cell; lymphoma-like and pleomorphic [30,31]. Melanoma cells are larger than normal melanocytes, with large and irregular nuclei, well or poorly clustered into nests (Figure 1). The higher the number of mitoses, the worse the diagnosis [16].

Immunohistochemistry (IHC)

ARMM is characterized by positive IHC expression to HMB45, S100, Melan A [1,16,17,30] and negative to Keratin [30]. In Figure 4, we report diffuse positive expression of tumor cells to HMB45, S100, Melan A.

Differential diagnosis (DD)

Differential diagnosis is required with some diseases such as as Paget, Bowen, lymphomas, undifferentiated carcinomas, sarcomas and gastrointestinal stromal tumor (GIST) [29,31,32]. It is achieved by strict immunohistohistochemical analysis. Thus, especially in amelanic ARMs (but also in melanocytic ones), immunohistochemistry should be performed - the study of protein expressions of melanocytes [32].

Complex treatment

The surgical treatment with curative intent should be proposed, considering the disease stage and the clinical conditions of each patient [17]. Most frequent approaches include: Abdominoperineal Amputation (APA) and Wide Local Excision (WLE). For a long time, the APA was considered the standard therapy, but several studies have demonstrated no significant difference in survival when comparing it to more conservative approaches (APAversus WLE) [17-24,33]. APA should be performed in case of larger tumors, recurrences, disease with locoregional invasion or when a good local control is required [16]. Despite the treatment options and attempts, the prognosis remains guarded, with survival rates in five years as low as 6% and mean survival of 25 months [17-24,34], regardless of the treatment type [35,36]. Radiotherapy (RT) and chemotherapy (Ch) are considered ineffective for treatment of ARM. Some authors who have used RT-Ch reported that they did not observe any advantage [37,38]. One of the subgroups of ARM, with mutations in the BRAF gene, respond to the action of BRAF inhibitors (PLX4032 and RAF265), leading to regression of disease in up to 70% of patients with metastatic melanoma with BRAF V600E mutation [39]. The medications used in adjuvant therapy are cisplatin, vinblastine, dacarbazine, interferon B, and Interleukins IL-2. Dacarbazine is the most commonly used single agent and usually initiates a partial response in 20% of patients in 4-6 months after treatment [6,28].

Solitary fibrous tumors (SFT) are uncommon fibroblastic mesenchymal neoplasms estimated to account for <2% of all soft tissue neoplasms and occur typically in the fifth or sixth decade [40]. Since then, nonpleural SFTs have been described as originating from almost every anatomic location of the human body, but reports of SFTs in the abdominal cavity are rare [41]. Little is known about the natural history and malignant potential of these; however the literature suggests that the majority (78-88%) are histologically benign [42]. There were only

six SFT cases arising from the stomach reported in the literature with none having features of dedifferentiation and early metastatic spread to liver [43-44].

Pathohistological diagnosis is often difficult due to the rare incidence of SFT and the wide range of benign and malignant mesenchymal tumors. Soft tissue tumors with hemangiopericytoma (HPC) - resembling a growth model are divided into three categories: 1) solitary-fibrous tumor group with histological variants; 2) lesions with clear evidence of myoid/pericyte differentiation and the corresponding "true" HPC (Myopericytoma/glomangiopericytoma and the subgroup of the sinonasal HPC; 3/ neoplasms that occasionally show HPC-like functions (synovial sarcoma) [45,46]. SFTs are neoplasms, often showing a hemangiopericytoma-like vascular arrangement pattern. Macroscopic, histological and IXX analysis are crucial for diagnosis [47]. **Macroscopically,** most of the SFT are encapsulated and rounded, sometimes lobulated with a homogeneous density. The tumor may be large, with a yellowish-brown cut surface, and in the presence of fatty differentiation (lipomatous variant), myxoid and hemorrhagic changes may be observed [48-53]. Tumor necrosis and capsular invasion are criteria for aggressive and malignant tumors (10% of cases) [48,51,52].

The cytological characteristics of SFT include 1) round to oval moderately atypical cells; 2) increased finely granulated chromatin; 3) absence or presence of barely noticeable nucleoli; 4) background of irregular collagen fragments; 5) scarce and unclear cellular cytoplasm [54-56]. Morphologically, it is difficult to distinguish benign from malignant SFT. Tumor cell polymorphism and dyskaryosis are cytological features of a malignant tumor. In general, benign SFTs do not contain a nucleus [57].

Pathohistologically SFT are presented mainly by the absence of a specific cellular pattern of distribution [58], characterized by a combination of hypo- and hypercellular proliferation of oval or spindle-shaped cells, areas separated by hyalinized fibrous bundles and the presence of elongated and dilated vessels and often hyalinized walls or multiple thin-walled blood vessels with a deer antler-like configuration [59,60], i.e., hemangiopericytic-like vascular branches. Our observations from the gastric solid fibrous tumor take into account the randomly arranged cells of different types: some of the cells have rounded nuclei, others with drained nuclei and others with morphology of uni- and multilocular lipoblasts with low mitotic activity (Figures 2A, 2B and 3). Cellular atypia is not seen in **benign STFs**. Mitotic figures are rare, no necrosis, hemorrhage or vascular invasion [46]. **Atypical tumors** present by cells containing sparse cytoplasm with unclear borders and dispersed chromatin in vesicular nuclei. Mitoses are scarce, rarely 3 mitoses on a pallet with an increase of 10. Some SFTs may contain in separate areas mature adipose tissue and/or multinucleated giant stromal cells, overlapping with the so-called lipomatous hemangiopericytomas and giant cell angiofibromas [47]. **The malignant variant of SFT** usually consists of hypercellular lesions showing at least focal-moderate cytological atypia, tumor necrosis, multiple mitoses/more than 4 mitoses of the field with an increase of 10 and capsular invasion [48,51,52]. **Rare myxoid SFTs** can create a problem with the differential diagnosis (DD) of much more aggressive neoplasms or soft tissue tumors with other differentiation. Branches and dilated blood vessels typical of SFT, known as hemangiopericytoma-like vessels, may be a feature of several other malignant soft tissue tumors (synovial sarcomas or peripheral neural malignancies), indicating that pathohistological DD should be considered. a wide range of other soft tissue neoplasms [59]. The so-called "growth pattern without a model" or a combination of different histological features such as fascicular, neural, and diffuse sclerosing can lead to a misdiagnosis [61].

Immunohistochemistry (IHC)

In SFT with different organ localization, no histological and IHC difference is reported [54,62-65]. CD34 antigen, which is a transmembrane glycoprotein, helps in the diagnosis of SFT [43,44], as it is highly positive in 90% -95% of patients [45,47-50,52,66-76]. In the presented clinical case, strong diffuse expression to CD34 was reported (Figures 5A and 5B). Tumor cells show high expression to CD99 in 60-70% of cases [47,59,67,70,72]. In 20% to 35%, variable positivity to EMA and B-cell lymphoma 2 (BCL-2) was observed in 30% - 50%; as well as less frequently to SMA [47,51,52,66,69,70,77]. Focal or limited reactivity was reported for S-100 protein [51,52,66,69,72] (Figure 5C). Spindle cells are positive for Vimentin [68]. Tumor cells are negative for Cytokeratin [67-69,72]. Pancytokeratin, CD117 (c-kit), Desmin [69] and Factor VIII [59]. High levels of expression to progesterone receptors are possible [73]. In the presented clinical case we report negative reaction for CK AE1-AE3 in tumor cells, but positive expression in normal gastric epithelium adjacent (Figure 6A); negative reaction for SMA and Desmin in tumor cells, but positive in blood vessels (Figure 6B and 6C); and negative reaction for Myogenin (Figure 6D). In the presented clinical case we report low cellular mitotic activity of 1% -2%, which determines the benign nature of SFT (Figure 3).

Differential diagnosis (DD)

SFT may resemble other tumors, so DD is based primarily on ICH to CD34, Vimentin, and CD99 [78]. DD includes a number of benign lesions, such as leiomyoma, schwannoma, benign fibrous histiocytoma to malignant lesions such as well-differentiated fibromyxoid sarcoma, malignant tumor of the peripheral nerve sheath, and malignant fibrous histiocyte, which necessitates ICH [46,47]. The differential diagnosis of gastric SFT includes gastrointestinal stromal tumor, calcifying fibrous tumor, fibromatosis, schwannoma, leiomyoma, leiomyosarcoma, inflammatory myofibroblastic tumor, fibrosarcoma, malignant fibrous histiocytoma, hemangiopericytoma, synovial sarcoma, and malignant mesenchymoma [41-80]. Differentiation from highly malignant sarcomas, benign and malignant fibrous histiocytes, as well as desmoid tumors is due to their negative expression to CD34 [59,81]. Monophasic synovial sarcoma is evidenced by a uniform cell growth pattern and ICH focal expression to Keratin [75,82,83]. Neurofibroma and peripheral nerve sheath malignancy show different expression to CD34 and bcl-2, but SFTs are strongly positive for these markers [81].

Criteria for malignancy

The general criteria for malignant SFT with aggressive biological development include: 1/increased number of cells /accumulation of many cells; 2/ moderately atypical cells; 3/ high degree of mitosis/4 in a field with a magnification of 10; 4/ invasion and/or necrosis [66,72,84]. In atypical or malignant tumor variants, visibly increased cellularity, cellular atypia (nuclear pleomorphism, nuclear hyperchromasia), increased mitotic index, and tumor necrosis have been reported [69].

Complex treatment

The main treatment for SFT is surgery. Surgical management of SFTs is similar to most soft tissue sarcomas with a goal of wide resection margins and preservation of any critical surrounding organs or other structures. Obtaining adequate negative margins has been shown to decrease the rate local disease recurrence and improve survival [85]. Several case series have demonstrated complete resection to be associated with low rates of local recurrence and progression to metastatic disease [86]. Positive margins, tumors size greater than 10 cm or malignant histology, are risk factors for local failure for extra-pleural

SFTs [87]. The addition of adjuvant radiotherapy has been reported in select cases, when there is incomplete resection of the tumor especially for the malignant variety [88]. Similar to SFT of the pleura, systemic therapy with ifosfamide or doxorubicin may be considered in recurrent cases or those that show malignant features [89].

Conclusion

Anorectal malignant melanoma is an extremely rare and aggressive disease which is associated with a poor prognosis. Gastric localization of SFTs is a very rare disease, which by 2018 was published in seven patients. For the first time in the English medical literature, a clinical case with synchronous tumors - rectal achromatic malignant melanoma and gastric solitary fibrous tumor is presented. The article emphasizes the importance of pathohistological and immunohistochemical analysis for the correct oncological diagnosis and differential diagnosis. We report a one-year disease-free survival with a good quality of life after complex treatment, including surgery and adjuvant radiotherapy of the rectal achromatic malignant melanoma and surgery of the benign gastric tumor.

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