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Case Report

Primary vaginal leiomyosarcoma: A case report with complete morphological, immunohistochemical and ultrastructural study

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ABSTRACT

Objective: Primary vaginal leiomyosarcomas (LMS) are rare, easily recurrent tumours with an unknown etiology; the prognosis is poor and there is no consensus guideline on their management.
Case report: A nodular, 25 × 23 x 28 mm-mass, infiltrating the urethra, was found in a 58-year-old woman. A biopsy showed a LMS of the vagina that was positive for vimentin, alpha-smooth muscle actin, caldesmon, desmin, p16 and p53. An anterior pelvic exenteration was performed. The sample was fixed and prepared for light microscopy, transmission and scanning electron microscopy, confirming the diagnosis of LMS.
Conclusions: Best outcomes occur when the tumour is small, localized, and can be removed surgically with wide, clear margins, as in this case. As there are different kinds of malignant mesenchymal tumours, biopsy followed by immunohistochemistry and electron microscopy still represents a good diagnostic choice and surgical resection is generally the gold standard in these cases.

Introduction

Primary vaginal leiomyosarcoma (LMS) is a rare, easily recurrent, smooth-muscle tumor accounting for 2–3% of all malignant vaginal neoplasms [1]. It represents the most common vaginal sarcoma in adult women [2,3]. The etiology is still unknown, the prognosis is poor and there is no consensus guideline on its management. Diagnosis is usually made during the 5th decade of life due to the presence of a vaginal mass or nodule(s) [2]. Current medical literature reports up to 200 cases (PubMed®); only few studies have considered the ultrastructure. Fine details on the ultrastructure of other types of leiomyosarcomas have been reported and nicely illustrated by Ferenczy [4]. Herein a case report of a primary vaginal leiomyosarcoma is presented and discussed.

Case description

The patient was a 58-year-old Caucasian woman who was hospitalized on April 2016. At the anamnesis she had a body mass index (BMI) of 26 kg/m^2; menarche presented at 14 years old; menopause was at 53 years old; she had regular feeding and bowel movements as well as physiological diuresis. There were antecedents of breast cancer in her family. In 2014 she underwent a thyroidectomy due to a papillary cancer; she followed radiometabolic therapy and is now under hormone replacement therapy (Eutirox® 175 mcg/die). In 2015 she underwent a vaginal hysterectomy due to a uterus prolapse, preserving adnexa.

After the appearance of a vaginal nodule, the patient applied for a gynecological examination, which showed a red vaginal mass located in the anterior vaginal wall (Fig. 1A).

The sagittal MRI confirmed the absence of the uterus (Fig. 1B). A hyperintense irregular 25 × 23 × 28 mm mass was evidenced near the urinary bladder. The mass infiltrated the inferior third of the vagina, the inferior segment of the urethra and the right bulbospongiosus and pubococcygeus muscles but there were no signs of infiltration of the vaginal septum (Fig. 1B). A total body CT excluded the presence of distant metastasis.

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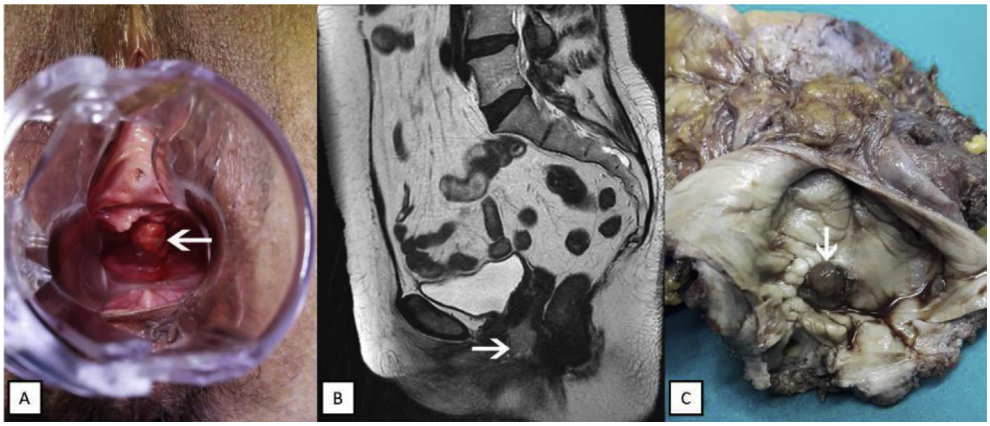

Fig. 1. Gynecological examination showing a red mass in the anterior vaginal wall (arrow) **(A)**. Sagittal Magnetic Resonance Imaging T2-weighted showing a hyperintense irregular mass near the urinary bladder (arrow) **(B)**. Surgery specimen after anterior pelvic exenteration. A granulomatous nodule (arrow) is present in the superior vaginal wall **(C)**.

An anterior pelvic exenteration with urostomy was performed (Fig. 1C). The histologic examination confirmed the diagnosis of early leiomyosarcoma of the vagina. The resection margins and the iliac lymph nodes were negative. The tumor was surrounded by granulomatous chronic inflammation, as a foreign body reaction. The pseudocapsulated, brownish, rounded mass was further examined. The sample was fixed and prepared for transmission (TEM) and scanning (SEM) electron microscopy.

Light microscopy revealed that the mass contained a storiform pattern of spindle-shaped cells with blunt-ended nuclei. Cells were arranged in interwoven fascicles within a dense and richly vascularised stroma, suggesting an active neoangiogenesis (Fig. 2A and B). The histopathological analysis revealed a coagulative focal necrosis and low to moderate mitotic indexes, about 1–4/10 high power fields (HPF). The immunohistochemical analysis revealed positive staining for vimentin (Leica Biosystems, Clone V9); α-smooth muscle actin (Leica Biosystems, Clone ASM-1); caldesmon (Agilent DAKO, Clone h-CD); desmin (Leica Biosystems, Clone DE-R-11); p16 (Roche, Clone E6H4); and p53 (Leica Biosystems, Clone DO-7); immunoreactivity for ki-67 (Leica Biosystems, Clone K-2) was about 40% (Fig. 2C–H). Light microscopy of semithin sections embedded in epoxy resin and stained with a trichromic method (methylene blue-azur B and basic fuchsine) showed numerous small blood vessels and a dense stroma (Fig. 2I).

SEM evidenced a dense collagenous stroma with numerous small blood vessels. Morphological signs of neoangiogenesis and tumoral cells were recognized (Fig. 3A and B). TEM showed invasive neoplastic and pleomorphic cells with complex labyrinthic cytoplasm projections (Fig. 3C and D) and atypical mitoses (Fig. 3D). Tumoral cells contained paranuclear crowds of dilated mitochondria, free ribosomes and a well-developed rough endoplasmic reticulum. Nuclei were large, mostly hyperchromatic, usually

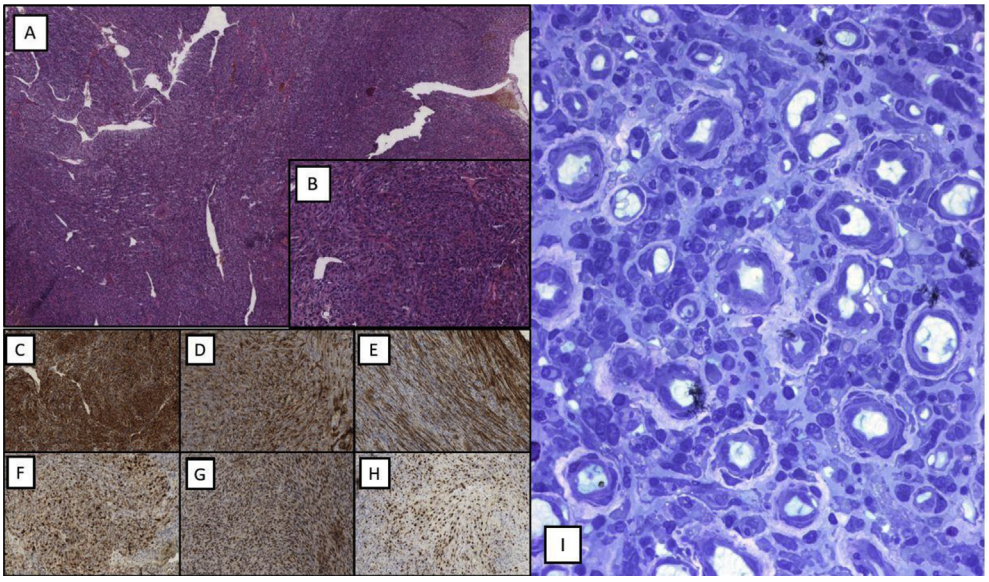

Fig. 2. **(A)** Histological analysis (paraffin section). Low-power photomicrograph showing a proliferation of spindle cells with centrally located and blunt-ended or cigar-shaped nucleus and pink to deep red cytoplasm (hematoxylin-eosin, magnification 4*x*); **(B)** Medium-power photomicrograph showing neoplastic cells arranged in fascicles of varying size, sometimes around small vascular spaces (hematoxylin-eosin, magnification 20*x*). Medium-power photomicrographs showing immunoreactivity of neoplastic cells for: **(C)** Vimentin; **(D)** α-smooth muscle actin; **(E)** caldesmon; **(F)** p16; **(G)** p53; **(H)** proliferative index, evaluated by immunoreactivity for Ki-67, is about 40%, which together with p16 and p53 positivity indicates a very aggressive behavior of this tumor (magnification 20*x*). **(I)** Histological analysis (epoxy resin section). The nodule shows a dense vascularized stroma. Numerous small blood vessels are recognized, suggesting neoangiogenesis (semithin section, trichromic stain with methylene blue-azur B and basic fuchsine, magnification 40*x*).

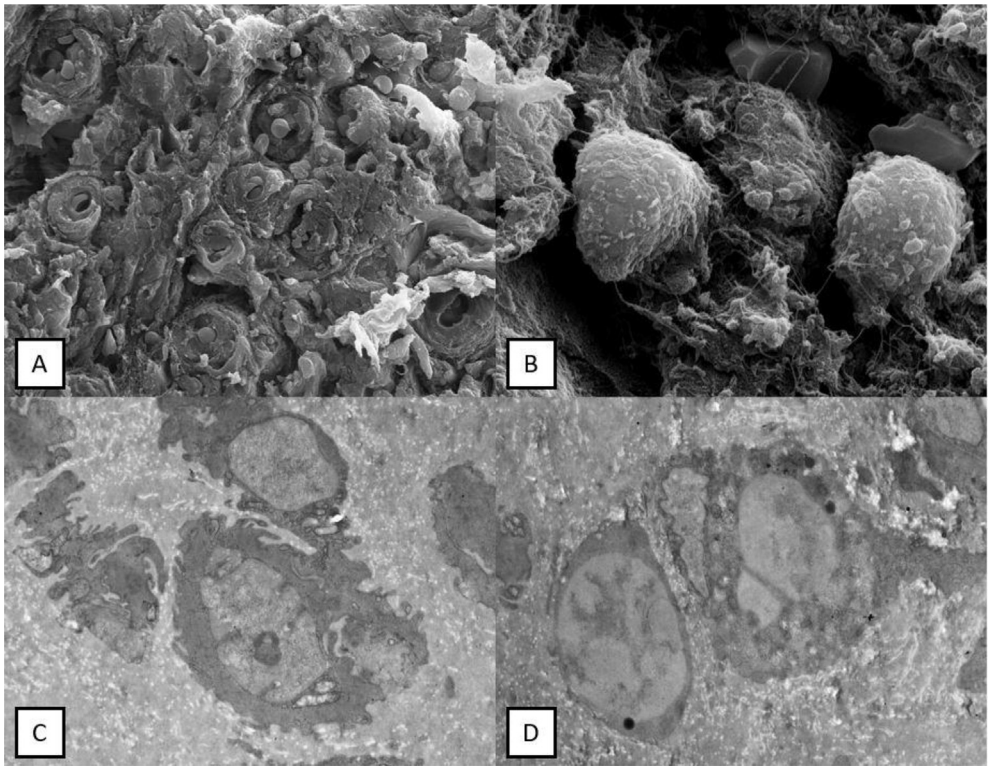

Fig. 3. Electron microscopy analysis. **(A)** Numerous small blood vessels are recognized within a dense stroma (SEM, magnification 500*x*); **(B)** A higher magnification showing two tumoral cells (SEM, magnification 2500*x*); **(C)** Neoplastic, pleomorphic cells, with irregular cytoplasm projections. The nuclei are large, indented, and with a promiscuous nucleolus (TEM, magnification 13400*x*); **(D)** Atypical mitosis; note the dense stroma (TEM, magnification 13400*x*).

multilobed/indented, with prominent nucleoli and characteristic nucleolonema (Fig. 3C). The dense intercellular space contained dense bundles of collagen fibers. Tumoral cells showed a well developed rough endoplasmic reticulum. Blood vessels were usually lined by a high and reactive endothelium (not shown).

No adjuvant therapy (chemotherapy or radiotherapy) was administered. Currently, after two years of surveillance follow-up, the patient is disease free.

Discussion

The most common histologic type of vaginal sarcoma in adult women is LMS but its etiology is still unclear [2]. Some cases are reported to occur after pelvic radiotherapy [2], which, however, was not this the case. Several reports document the carcinogenic potential of implanted foreign bodies (i.e. Dacron grafts; shrapnel bullets; retained surgical sponges) and the different sarcomas that may result secondary to the tissue inflammatory and repair process [5]. In our case, the histologic analysis revealed the presence of the neoplastic mass surrounded by inflammatory tissue and the patient had been previously undergone a vaginal hysterectomy. Although no foreign body as such was present in our case, the surgery itself may have triggered the inflammatory process. Indeed, there are several reports in which a vaginal LMS appears in patients who have undergone hysterectomy or other kinds of vaginal surgery [5]. Although we cannot consider surgery a risk factor for the development of LMS, it should be borne in mind that inflammation associated not with one condition alone, but with a range of conditions, may play a role in its pathogenesis. The site of origin of vaginal LMS is any part of the vagina but it usually arises from the submucosa and the smooth muscle of the vaginal wall. Nevertheless, due to anatomical proximity, it may arise from smooth muscle cells in any tissue adjacent to the vagina [1].

There is still no consensus on the fact that the LMS arises de novo or as a malignant change from a leiomyoma [2]. On the other hand, there is no evidence that the smooth muscle of the rectum, the urinary bladder or the urethra might also take part in the pathophysiology [6]. Some of the patients presenting LMS show concomitant uterine leiomyomas; the transformation of a leiomyoma into a LMS is considered a rare phenomenon [1,3]. Moreover, Keller and Godoy reported that approximately 0.5% of women who have hysterectomies for leiomyomas are found to also have a LMS [1]. Interestingly, Cooney et al. [3] reported the possibility that uterine manipulators used in laparoscopic hysterectomies may seed the vagina with atypical leiomyomas already present in the uterus, thus favouring vaginal LMS. In addition, Yanai et al. reported that malignant transformation can occur even in relatively small leiomyomas [7]. According to this study, patients showing LMS with a leiomyoma component have a favorable prognosis, whereas p53, p16 and Ki-67 are useful markers for recognizing a malignant focus. This consideration could represent another hypothesis on the etiology of our vaginal LMS: our patient had uterine leiomyomas and the vaginal hysterectomy might have seeded atypical cells in the vagina. However, paraffin blocks of the uterus were analysed and no atypical cells were found.

Owing to its rarity, there is no standard procedure for the treatment of vaginal LMS. Surgical resection is generally the primary management and Peters et al. [8] demonstrated a longer survival with a wider resection, such as provided by pelvic exenteration. Adjuvant therapy in these kinds of tumors has been widely discussed. When Ciaravino et al. [9] compared patients treated with surgery alone and surgery followed by chemotherapy and/or

radiotherapy, they did not observe any differences in terms of survival. Nevertheless, radiotherapy and chemotherapy can have a role in case of positive surgical margins and metastatic disease. In our case, since the patient had undergone an anterior exenteration and surgical margins were negative, no adjuvant therapy was proposed.

Light microscopy and ultrastructural features

Malignancy is diagnosed histologically –at least a biopsy of the vaginal nodule-on the basis of hypercellularity; high mitotic activity; moderate cellular pleomorphism and atypia as well as low number of myofilaments [3,4]. Useful markers for leiomyosarcoma are vimentin, α-smooth muscle actin or HHF35, a muscle-actin-specific monoclonal antibody, and caldesmon.

The ultrastructural features confirm the hypercellularity, moderate mitotic index, nuclear pleomorphism, indented nuclear membrane, prominent nucleoli, scantiness of myofilaments and absence of intercellular junction complexes. Nevertheless, no dark, intermediate nor light cells could be recognized as originally reported by Ferenczy et al. [5]. The latter may be due to a highly undifferentiated tumor. According to established recommendations, tumors over 3 cm in diameter, fulfilling the other prerequisites of hypercellularity, atypia and mitotic index, should be classified as LMS [10]. Although the tumoral nodule in our case was under 3 cm and the number of mitosis was less than 5/10 HPF, the presence of atypical mitoses (Fig. 3D) and the immunohistochemistry, which revealed positive staining for p16, p53 and a ki-67 of 40%, confirmed the very aggressive behavior of this tumor [7].

In conclusion, the primary management of this rare and aggressive tumor is surgical resection in conjunction with radiotherapy or chemotherapy, if necessary. Best outcomes occur when the tumour is detected early, when it is small, localized, and can be removed surgically with wide, clear margins. As there are different kinds of leiomyosarcomas, biopsy followed by specific immunohistochemistry and electron microscopy still represents a good diagnostic choice. The question regarding the origin of vaginal LMS still remains open.

Informed consent

Written informed consent was provided by the patient for publishing patient information and images.

Declaration of Competing Interest

None of the authors has any financial support or relationships that may pose a conflict of interest.

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