CASE REPORT

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# Hemorrhagic polypoid gastric and colonic metastases nine years after uterine leiomyosarcoma – case report

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## Abstract

*Introduction*: Uterine leiomyosarcoma (ULMS) is a rare tumor, representing 1–2% of all uterine malignancies. It is highly aggressive, with high metastatic rate, especially in lungs, peritoneal cavity, retroperitoneum, bones and liver, usually during the first years after diagnosis. *Case presentation*: A 58-year-old woman, with subtotal hysterectomy and bilateral adnexectomy, followed by radiochemotherapy for spindle-type ULMS nine years ago, presented with gastrointestinal bleeding and severe anemia. Three polyps ranging from 2 cm to 5 cm in diameter were found at gastroscopy, the largest being ulcerated, which required a total gastrectomy three months later. Colonoscopy identified two pedunculated polyps on the descending colon, 2 cm and 3.5 cm in diameter. Histologically, both sites revealed proliferations of spindle cells with whorled pattern, moderate to severe nuclear atypia, 5 to 8 mitotic figures (MFs)/10 high-power fields (HPFs) and additional necrosis in the gastric tumors. Immunohistochemistry was negative for CD117, DOG1, S100 and CD34 and positive for smooth muscle actin (SMA), estrogen receptor (ER) and progesterone receptor (PR). Twenty percent of nuclei stained positive for Ki67. The diagnosis was synchronous hemorrhagic gastric and colonic polypoid metastases of ULMS. Thoracic computed tomography (CT) and abdominal ultrasonography were negative for other metastatic lesions, while abdominal CT revealed abdominal and pelvic lymphadenopathy. *Conclusions*: This case illustrates a distinct pattern of metastasis that is an extremely rare gastric and colonic location and an expanded disease-free period of nine years since the initial treatment. A long-term clinical and imaging follow-up of this patient is essential.

***Keywords***: uterine leiomyosarcoma, polyp, colonic metastasis, immunohistochemistry.

## Introduction

Uterine leiomyosarcoma (ULMS) represents 1–2% of all uterine malignancies and more than 50% of uterine sarcomas, excluding carcinosarcoma [1, 2]. It affects women with a median age of 50–55 years. It is a highly aggressive tumor, presenting an overall five-year survival rates of 15–25% [1]. At the time of the first diagnosis, a large number of cases are confined to the uterus [3], but near one-third of cases are stage III or IV [2]. Between the favorable prognostic factors are the low stage (I and II), with a five-year survival rate of 40–70%, a small size for tumors confined to the uterine corpus (less than 5 cm in diameter), the histological type (late recurrence, up to 10 years for the myxoid or epithelioid variant, *versus* recurrence within two years for the spindle cell variant), and in some series a low mitotic index or pre-menopause [1, 2]. The treatment is surgical resection – hysterectomy with or without bilateral salpingo-oophorectomy, with adjuvant therapy [2, 3]. The role of pelvic radiation appears to be limited, preventing local and regional recurrences, with no survival benefit [2]. Chemotherapy, such as Dacarbazine, Gemcitabine and Docetaxel, is associated with slightly improved survival [2–4]. Altogether, these may reduce the recurrence rate, but despite the extensive treatment, the clinical outcome remains poor [5].

Most patients with uterine leiomyosarcoma relapse loco-regionally and hematogenously [2]. Metastases can occur by peritoneal seeding, hematogenous route or rarely *via* lymphatic route. ULMS metastasizes most frequently in the lung, followed by peritoneal cavity, retroperitoneum, bones and liver [6–8], but isolated cases have been also reported to spread to the muscle, thyroid, brain, heart, parotid gland, pancreas, oral cavity, gastrointestinal tract, skin, etc. [8–13]. Metastases involving the gastrointestinal tract are extremely rare and raise the question of differential diagnosis between primary and secondary tumors [12, 13].

This report presents a very rare case, manifesting with digestive bleeding secondary to synchronous metastases in the stomach and the colon that had arisen as first metastatic site nine years after an ULMS.

## Case presentation

In August 2015, a 58-year-old female was admitted at the Emergency County Hospital, Cluj-Napoca, Romania for pulmonary thromboembolism. Afterwards she presented

to different hospitals with a series of clinical manifestations, including severe anemic syndrome and gastrointestinal bleeding. Her history revealed ULMS treated with subtotal hysterectomy, bilateral adnexectomy and radio- and chemotherapy in 2006. The pathology report described a 9 cm diameter, stage IB uterine mass, which histologically showed marked cytological atypia, coagulation necrosis on approximately 50% of the examined surface and a mitotic index of 10 mitotic figures (MFs)/ 10 HPFs (high-power fields). Clinical and imaging follow-up showed no evidence of metastatic disease until 2015.

Two months after the pulmonary thromboembolism, she presented again with hematemesis and melena and laboratory findings of marked anemia. The abdominal ultrasound did not find any remarkable lesion. Abdominal and pelvic computed tomography (CT) revealed circumferential thickening between 2 cm and 3.4 cm of the gastric tuberosity, raising the suspicion of a malignant tumor (Figure 1a). Enlarged lymph nodes in the following locations were also observed: perigastric, periceliac, mesenteric, interaortocaval, perivaginal and inguinal. Thoracic CT was negative for metastatic lesions in the lungs. Two pedunculated polyps of 1.5 cm and 2 cm were found in the antrum, without ulceration or bleeding, and one ulcerated polypoid tumor, around 5 cm in diameter, with irregular surface was located in the subcardial region, during upper endoscopy. As the patient was on oral anticoagulant therapy for pulmonary thromboembolism and had a high risk of post-polypectomy bleeding, only superficial biopsies were performed, which detected non-relevant inflammatory mucosa. Colonoscopy identified two ulcerated slightly polylobated nodules or polyps on the descending colon, 2 cm and 3.5 cm in diameter, the latter being centrally depressed (Figure 1b). Histologically, both colonic polyps revealed very well delimited proliferations of spindle cells, with whorled pattern, mildly atypical nuclei (Figure 2b), 5 and 7 MFs/10 HPFs respectively (Figure 2c), both limited and expanding the submucosa, with intact muscularis mucosa (Figure 2a), without necrosis, excepting the focal ulceration of the mucosa. Twenty percent of nuclei stained positive for Ki67 (Figure 3c). Immunohistochemistry was negative for CD117, DOG1 and CD34, not favorable for a gastrointestinal stromal tumor (GIST), and positive for smooth muscle actin (SMA) (Figure 3a), estrogen receptor (ER) (Figure 3b) and progesterone receptor (PR), indicating a leiomyosarcoma with uterine origin. Figures 3b and 3c highlight the difference between the immunohistochemical expression of ER in the muscularis mucosa, which was negative and the tumor itself, positive, and also the difference in their Ki67 proliferation index. Considering the patient's history and the immunohistochemical profile, both polyps were diagnosed as colonic polypoid metastases of uterine leiomyosarcoma, with additional gastric polyps.

Three months later, after a second episode of upper gastrointestinal bleeding, an emergency total gastrectomy was performed, which microscopically confirmed the leiomyosarcomatous nature of the gastric polyps. The resected specimen presented proximally a vegetant tumoral mass on the greater curvature, with broad implantation, much larger than first described, measuring 10/7/5.5 cm. The tumor was solid, had a grey-white color with hemorrhagic areas and appeared to infiltrate all layers of the gastric wall. The tumor interested the mucosa, which it ulcerated, the submucosa and the muscularis propria. Intratumoral hemorrhage, 7% intratumoral necrosis, lymphatic invasion and 8 MFs/10 HPFs. A second vegetant tumoral mass that extended to the mucosa and submucosa, with the same morphological appearance was identified on the posterior wall of the stomach. Eighteen perigastric lymph nodes were examined, all free of tumor cells. The morphological aspect and the immunohistochemistry was compatible with gastric metastasis of ULMS. No peritoneal seeding or pelvic local recurrences were observed. After successful recovery, imaging-staging workup was performed, with no other metastatic sites described. Chemotherapy with Doxorubicin, Ifosfamide and Mesna was started.

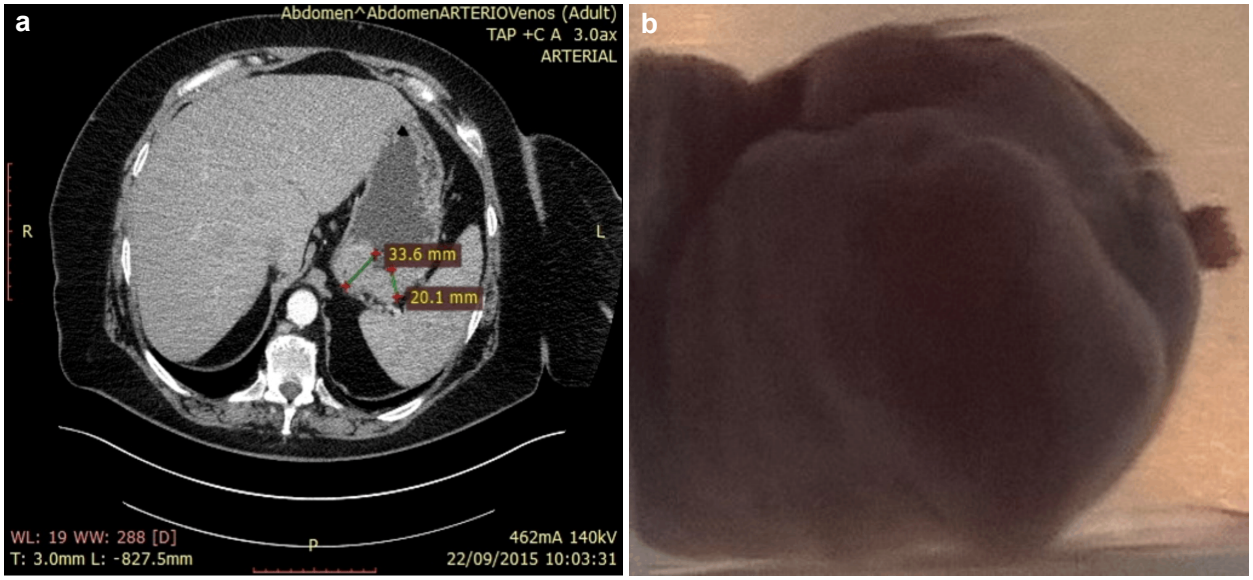


**Figure 1** – ***(a) Abdominal CT revealed circumferential thickening of the gastric tuberosity, between 2 cm and 3.5 cm; (b) Polypoid colonic nodule, with irregular contour, smooth surface, centrally depressed, 3.5 cm in diameter.***

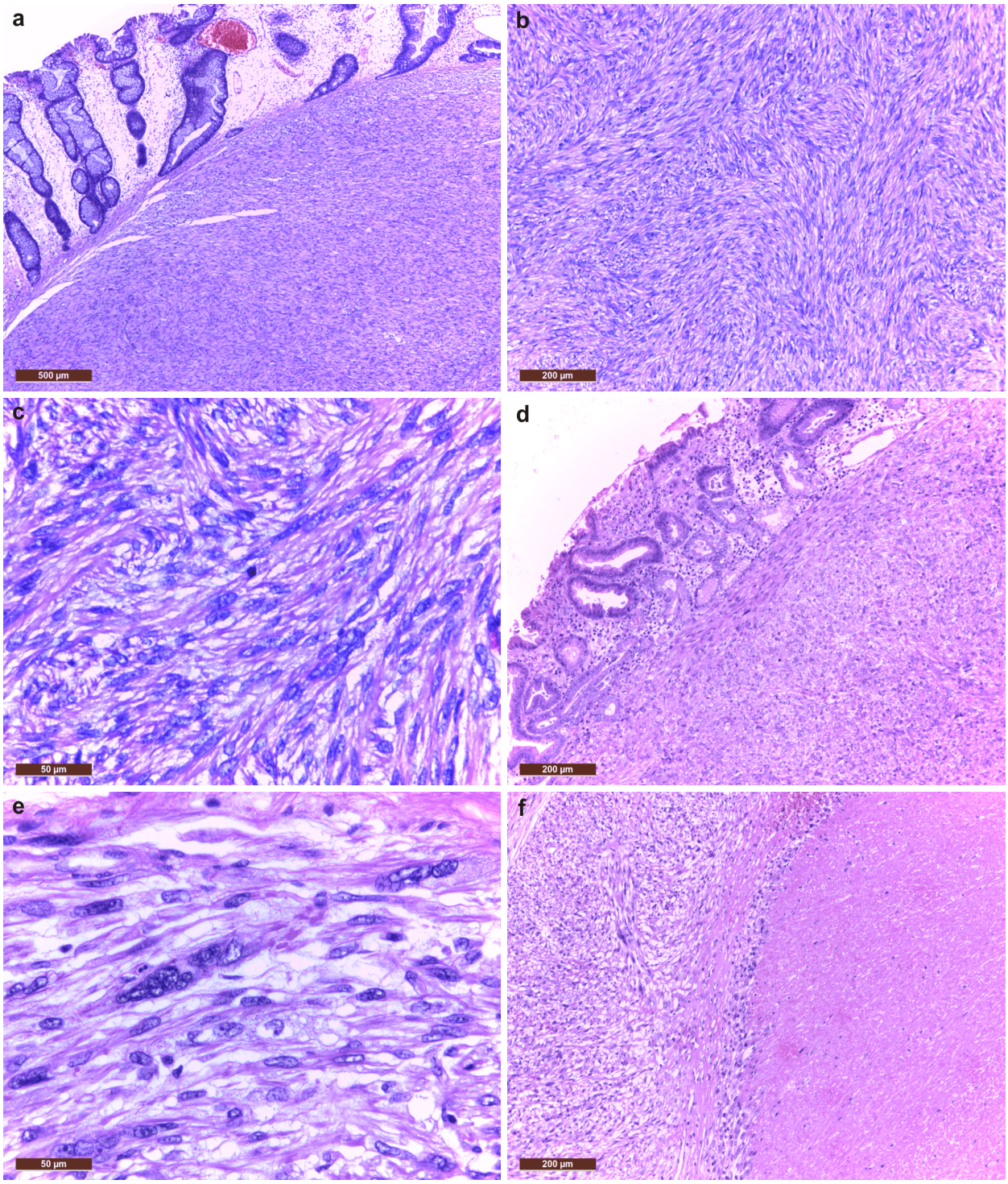


**Figure 2** – ***Microscopic aspect in Hematoxylin–Eosin staining: (a) Leiomyosarcomatous proliferation in the colonic submucosa, well delimited by the muscularis mucosa (×40), represented by (b) fascicles of monotonous spindle cells (×100) (c) with mildly atypical nuclei and rare mitotic figures (×400); (d) Leiomyosarcomatous proliferation in the gastric submucosa and musculosa, slightly invading the mucosa (×100), with (e) areas of highly atypical nuclei (×400) and presenting (f) large areas of coagulative necrosis (×100).***

The third metastatic site was found incidentally after three months, subsequent to the fourth course of chemotherapy, as a polylobulated tumoral mass located in the soft tissue of the proximal third of the left thigh. The tumor measured 14/11.5/9.5 cm had a grey-white appearance with areas of hemorrhage and necrosis. This was microscopically and immunohistochemically confirmed as a metastasis of the previous ULMS.

## Discussion

The aggressive behavior of ULMS resides in its high local recurrence and metastatic rate. In a study of Tirumani *et al.*, the local recurrences appeared in about 50% of patients during a median follow-up of 45 months [6]. Almost all of these patients associated distant metastatic disease, which appeared, in a slightly descending order of frequency, before, at the same time or after the local

recurrence [6]. Most frequently, distant metastases appeared early in the evolution of the disease, usually in the lungs and before local recurrence [6]. Conversely, local recurrences were associated first with lung and secondly with peritoneal metastases, the latter being however the most frequent companion of local recurrences [6]. In descending order of involvement, the lung metastases were commonly associated with other sites of hematogenous metastases, such as bone, liver, and muscle [6]. This patient presented a very rare site of recurrence, in the gastrointestinal tract, the result of hematogenous metastasis, followed by soft tissue involvement, without local recurrence and peritoneal seeding. Regardless of the primary tumor, hematogenous metastasis to the stomach is usually rare, the leading primary source being tumors of the breast, lung, esophagus or melanoma and occurring most frequently on the greater curvature of the middle or upper third of the stomach, as in this case [12, 14, 15]. Colorectal metastasis is also exceptional (0.338%), the main source of metastasis being the breast, followed by melanoma [13, 16]. Extremely rare ULMS metastases were however reported in the stomach [15], in the small bowel [17, 18] and exceptionally in the colon [13].

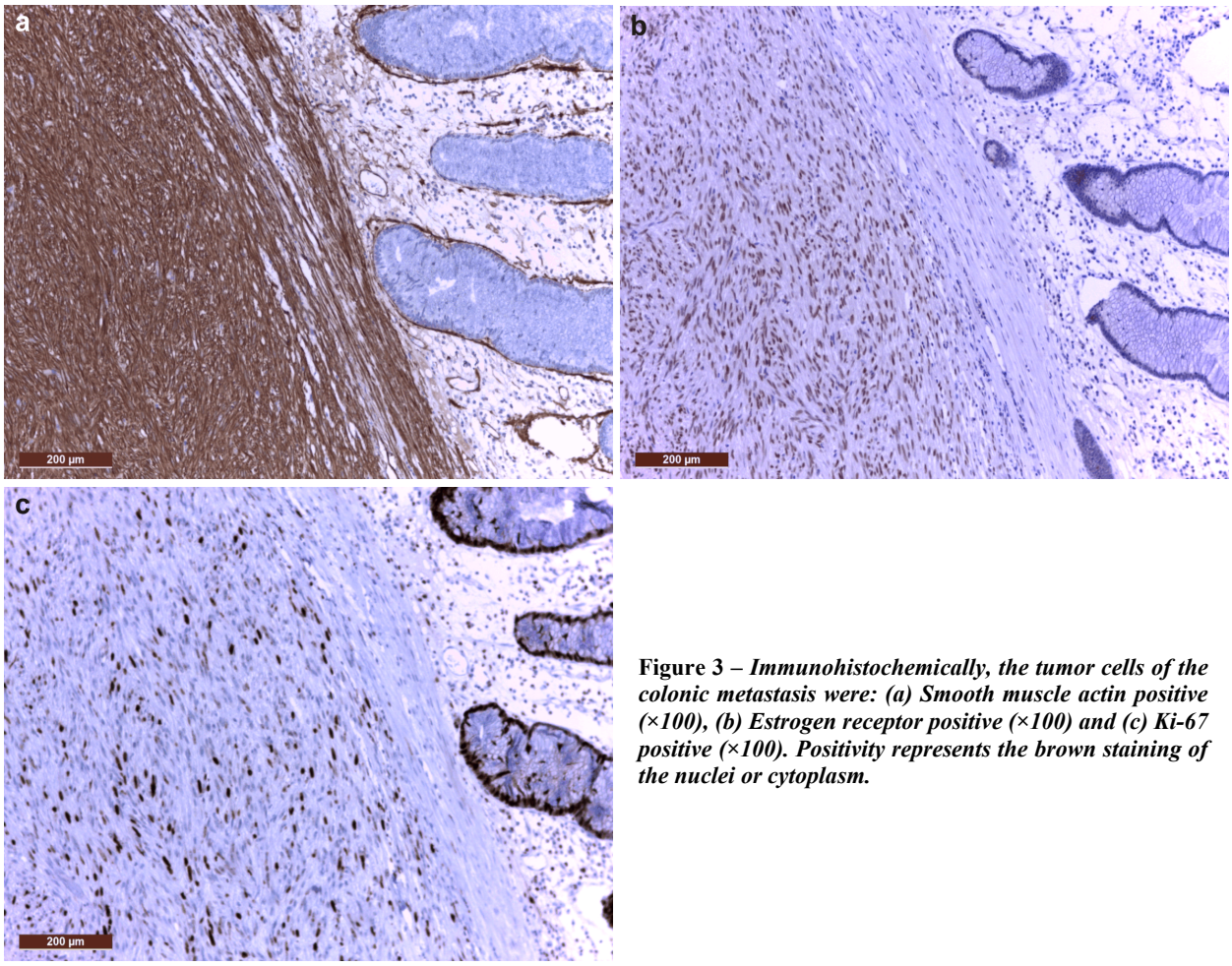


**Figure 3 –** ***Immunohistochemically, the tumor cells of the colonic metastasis were: (a) Smooth muscle actin positive (×100), (b) Estrogen receptor positive (×100) and (c) Ki-67 positive (×100). Positivity represents the brown staining of the nuclei or cytoplasm.***

The symptoms of gastrointestinal metastases are highly non-specific: mainly dyspepsia, epigastric pain and bleeding in gastric location [12], acute abdomen caused by obstruction in the small bowel [17, 18], or abdominal pain, bleeding and symptoms related to colorectal obstruction or perforation in the case of large bowel metastases [13]. Given the current clinical context of gastrointestinal bleeding and anemia associated with pulmonary thromboembolism in a patient with no sign of metastatic disease, the diagnosis of the gastric and colorectal polyps as metastases from an ULMS was unexpected and needed differential diagnosis, especially after nine years disease-free survival. Consequently, the pulmonary thromboembolism was reconsidered as being paraneoplastic.

The most important differential diagnosis among the gastric or colonic tumors is between the primary and secondary tumors. In the present case, the possibility that the leiomyosarcoma in the stomach and in the large bowel might have been a primary tumor has also been raised, but there are several arguments against it: firstly, the location in the upper and middle third of the stomach and mainly in the submucosa with secondary ulceration of the mucosa, multiple lesions (three in the stomach and two in the colon), their synchronous occurrence and rapid growth (the gastric polyps doubling their size in three months). Secondly, the immunohistochemical profile does not favor other mesenchymal tumors such as GIST (negativity for c-Kit, DOG1, CD34), peripheral nerve sheath tumor (negativity for S100), inflammatory fibroid polyp (negativity for CD34), but, with the additional clinical history of ULMS, the positivity for ER, PR, SMA and desmin confirms the uterine smooth muscle origin. The Ki67 proliferative index of 20% and the mitotic index between 5 to 10 MFs/10

HPFs also confirm malignancy, knowing the fact that outside the uterus, any smooth muscle tumor which reveals a single mitotic figure (more than 1 MF/50 HPFs) raise the suspicion of malignancy.

The majority of cases with ULMS present a median disease-free survival of 14 months and overall survival of 27 months [3]. However, there are isolated case reports of extended disease-free survival of seven years, 15 years, the longest being of 18 years [7]. Recurrences may arise from metastatic seeding which probably remains dormant for many years before becoming newly active. Usually, long survival with long interval before and after a recurrence is often detected in atypical leiomyoma with low risk of recurrence, or in smooth muscle tumor of uncertain malignant potential (STUMP) [2], which was not our case, the primary uterine tumor fulfilling the histological criteria of a typical leiomyosarcoma (presence of coagulative necrosis, severe atypia, 10 MFs/10 HPFs). The newly active metastatic deposits were histologically similar with the primary tumor in the gastric location, but presented less ominous histological features in the colonic polyps (without coagulative necrosis, mild atypia, less than 7 MFs/10 HPFs). It is to be highlighted here the three months longer evolution and growth of the gastric polyps compared to the colonic ones until the surgical resection. The growth of initially dormant and probably multiple metastatic deposits in the gastrointestinal tract must be the result of molecular tumor progression, responsible not just for their activation, but also for their secondary dissemination, in this case in the thigh. Interesting, in a study of Davidson *et al.*, that evaluated gene expression profiling of a series of 28 ULMS primary and metastases, it was found that primary and respectively metastatic ULMS, in spite of their similarities, presents unique molecular signatures, which differentiates the primary tumors from the metastatic deposits. This may aid in understanding the tumor progression and metastasis, and also may provide new potential therapeutic targets [19].

Regarding the prognostic factors and survival, several studies proposed survival algorithms for ULMS, with many other variables than listed at the beginning of this report: the ability to obtain complete resection with histological free margins at the time of surgery for the recurrent disease, recurrence time greater than 12 months from the initial diagnosis, single tumor recurrence. Factors that do not affect survival are stated to be: the type of procedure performed for resection, local *versus* distant recurrence, the use of chemotherapy and/or radiation in the perioperative period [3, 20, 21]. The low grade of the tumor was associated with a positive prognostic factor in some studies, but did not correlate with survival in others.

Colorectal metastases usually mean a late stage disease with poor prognosis. In a study of Mourra *et al.* [13] there was no patient alive five years after the diagnosis, regardless of the primary tumor and of the management of the colorectal metastases (surgical resection or biopsy and systemic therapy). However, they obtained some slightly better results in patients with surgical treatment than in those without surgery [13].

The case reported meets some of the criteria for an extended survival: the patient had a prolonged time of nine years until the first recurrence, surgeons performed total gastrectomy and polypectomy in the colon and the patient underwent radiochemotherapy after the primary tumor and chemotherapy after the recurrences. Still, the efficacy of the adjuvant treatment is uncertain, since up to now, studies have not statistically correlated this therapy with a good survival rate.

## Conclusions

The peculiarity of the case stands in both the extended disease-free survival of nine years and the gastrointestinal involvement as first metastatic site. Regardless of the primary tumor, gastric metastases are unusual, while colonic metastases are exceptional. The recurrence in the tight is not necessarily remarkable, but altogether, the three different secondary sites are curious in the absence of pulmonary involvement. In the gastrointestinal tract, the symptoms and the gross appearances of the lesions were comparable to other types of polyps; therefore, the patient's history is essential, while immunohistochemistry helps to differentiate it from primary leiomyosarcoma or other mesenchymal tumors. The infrequency of ULMS impedes designing large studies targeting achievement of extended survival. As the experience is limited, multi-disciplinary approach and long-term follow-up in managing such patients may be the best available option.

**Conflict of interests**

The authors declare that they have no conflict of interests.

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