Two cases of rare malignant mesodermal uterine tumors. Diagnostic features analysis

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Summary

Two cases of uterine malignant mesodermal tumors are presented: a case of malignant fibrous histiocytoma (MFH) and a case of endometrial stroma sarcoma (ESS). The patients were 51 and 28 years old, respectively. The former died shortly after diagnosis. The latter is still alive. The macroscopic and microscopic features, clinical findings and the operations are reported and discussed, along with a review of the literature.

Key words: Uterine; Mesodermal; Sarcoma; Histiocytoma.

Introduction

Solid tumours of the uterus, also known as malignant mesenchymal tumours, are rare with sarcomas being about 3% of uterine malignancies and less than 1% of all gynaecological cancer.

In general, the malignant mesenchymal tumours rise from two distinct tissue components; myometrial muscle is the tissue type for leiomyosarcomas (LMS) and endometrial stroma is the origin for endometrial stromal sarcomas (ESS), while both muscle and stromal tissue types give rise to malignant mixed mesodermal (MMMT) sarcomas.

In addition, uterine sarcoma is subclassified into homologous (consisting of cells native to the uterus) or heterologous (cells usually not found in the uterus).

The mixed Mullerian tumour consists of malignant elements of both epithelial and stromal elements, therefore this is also known as carcinosarcoma.

This report will focus on both an endometrial stromal sarcoma (ESS) and an extremely rare heterologous sarcoma also know as malignant fibrous histiocytomas (MFH).

Case 1

A51-year-old menopausal patient (gravida 1, para 1) was admitted to S.Giuseppe Hospital of Marino (Rome) on December 2001, complaining of vaginal spotting of several months duration and a sudden 25 kg weight loss.

The patient had no history of other diseases apart from rubella, chickenpox and right upper lobe pneumonia.

On examination the uterus was enlarged. Diagnostic hysteroscopy showed the uterine cavity as completely filled by atypical fat-like tissue. The endometrial specimen was diagnosed as carcinosarcoma.

Thereafter the patient was operated on and a total abdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy was successfully performed. The omentum was tightly attached to the fundus uteri surrounded by a neoplastic cap-like spread on the top (Figure 1). On gross examination the uterus measured 10 x 15.7 x 7 cm.

On sectioning the operative specimen it was clear that an ulcerate nodule of 9 cm in diameter, protruding into the uterine cavity, infiltrated almost the entire myometrium and had a white, homogeneous cut surface with extensive necrotic areas. The adnexae seemed to be normally atrophic.

Tissue was fixed in formalin-paraffin and stained with hematoxylin and eosin. Immunohistochemical staining was performed as a secondary step in order to be assured of no primitive muscular or neuroectodermic origin of the neoplasm.

Histologically the tumor resembled a sarcoma with an admixture of mononuclear rounded and spindle cells with multinucleate giant tumor cells. The cytoplasm of the giant cells was eosinophilic and voluminous. Mononuclear cells resembling histiocytes were pleomorphic with abundant cytoplasm and also had vesicular nuclei showing a storiform arrangement. The stroma showed areas of perivascular collagen accumulation, hyalinization and necrosis with hemorrhage, along with chondroid metaplastic zones (Figure 2). There were foci of chronic and acute inflammatory infiltrates. Mitotic activity was high more than 20 mitoses/10 HPF, with a rather strong prevalence of atypical features. The tumor was unencapsulated and nests of neoplastic cells were detectable throughout the entire depth of myometrium.

The neoplastic tissue samples were negative for actin and desmin, thus excluding a diagnosis of either rhabdomyosarcoma or leiomyosarcoma.

Moreover, CD 57 staining was also negative, supporting a non-neuroectodermic origin of the neoplasm. The chondroid component was positive when treated with anti 5100-protein marked antibodies.

Eventually the whole pathologic aspect led to the diagnosis of pleomorphic malignant fibrous histiocytoma (MFH) of the uterus.

Because of a low performance status, the patient did not receive any additional therapy and died after three months with disseminated metastases.

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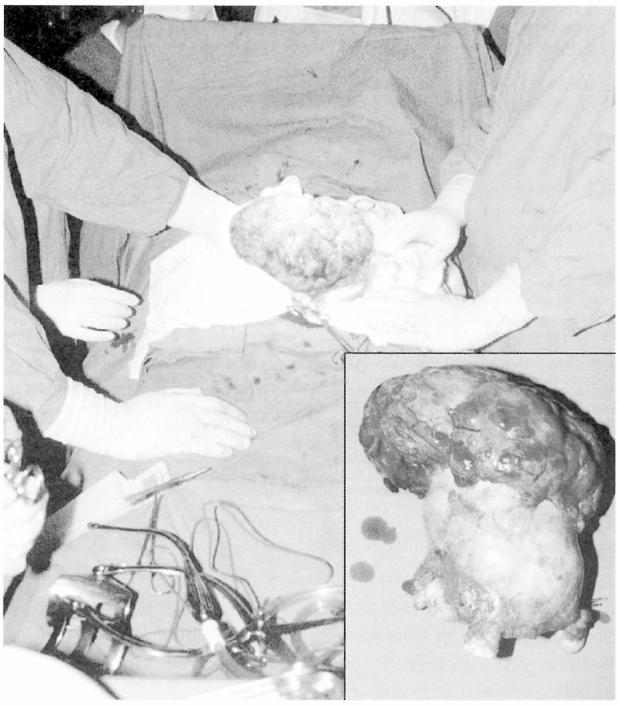

Figure 1. — Total abdominal hysterectomy with bilateral salpingo-oophorectomy and omentectomy. The uterus was 5-fold enlarged. The omentum was tightly attached to the fundus uteri surrounded by a neoplastic cap-like spread on the top and an ulcerated nodule of 9 cm in diameter, protruding into the uterine cavity, infiltrated almost the entire myometrium and had a white, homogeneous cut surface with an extensive necrotic area.

Case 2

A 28-year-old, para 0, patient was admitted to Gynecology department of S. Giuseppe Hospital in Marino (Rome) in February 2003, with atypical uterine bleeding and abdominal-pelvic pain lasting for two months. The patient had no history of other diseases.

The gynecological visit showed a 5-fold enlarged uterus. It was difficult to enter the uterine cavity by office hysteroscopy and the endometrial biopsy did not show cells of sure neoplastic origin.

Transvaginal ultrasounds demonstrated an enlarged uterus with a thin myometrium and a thick and rough endometrium. A total abdominal hysterectomy with bilateral oophorectomy was performed.

Histologically the tumor resembled an endometrial stroma sarcoma with gross monomorphic mononuclear cell invasion of the myometrium that was reduced to a 5 mm layer (Figure 3). The cytoplasm of giant cells was voluminous (Figure 4). Small spiralyzed arteries appeared to be disseminated throughout the neoplastic mass and the mitotic activity was high (10 mitoses/10 HPF).

The patient underwent combined adjuvant therapy (split course radiotherapy and cyclophosfamide/cysplatinum administration), as advised, and she is now alive without evidence of residual disease.

Discussion

The topic of fibrohistiocytic differentiation was first built on the premise that some tumors were composed of cells resembling fibroblasts and plumper cells with vesicular rounded nuclei, resembling histiocytes. These lesions often show an admixed inflammatory component including foamy macrophages and osteoclastic giant cells with phagocytic properties.

These findings are now largely considered as misjudged and it is generally accepted that none of these lesions shows a true histiocytic differentiation. Electron microscopy and immunohistochemistry indicate that the main cells, other than the obvious foamy macrophages, are not histiocytes in most benign and malignant fibrous histiocytomas. Rather they are fibroblasts, myofibroblasts, and primitive undifferentiated mesenchymal cells, some of which show phagocytic properties. It may be that a significant number of MFH are the result of "de-differentiation" rather than originating as a unique undifferentiated neoplasm with recognizable fibroblasts and myofibroblasts.

Based on these premises, the term "fibrohistiocytic" is technically incorrect and holds together a wide variation of heterogeneous lesions, many of which are probably unrelated. Nontheless, this term is still used in order to facilitate diagnostic uniformity in clinical practice.

MFH, in spite of considerable doubt about its validity as a diagnostic entity [1], is one of the most common soft tissue tumors that rarely occurs elsewhere. There are several reports on primary MFH of the uterus [2, 3]. Particularly Fujii *et al.* dealt with a case with the same clinical, pathological and immunohistochemical patterns found in the present report [4]. Karseladze *et al.* reported a case of MFH with a specific overview of the immunohistochemical patterns of their findings. Diagnosis was based on a wide variation of marked antibodies (anti-vimentin, desmin, actin, myogenin, laminin, Col IV, F8, CAM 5.2 etc.), irrespective of the firm common belief that the immunohistochemical approach must be judged as an ancillary one [5].

Kiyozuka *et al.* described two cell lines (Nara-H and Nara-F) with different phenotypes arising from a myxoid MFH of the uterus. In vitro, Nara-F grew in sheets showing a storiform arrangement and Nara-H in raised colonies [6]. The former growing pattern was the same we found in our sections, whereas we did not find a colony-like picture within the biological materials from our patients.

The precise diagnosis is complicated by the fact that MFH shares many microscopical patterns with other sarcomatous uterine tumors.

In the present cases a well-done sampling and evaluation of hematoxylin and eosin-stained sections led us to the final diagnosis.

In fact, this tumor lacks a specific antigen pattern to provide strong support for its identification. Thereafter immunohistochemistry plays an ancillary role, primarily useful in excluding other pleomorphic tumors that may

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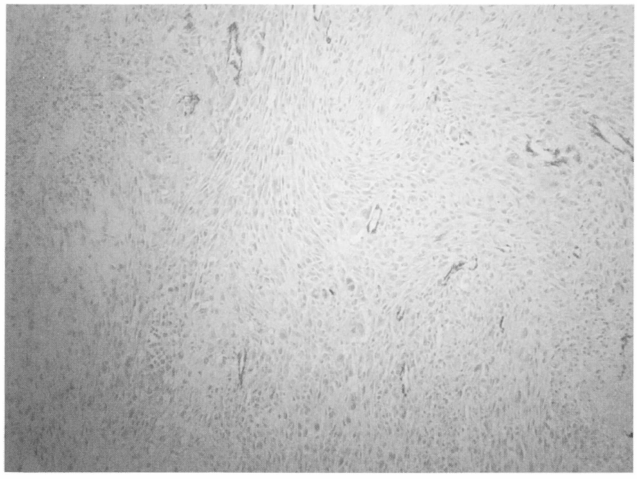

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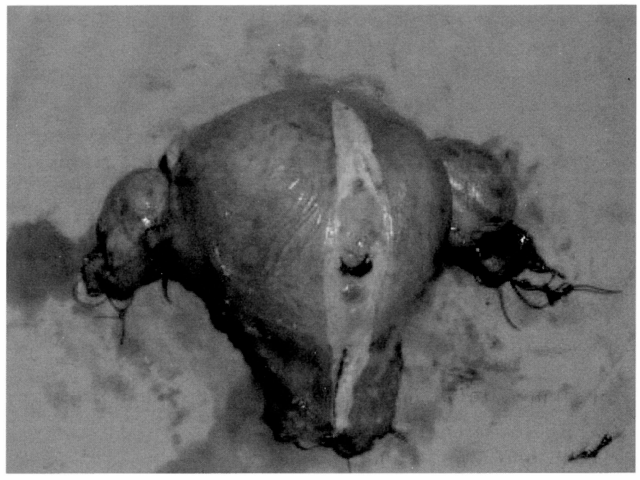

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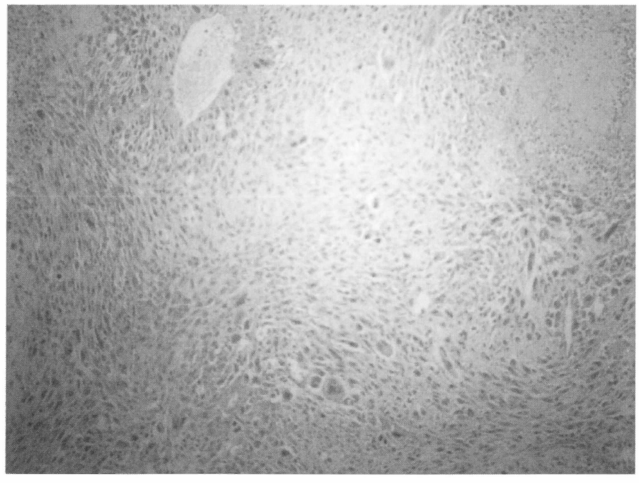

Figure 2. — Anti-actin antibody staining. Giant cells and perivascular collagen accumulation and hyalinization (10 x magnification).

Figure 3. — Myometrium that was reduced to a 5 mm layer.

Figure 4. — Hematoxylin/eosin stain. Mitotic activity was very high, and a great number of small monomorphic lymphocyte-like cells were present (10 x magnification).

bear a resemblance to malignant fibrous histiocytomas, thus facilitating the establishment of proper histogenesis and diagnosis.

Eventually, the negative immunoreactivity for CD 57, actin and desmin and the contemporary 5100-protein detection is not sufficient in itself, but it does corroborate in the diagnosis of malignant fibrous histiocytomas, notwithstanding that the remaining immunohistochemical markers are negative.

The role of electron microscopy in this case would have been very limited indeed, because it has little or no advantage over hematoxylin-eosin stained sections or immunohistochemistry in excluding muscle or neural differentiation.

Endometrial stromal sarcoma (ESS) principally develops within the myometrium, with neoplastic cells resembling the stromal cells of the prolipherative stage of the endometrium. Myometrial vessel invasion is common [7].

Based on mitotic activity, ESS is usually classified as "low grade" and "high grade", when less than 10 or more than 10 mitoses per field are observed, respectively [8].

Low-grade ESS usually occurs in postmenopause and it is often limited to the uterus [9]. Simple hysterectomy may be the therapy of choice, even if one-third of these patients experience a long-term recurrence.

High-grade ESS affects young women, with an aggressive pattern and a survival median lower than two years.

Two rare cases of uterine mesodermal tumors have been reported. The symptoms were acute and both patients had had atypical uterine bleeding from the beginning. The instrumental office examinations did not allow a clear diagnosis and the biopsies were not conclusive for a definitive intervention, like extensively reported elsewhere [10].

To date only the patient with ESS is alive and without signs of disease relapse.

A precise diagnosis of these uterine mesodermal tumors is complicated by the fact that MFH and ESS share many microscopical patterns with other sarcomatous uterine tumors.

Immunohistochemical techniques facilitate the establishment of proper histogenesis and diagnosis, and should be used as ancillary tools to exclude other neoplasms, such as leiomyosarcoma, rhabdomyosarcoma and neurofibrosarcoma.

The histologic appearance of leiomyosarcoma varies according to the degree of differentiation but a minimum requirement is the presence, at least focally, of fascicles of brightly eosinophilic spindle cells with vesicular, cigar-shaped nuclei showing uniform strong positivity for

smooth muscle actin and/or desmin [11]. Muscle specific actin can be detected within most leiomyosarcomas. Desmin is most variable: no more than 70-80% are desmin positive (often only focally) and this may reflect not only loss of differentiation but also the varied phenotype of normal smooth muscle. Importantly, 30-40% of leiomyosarcomas are immunopositive for cytokeratin and epithelial membrane antigen; this pattern may be focal, dot-like or extensive and it is seen with most of the commonly used antibodies. Additional diagnostic aids include fuchsinophilia on a trichrome stain and PAS-positive intracytoplasmatic glycogen in well-fixed cases [12].

Cytoplasmatic cross-striations are present in no more than 20-30% of rhabdomyosarcomas but, even in tumors with almost no discernible rhabdomyoblasts, desmin or muscle actin immunostains are positive in more than 95% of cases [13, 14].

Histologically, the majority of neurofibrosarcomas have a spindle-celled fascicular appearance; distinctive features that may suggest neural differentiation are the abrupt alterations between cellular and myxoid areas and the apparent perivascular accentuation or whirling of tumor cells, which sometimes extend directly into vessel walls and lead to thrombosis. Nuclear palisading is infrequent (and, in fact, is probably no more common than in leiomyosarcoma) and mesenteric differentiation is rare [15].

Electron microscopy has limited advantages in all these diagnoses. Its most common use is to search for evidence of Z-bands or thick and thin filaments that would indicate the tumor as a pleomorphic rhabdomyosarcoma, rather than a pleomorphic malignant histiocytoma, or to search for evidence of neural differentiation.

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