Low-grade fibromyxoid sarcoma: report of three cases and review of the literature

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Abstract

Background: Low-grade fibromyxoid sarcoma or Evans tumor is a variety of soft tissue sarcoma that represents 1% of all malignancies. It is most common in limbs and trunk (50%). We present three new retroperitoneal cases, reviewing their characteristics and carrying out a literature review.

Clinical case: The retroperitoneal location highlights the poor specificity of clinical symptoms, demonstrating, according to their growth and size, as a painless abdominal tumor or by compression and/or invasion of nearby structures. In the cases that we present, the most important finding was the presence of a palpable abdominal tumor without other symptoms, despite remarkable infiltration to other organs that should be included in surgical resection.

Conclusions: We emphasize the difficulty of correct preoperative diagnosis because preoperative studies are inconclusive. Only histological and immunohistochemistry allow precise identification.

Key words: low-grade fibromyxoid sarcoma, soft tissue sarcoma, retroperitoneal tumor.

Introduction

According to the International Classification of Oncological Diseases (ICD-O), low-grade fibromyxoid sarcoma (FMS) corresponds to one of the varieties of soft tissue sarcoma included within the group of fibroblastic-myofibroblastic tumors, which also includes adult fibrosarcoma, myxofibrosarcoma, hyalinizing spiculated tumor cells and sclerosing fibrosarcoma. These correspond to soft tissue sarcomas with a frequency of 1% of all malignant tumors.1 These usually occur in young patients or during middle age, although it has also been described in children (15%). Its incidence is the same for either gender.2 Embryonic origin is unclear, although it appears to have a mesodermic origin, which allows it to be present in different tissues such as muscle, tendons, synovial, fatty tissue, fibrous tissue and including vessels and nerves.3 It is most frequent in the extremities and trunk with a frequency of 50% and sporadically in other locations such as the retroperitoneum, head, kidneys, etc. The majority of the cases are at the subfascial level, but the skin or subcutaneous cellular tissue may also be similarly affected.3,5

Its etiology is known as well as the risk factors, although they are related with genetic factors manifested by Von Reklinghausen disease, Gardner-Wermer syndromes and basal cell nevi, Li-Fraumeni, tuberous sclerosis, lymphedema, previous trauma, postpartum, and chemical agents such as phenoxyacetic acid and chlorophenols, arsenic, and polyvinyl chloride.5,7

Histologically, these tumors have a benign appearance, but with a high potential for metastasis characterized by long intervals between the appearance of the primary tumor and metastasis.1,7,9 The AJCC or TNM staging system tends to be used for its classification, including four prognostic factors: a) histological grade, b) tumor size, c) presence of lymphatic metastasis, and d) distance metastasis.10

Histological grade is considered to be the most important prognostic factor, placing the risk of metastasis at 5-10% for low-grade lesions (grades 1 and 2) and 50-60% for high-grade lesions (grades 3 and 4). The prognosis linked to size comprises four groups: <5 cm, between 5 and 10 cm, 10-15 cm, and >15 cm.

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Lymph node involvement for sarcomas is from 5%, and in some histological types such as rhabdomyosarcoma, epithelial sarcoma or clear cell could reach up to 20% and in FMS of 10%. The presence of distance metastasis is found in between 5 and 10%.

**Clinical Cases**

**Case 1**

We present the case of a 57-year-old male who presented for consultation due to intense asthenia and abdominal distention of 2 months duration. On physical examination, the presence of an ~8-10 cm periumbilical mass is noted. Laboratory examinations were compatible with an unspecified inflammatory process. Of the complementary examinations, we noted the echography and abdominal CT demonstrated a tumor of 19 × 10 cm in the anterior abdominal region causing displacement of the small intestine, without planes of separation between the loops and without being able to determine its origin or infiltration to the small bowel loops. Biopsy with a CT-directed large caliber needle reported a histologically low-grade mesenchymal tumor (Figure 1).

The patient was surgically intervened with 50 cc of serous peritoneal free fluid obtained (negative cytology for tumor). The previously described mass infiltrated the mesentery including ~20 cm of the mid-jejunum; therefore, en bloc resection was decided upon.

Macroscopic description of the 3140 g surgical specimen includes a 24 × 21 cm solid, straw yellow color soft mass with apparently cystic areas, areas of vascularized appearance and wide myxoid areas without foci of necrosis or calcifications. The tumor infiltrated the intestinal wall ulcerating the mucosa and extruding from the intestinal lumen with a diameter of 3.5 cm.

Microscopically, the mass corresponded to a fusiform cellular proliferation with low cellular density, oval and hyperchromatic nuclei and mild pleomorphism. Finely grouped chromatin and one or various small nucleoli were observed with very little mitotic activity (5 mitosis-50 CFU) and scant, sometimes stellate, distinctive pale eosinophilic cytoplasm. Cells are deposited in a myxoid stroma, which varies in the tumor with transitions between them. Lymphoplasmic inflammatory infiltrate is observed with the occasional presence of eosinophils in the areas of higher cell density and are associated with areas of infarction. Capillary size, branched, and generally curvilinear red blood vessels mainly affecting the myxoid zones with cellular disposition surrounding it are notable (Figure 2). The tumor sits in the mesentery, penetrates the wall of the small intestine into two zones, and is associated with mucosal ulceration. No giant rosettes are observed with hyalinizing tumor cells nor is there a clear alternation between hypercellular and myxoid areas. Within the tumor there are occasional hemosiderin deposits, and cystic degenerative changes, but no calcifications or bone or chondral metaplasia. Immunohistochemical (IHC) study is detailed in Table 1.

**Diagnosis**

Diagnosis was low-grade FMS with myofibroblastic differentiation with infiltration of the intestinal wall into two zones (Figure 3). The clinical outcome was favorable and

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*Figure 1. Abdominal computed tomography with oral and intravenous contrast. Tumor is shown with hypodense areas in relation to necrosis that displaces and envelops small bowel loops without fat separation plane.*

*Figure 2. Actin (1A4) 20x: Immunohistochemical stain (IHC) with actin positive in the majority of the tumor cells.*
We present the case of a 28-year-old male who was due to a left varicocele, nonspecific abdominal pain, fatigue and unquantified weight loss. Physical examination demonstrated the presence of an abdominal tumor. Clinical laboratory results were within normal limits. Complementary examinations such as testicular ultrasound demonstrated left varicocele. Abdominal ultrasound, abdominal MR and chest/abdomen CT demonstrated a $25 \times 20 \times 14$ tumor compressing and displacing abdominal structures, cava and left renal vein. Bone scan was negative. Fine needle aspiration showed atypical mesenchymal cells suspicious for malignancy. The patient was surgically intervened with a radical nephrectomy for tumor excision. Postoperative course was without complications. The patient was discharged on the seventh postoperative day. The anatomic pathology report described a 4960 g tumor measuring $27 \times 23 \times 15$ without visualization of the kidney. Microscopic description corresponded to myxoid mesenchymal tumor with histological characteristics of proliferation of fusiform cells of low cellular density, oval and hyperchromic nuclei, precisely grouped chromatin, and small nuclei with little mitotic activity. On these bases, diagnosis of FMS is made (Figure 4).

One year later and due to tumor recurrence, the patient was surgically reintervened with a new tumor resection that included resection of the spleen and tail of the pancreas. Histological description corresponded to a malignant mesenchymal neoplasm. IHC study (Figure 5) is detailed in Table 1.

Histological findings of the recurrence compared with the prior biopsy demonstrated a higher index of mitosis and the patient is currently asymptomatic without having received adjuvant treatments.

**Table 1. Immunohistochemistry**

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<td>Actin (1A4)</td>
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<td>Ki 67</td>
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<td>20–30%</td>
<td>5–10%</td>
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**Case 2**

![Figure 3. HE 10x: Mesenchymal tumor intimately adhered to the wall of the small intestine in relationship with the muscle layer constituted by spindle and stellate cells of myofibroblastic wrap immersed in a myxoid stroma.](image_url3)

![Figure 4. HE 40x: Spindle and stellate cells with a mildly myxoid stroma with light nuclear atypia and without signs of mitosis.](image_url4)
Low-grade fibromyxoid sarcoma of cellular proliferation, corresponding to a sarcoma of a higher degree of malignancy, thereby confirming the clinically aggressive behavior and rapid growth in 1 year. IHC study did not express markers towards any cellular line and thereby the diagnosis of high-grade retroperitoneal sarcoma compatible with a fibrosarcoma is established (Table 1). Treatment with chemo- and radiotherapy was completed in spite of this. Four months later the patient presented with a new recurrence of the lesion and new cycles of chemotherapy were administered. The patient died 8 months later.

Case 3

We present the case of a 54-year-old female seen in consultation due to a 15-cm abdominal tumor in the right flank. Relevant history includes right hepatectomy in 2002 (at another facility) due to tumor recurrence in hepatic III segment, with tumor resection without histological definition due to tumor necrosis. In 2009 the patient had a hysterectomy and double adnexectomy with a diagnosis of leiomyosarcoma. Preoperatively, abdominal CT demonstrated a solid flank and right iliac crest tumor (30 × 20 × 16 cm) with extensive zones of central necrosis and peripheral neovascularization compatible with tumor recurrence. The tumor compressed and displaced the cecal pole and terminal ileum and small bowel loops towards the left. Adjacent to the tumor were three solid masses of 1, 1.5 and 2.5 cm, compatible with peritoneal implants. There were 1-cm adenopathies seen in the bifurcation of the right internal and external iliac chain. There are sequelae of surgery in the liver without other focal lesions. There is a 1.5-cm nodule in the left adrenal gland compatible with adenoma. No bony lesions are observed.

The patient underwent surgery and tumor resection was carried out together with the small bowel loops involved (Figure 6). Macroscopically, the mass, which altogether weighed 4400 g, consisted of several yellowish-white nodular fragments with grayish areas, smooth surface and a slightly gelatinous appearance. The nodules varied between 2.5 cm for the smallest and 32 × 26 × 10 cm for the largest, with a multilobulated appearance. All cuts demonstrated a mucoid-gelatinous appearance with areas of hemorrhage and others of yellowish-white appearance. Microscopically, they corresponded to a malignant mesenchymal proliferation with extensive areas of myxoid pattern with small capillaries between the cells with some red blood cells. The cells demonstrated multilobulated pleomorphic nuclei, markedly atypical with frequent mitosis and some stellate cytoplasm, sometimes eosinophilic and other times with a more elongated and spindle appearance, although there is a great predominance of stellate appearing cells. The areas are macroscopically described as hemorrhagic or necrotic situated in the center of the tumor and showing extensive zones of ischemic necrosis. In some areas the tumor is very intertwined with adipose tissue with the tumor cells appearing in relationship with areas of visually empty spaces. The general appearance of the lesion is myxoid in any areas recalling the myxoid liposarcomas with more pleomorphic or undifferentiated areas. The more relevant IHC study is shown in Table 1.

Histologically, the mass is compatible with a pleomorphic liposarcoma. The positivity for desmin indicates a myxoid differentiation in the mass, making it necessary to do a differential diagnosis with pleomorphic leiomyosarcoma. However, the remainder of the smooth muscle differentiation markers such as actin and caldesmon, caponin and myogenin are negative, being positive in leiomyosar-

**Figure 5.** Vimentin (V9) 20x: IHC stain with diffusely positive vimentin in all tumor cells.

**Figure 6.** Yellowish solid tumor that encompasses the small bowel loops presenting with infiltration of the intestinal wall.
Comas. Given that other non-leiomyosarcomatous tumors have been described with myoid differentiation and according to the location and the macroscopic appearance of the tumor, one must differentiate between the two previously described entities in order to rule out liposarcoma due to the absence of lipoblasts and the leiomyosarcoma due to the absence of other markers of smooth muscle differentiation. For this reason, diagnosis of undifferentiated sarcoma, myxoid, grade 3 of the FNCLCC (French Federation of Cancer Center Sarcoma Group) is proposed. Molecular study was not done because it was thought not to be useful in this case.

Discussion

Low-grade FMS is also known as Evans tumor because he described it for the first time. It is a rare tumor of benign histological appearance but with a potential aggressiveness that should not be ignored. There is a high rate of local recurrence (54%), normally during the first 2 years postsurgery. Distance metastasis is shown in 6% and overall mortality is close to 2%. Clinical manifestations of these tumors are dependent on their location and may exhibit little or no pain, which can cause a delay in diagnosis of up to 5 years in 15% of patients. On rare occasions its presentation may be acute causing respiratory distress and chest pain when it affects the chest wall or loss of mobility when the origin is intracranial.

Diagnosis is based on imaging techniques, mainly computed tomography and magnetic resonance, which allow for definition of the tumor margins although they are non-specific for tumor classification. Anatomic pathological diagnosis of these tumors is difficult due to the presentation of heterogeneous patterns. Cytology obtained via fine needle aspiration has very limited value as well as the large core needle biopsy obtained via computed tomography may on occasion not be representative of the mass. The ability to use a greater panel of immunohistochemical markers increases the possibility to perform a more reliable and accurate pathological diagnosis. However, histological study should be obtained from samples of the entire mass and even with IHC, we cannot establish a definitive diagnosis of FMS. These are tumors with fibroblastic differentiation in which the etiology or known risk factors have been established.

As a variant of the fibrosarcoma, it is characterized by a mixture of collagenous zones of scarce cellularity and other zones of myxoid cellular nodules. Tumor cells tend to be small with scarce eosinophilic cytoplasm, round or oval nuclei, and absent nucleolus, characterized by the absence of scarcity of mitosis and anaplasia or nuclear necrosis. Areas of high cellularity can also be present. There is an increase in mitotic activity, nuclear hyperchromatism and necrosis in 10% of the cases. IHC stain is positive only for vimentin and negative for a variety of antibodies such as desmin, keratin, S100 protein, epithelial membrane antigen (EMA), CD34 and CD31. Muscle-specific actin is positive in the wall of the small vessels of the tumor and strongly positive in the fibrous layer. The differential diagnosis includes those lesions of a spindle-cell pattern with a myxoid or fibrous component such as myxoid neurofibroma, myxoid liposarcoma, angiomyxomas, low-grade myxofibrosarcoma, neurofibromas, fibromatosis, fibrous histiocytoma, perineurinomas, peripheral nerve sheath tumors, desmoid tumors, desmoplastic fibrosarcoma and low-grade undifferentiated liposarcoma. It should be based on clinical features, location, age, macroscopic and histological findings and immunohistochemical characteristics.

Case 3 corresponds to a high-grade malignant myxoid sarcoma as has already been commented upon. Differential diagnosis was carried out with the pleomorphic liposarcoma due to the absence of lipoblasts and S100 protein and by the absence of other markers of myxoid differentiation, different from desmin in the case that we presented. Both the low-grade FMS as well as the giant rosette spindle-cell hyalinizing tumors present a common pattern of recurrent translocation t(7;16)(q33;p11) that codifies a fusion oncoprotein resulting from the fusion of genes FUS and CREBL2 (also known as BBF2H7). This characteristic also allows good molecular confirmation by RT-PCR in formalin-fixed, paraffin-embedded tissue or fluorescence in situ hybridization (FISH). The latter is more sensitive, but neither of the two methods has prognostic value. Another marker used in cases where differential doubt may arise between a benign mesenchymal tumor and low-grade sarcoma is the IHC study of the glycoprotein MUC4 expression (mucin 4). The prognosis of patients with this type of tumor is related to early diagnosis and timely treatment with complete surgical resection (with wide disease-free margins). If we add to this a low grade of histological malignancy and the absence of lymph node involvement, the surgical option would have been sufficient without requiring additional treatments. Treatment with radio- or chemotherapy is indicated in less favorable cases. Radiotherapy is indicated in mid- or high-grade tumors and in low-grade tumors with positive or questionable margins. Chemotherapy is indicated in stage III tumors or if there is lymph node involvement in which the estimated 5-year survival rate is <35%. Surgical reintervention due to recurrence or distance metastasis may determine a better prognosis for these patients because 15-20% of patients who relapse may be cured with rescue treatments. Monitoring of these patients is important and lifetime follow-up should be done because cases of metas-
tasis have been reported, even at 45 years from diagnosis and treatment.12

In conclusion, we present three cases of a rare tumor whose prognosis depends on early and correct diagnosis with timely surgical intervention in which care must be taken to ensure that there are tumor-free margins. Lifetime follow-up is done due to the possibility of late metastasis.

References