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Fibrosarcoma: a challenging diagnosis

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ABSTRACT

Fibrosarcoma represent a rare group of soft tissue malignancies derived from fibrous connective tissue and immature proliferating fibroblasts or undifferentiated anaplastic spindle cells. It affects patients in the fourth and fifth decade of life. Fibrosarcomas can be classified in subtypes such as low-grade fibromyxoid sarcoma (LGFMS) and sclerosing epithelioid fibrosarcoma (SEF), and others. Histological features that overlap between types of fibrosarcomas is well known and reported in the literature. We report the case of a 53-year-old patient who presented a tumor in the axillary fossa, which was initially diagnosed as a solitary fibrous tumor. Due to recurrence of the lesion, as well as the presence of distant metastases, the histological revision considered the diagnosis of breast metaplastic carcinoma, since the tumor expressed the p63 antigen and estrogen and progesterone receptors. Unexpected resistance to chemotherapy motivated the diagnosis re-evaluation, which was due to MUC4 expression and morphological characteristics concluded by a hybrid LGFMS-SEF tumor. The authors call attention to the difficult diagnosis in cases of soft tissue tumors. A broad panel of immunohistochemical research is required as the clinical course is essential to the final diagnosis.

Keywords: Fibrosarcoma; MUC4 protein, human; Drug Therapy; Surgical Procedures, Operative.

CASE REPORT

A 53-year-old female patient sought medical attention because of the relapse of a painful and progressive-growing mass in the right axillary fossa. Her past medical history also included the surgical removal of a right axillary nodule 3 years ago measuring 7.5 cm, which was compatible with the diagnosis of a solitary fibrous tumor (Figure 1). One year later, another nodule measuring 2.0 cm was excised, and the diagnosis was similar to the former (Figure 2). The entire immunohistochemical

panel used in the diagnostic work up of these two specimens is shown in Table 1.

At this time, physical examination showed the presence of a painful tumor, measuring 12 cm, which adhered to deep structures in the right axillary fossa. Breast examination, as well as laboratory analysis, was normal. The computed tomography (CT) of the axillary region showed three conglomerated solid nodules, (the biggest measuring 7.1 cm) with well-

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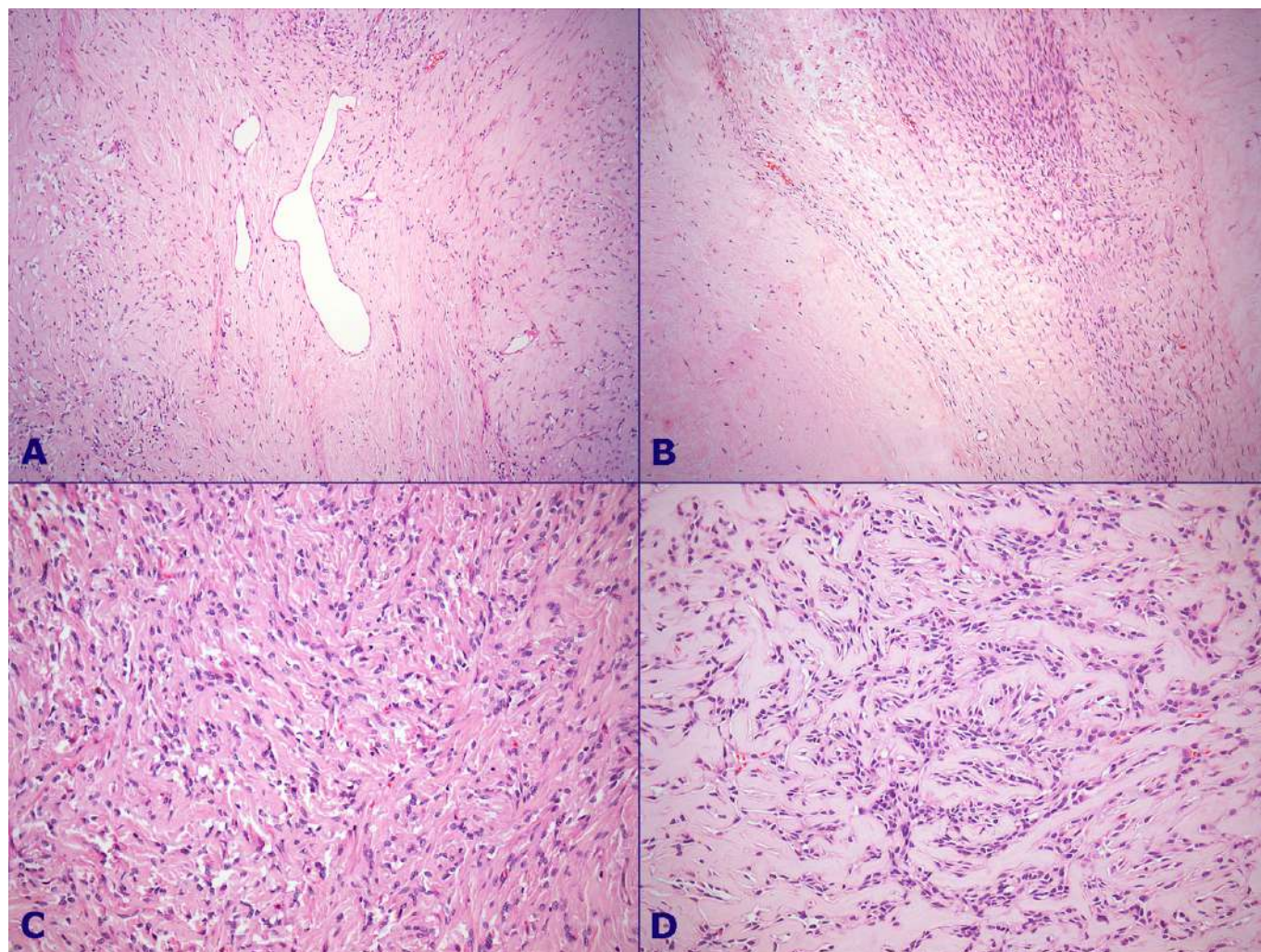


Figure 1 – Photomicrography of the first resected tumor. **A** - Hypocellular area showing a vessel with hemangiopericytoma-like pattern (H&E – 100X); **B** - Hypocellular myxohyalin area with a transition to a fibrous hypercellular area (H&E – 100X); **C** - Hypercellular area showing bland tumor cells with round to oval nuclei within an abundant hyalinized collagen stroma (HE – 200X). **D** - Hypercellular area with nests of epithelioid cells (HE – 200X).

defined limits and heterogeneous enhancement after the intravenous contrast medium injection.

The patient was submitted to the third surgical procedure, which showed an extensive tumoral mass infiltrating the axillary plexus, the great dorsal muscle, and the serratus muscle. An incisional biopsy was performed due to the non-resectability of the whole tumoral mass. The histological examination showed a spindle cell neoplasia presenting areas of epithelioid aspect, with mild nuclear atypia (Figures 3 and 4).

The immunophenotype was positive for p63, CD99, vimentin, and estrogen and progesterone receptors, interpreted as a metaplastic carcinoma (Figures 5A, B and C). Tumoral invasion was present in the adjacent fibro connective tissue and adipose tissues, as well as in the striated muscle.

Revising the first two specimens, positivity for p63 and estrogen receptors was also present.

Further disease staging showed the right hemithorax pleural effusion, pleural nodules measuring up to 1.5 cm and the scattered bilateral pulmonary nodules measuring up to 0.9 cm. Mammography revealed BI-RADS zero, and breast ultrasonography ruled out malignancy in the mammary parenchyma. The postoperative period was uneventful and the patient was referred to an oncological center.

Once in the oncological center, the patient underwent a pulmonary biopsy, which confirmed the presence of metastatic disease.

Chemotherapy based on carboplatin AUC 2 and paclitaxel 80mg/m² weekly (for 3 or 4 weeks

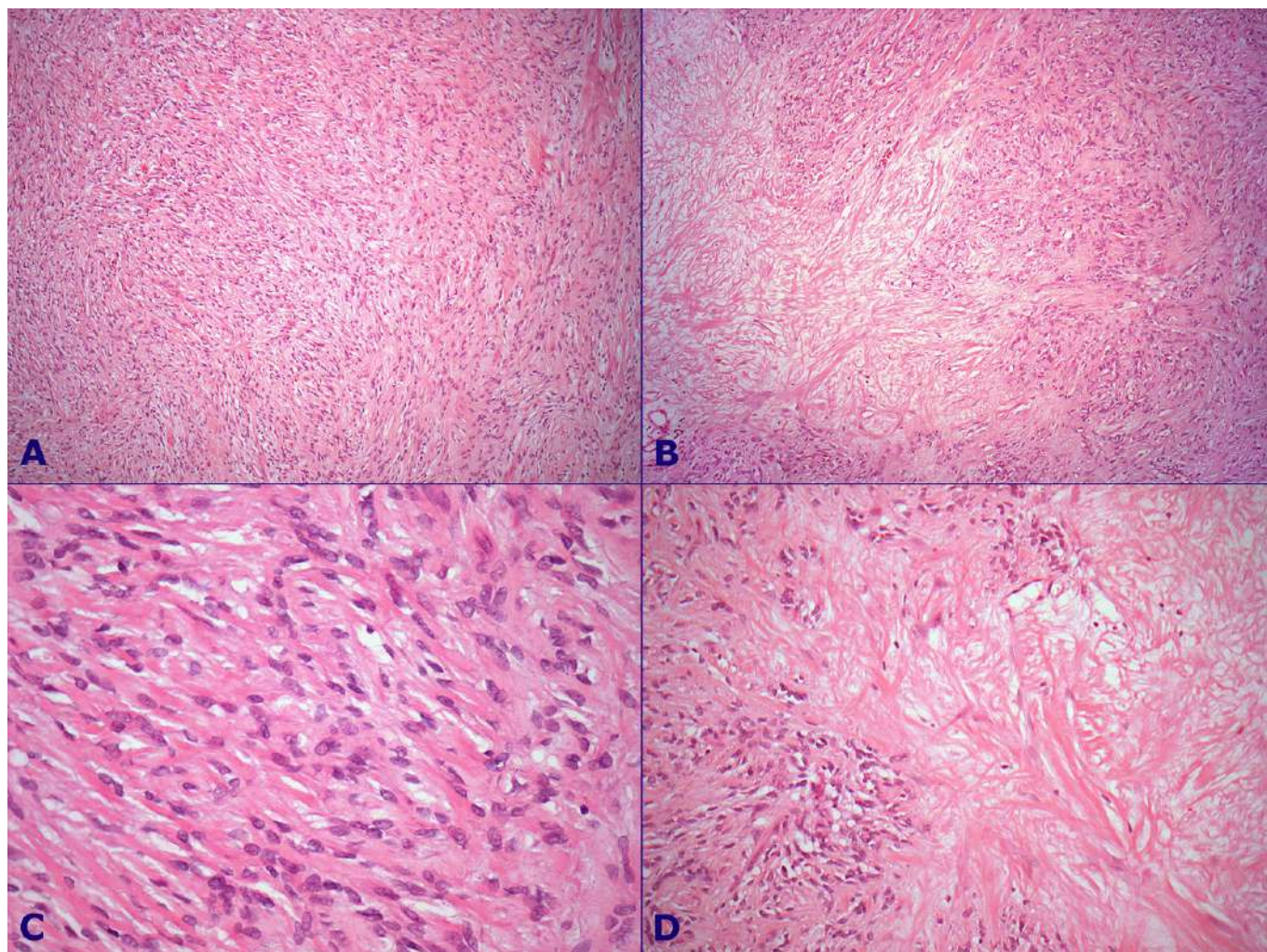


Figure 2 – Photomicrography of the second resected tumor. **A** - Hypercellular area of the tumor showing a fascicular pattern (H&E – 100X); **B** - Sharp transition between a fibrous hypercellular and a myxoid hypocellular area (H&E – 100X); **C** - Hypercellular area showing tumoral cells with round to oval nuclei within an abundant hyalinized collagen stroma (H&E – 400X); **D** - Detail of the sharp transition of the hypercellular area with nests of epithelioid cells and the myxoid area with bland spindle-shape cells (H&E – 200X).

Table 1 – Immunohistochemical panel used in the first two specimens

Antigen	Result	Antigen	Result
CD34	Negative	SMA	Negative
Bcl-2	Positive	CD117	Negative
Vimentin	Positive	S100	Negative
CD99	Positive	AE1/AE3	Negative
ER*	Positive	EMA	Negative
PR	Negative	Ki-67	1%
HHF-35	Negative		

SMA = smooth muscle actin; EMA = epithelial membrane antigen; ER = estrogen receptor; PR = progesterone receptor. * 6F11 clone, manufacturer Novocastra.

the right shoulder, and an enlargement of the right internal thoracic lymph nodes. Chemotherapy was discontinued and pleurodesis was performed.

Motivated by the unexpected chemotherapy failure, the histological and immunohistochemical examination was revised. This time the immunophenotype was positive for MUC4 (Figure 5D) and negative for CK5, CK34BE12, Desmin, S100, and HER-2. The entire immunohistochemical panel used in this revision is shown in Table 2. Thus, the diagnosis of the neoplasia was defined as a hybrid tumor: low-grade fibromyxoid sarcoma/sclerosing epithelioid fibrosarcoma.

each cycle) was started. After four cycles, CT showed progression of the disease by increment of pleural effusion, pleural nodes, a new bone lesion in

As the patient's clinical status remained steady and well, a surgical debulking is being planned.

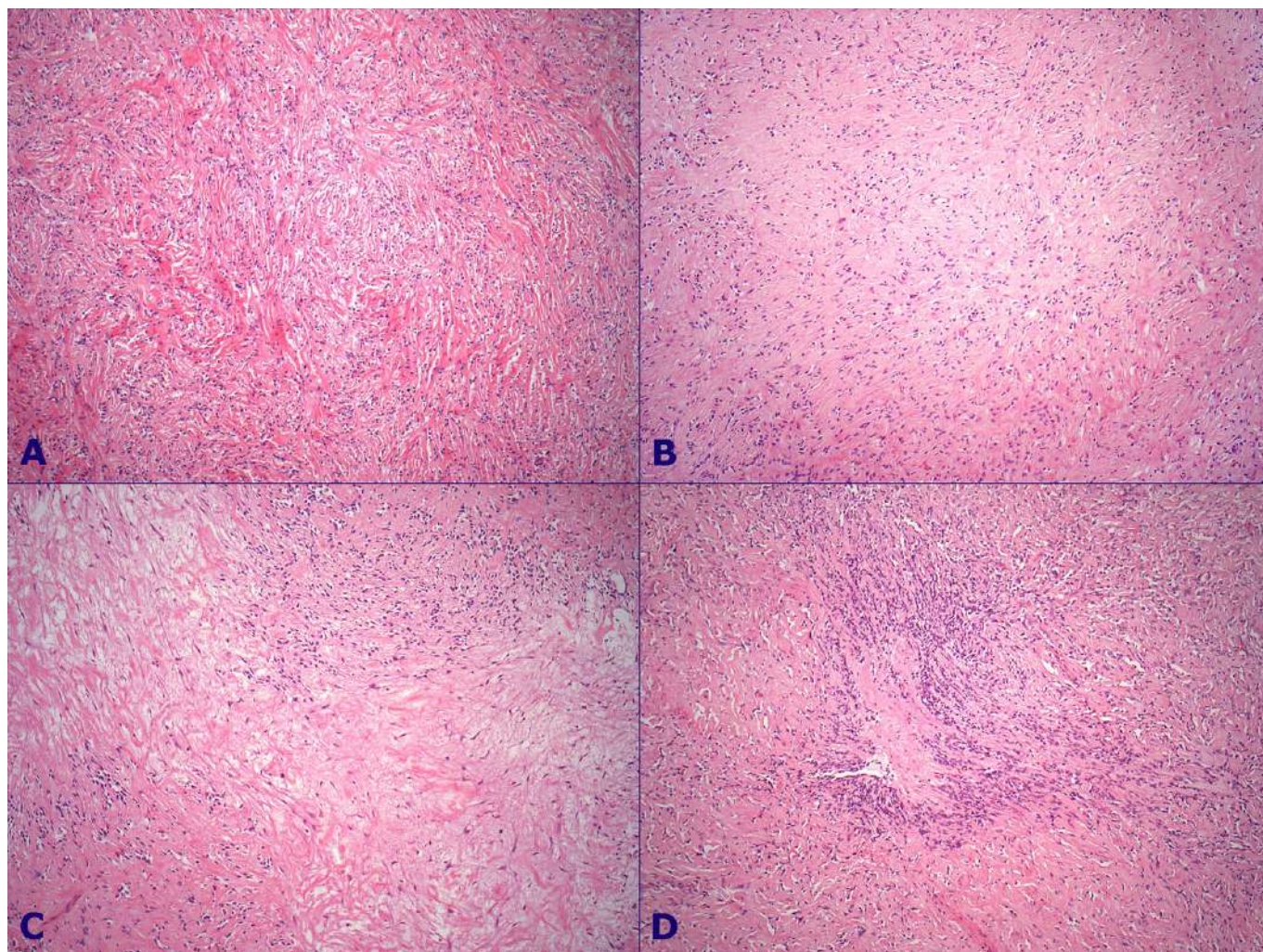


Figure 3 – Photomicrography of the third resected tumor. **A** - Hypercellular area showing cell cords within an abundant hyalinized collagen stroma (H&E – 100X); **B** - Hypocellular area showing bland, small cells within a collagenized stroma (H&E – 100X); **C** - Sharp transition between a fibrous hypercellular and myxoid hypocellular areas with spindle-shape cells (H&E – 200X); **D** - Area showing large collagen rosette surrounded by spindle-shape cells, a typical pattern of the hyalinizing spindle cells tumor with giant rosettes (H&E – 100X).

DISCUSSION

Fibrosarcomas, tumors composed of malignant fibroblastic cells, represent a large group of soft tissue malignancies, classified in the subgroups such as low-grade fibromyxoid sarcoma (LGFMS) and sclerosing epithelioid fibrosarcoma (SEF), which seem to share morphologic and molecular characteristics, suggesting a close relationship between these two types of tumor.¹

In 1987, Evans² described the first case of LGFMS, and since then it has remained a rare tumor that typically affects young adults, arising in the deep soft tissues of the proximal extremities or of the trunk. Studies on case series show an incidence of 0.18 per million, accounting for 0.6% of soft tissue sarcomas.³ LGFMS has a quite

variable morphological spectrum.⁴ In its classic form, LGFMS is composed by alternating fibrous and myxoid areas with bland spindle or stellate cells in a whorled growth pattern.^{4,5} A hyalinizing spindle cell tumor with giant rosettes is a variant of LGFMS, with prominent stromal hyalinization and collagen pseudorosettes.⁶ Sometimes, prominent hemangiopericytoma-like vasculature is also seen.⁵

Although low-grade soft tissue sarcoma rarely metastasizes, LGFMS metastases have been reported to vary from 5% to 41%. Due to the low grade of malignancy, and therefore the low mitotic rate of these tumors, it is not expected to be chemo or radio sensitive.³

The immunohistochemical profile of LGFMS is nonspecific, but it does have a role in the

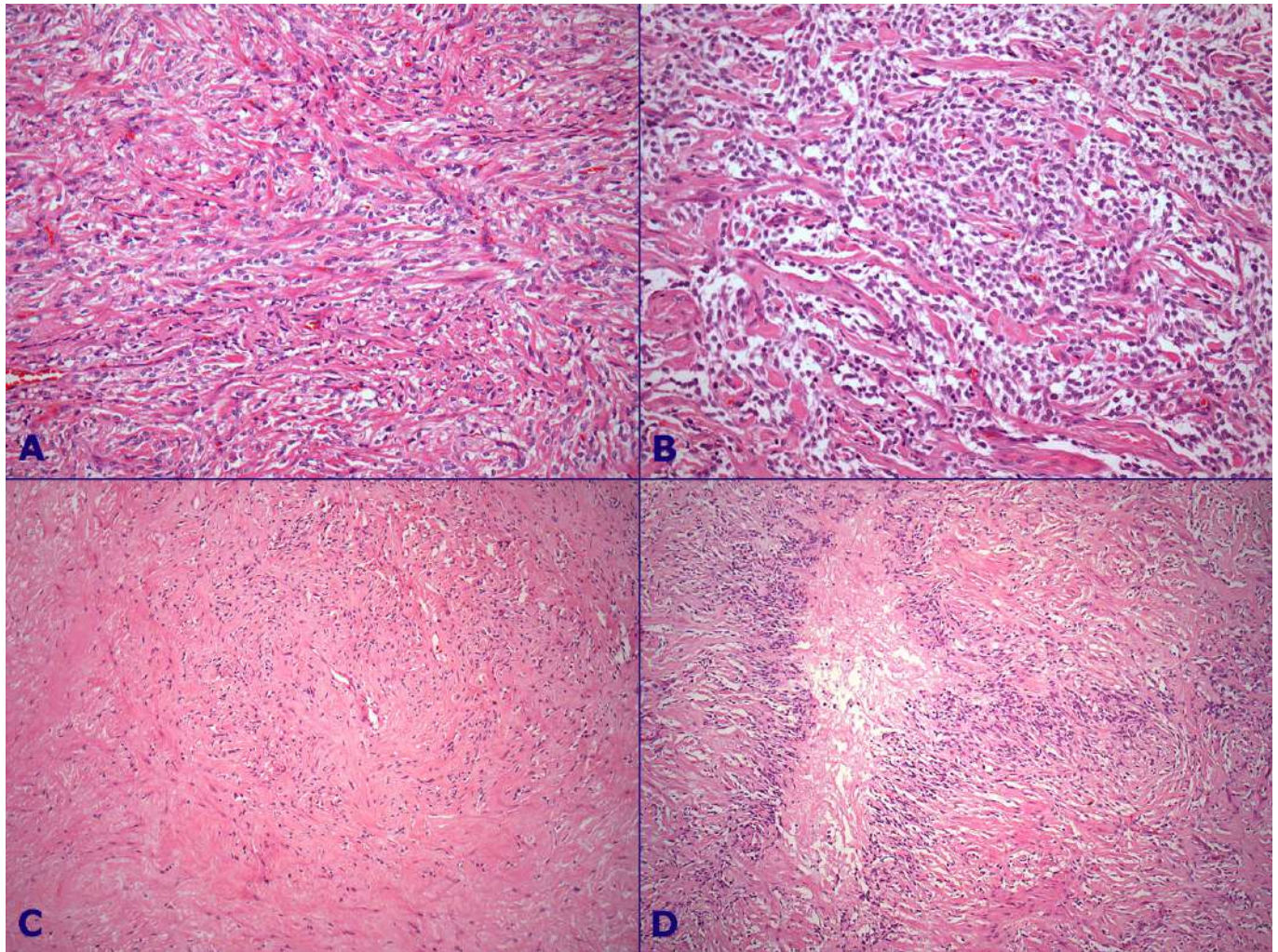


Figure 4 – Photomicrography of the third resected tumor. **A** - Hypercellular area showing cords of epithelioid cells with a clear cytoplasm and round to oval nuclei within an abundant hyalinized collagen stroma (H&E – 200X); **B** - hHypercellular area showing nests of epithelioid cells within an abundant collagenized stroma (H&E – 200X); **C** - Transition between hypocellular areas with spindle-shape cells (H&E – 200X); **D** - Large collagen rosette surrounded by spindle-shape cells (H&E – 100X).

diagnostic process. Epithelial membrane antigen (EMA) expression has been the most relevant marker in LGFMS (positivity in 43-91%). Focal positivity for smooth muscle actin (SMA), desmin, and CD34 is also reported.^{7,8} EMA positivity is often focal and is also observed in tumors that may mimic LGFMS, such as soft tissue perineurioma and a subset of solitary fibrous tumors, among others.⁵ LGFMS has a differential upregulation of the Mucin 4 (MUC4) gene with a corresponding overexpression of the transmembrane glycoprotein MUC4, which is expressed in many epithelial surfaces. Even though little is known about the role of MUC4 in normal mesenchymal cells or mesenchymal tumors, aberrant expression or overexpression of MUC4 has been reported in various carcinomas.⁵ Doyle et al.⁵ showed positivity in 100% in a series of 49 LGFMS patients. The detection of the oncogenic chimeric fusion gene *FUS-CREB3L2*, or rarely

FUS-CREB3L1, resulting from the translocation t(7;16)(q34;p11) or t(11;16)(p11;p11), respectively, represent an important tool in defining the diagnosis of LGFMS.⁷

LGFMS may display unusual histological features, such as areas of hypercellularity with capillaries, areas of pleomorphism or marked epithelioid cytomorphology mimicking SEF. Therefore, the presence of such findings does not rule out the diagnosis of LGFMS.¹ Folpe et al.⁶ reported that in a series of 77 cases of LGFMS and hyalinizing spindle cell tumor with giant rosettes (HSCT), 45% of cases showed epithelioid areas. The similarity of clinical and histological features between LGFMS and SEF was also reported by Reid et al.⁹

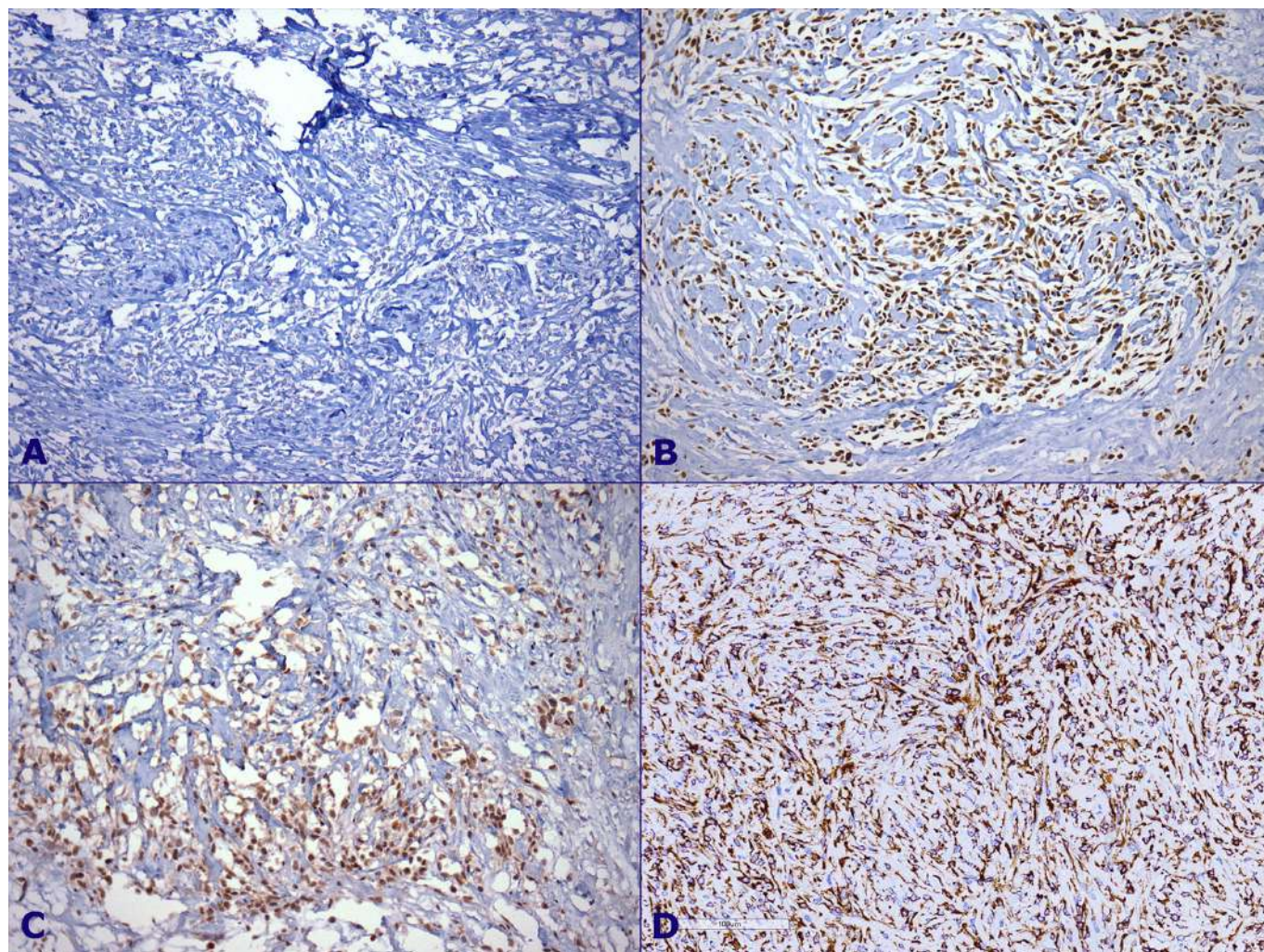


Figure 5 – Photomicrography of the third resected tumor. Immunohistochemistry. **A** - AE1-AE3 negative (200X); **B** - Diffuse and strong nuclear positivity for p63 (200X); **C** - Diffuse and moderate nuclear positivity for estrogen receptor (200X); **D** - Diffuse cytoplasmatic positivity for MUC4 (200X).

In 1995, Meis-Kindblom et al.¹⁰ described SEF as a rare variant of fibrosarcoma that occurs in the deep soft tissues of lower extremities, limb girdles, and trunk. Approximately 50% of patients develop local recurrence or distant metastases after resection. Clinically, SEF demonstrates aggressive behavior with a mortality rate of up to 57%. Although Pan et al.¹¹ reported a case with brilliant response to Irinotecan, SEF is known as a chemo-resistant tumor.

SEF usually is composed of epithelioid cells with clear or eosinophilic cytoplasm, which is arranged in nests or cords, within a densely sclerotic stroma. Hypocellular fibrous areas with a fascicular growth pattern and myxoid areas may be present in SEFs. In some cases, areas indistinguishable from LGFMS is also observed.^{10,12,13} Besides histologic overlap with LGFMS, SEF also shows FUS gene rearrangements.¹ Similarly to LGFMS, the immunohistochemical profile of SEF is nonspecific. The immunophenotype of SEF shows focal positivity for EMA and weak positivity for S-100.¹⁰ Recently, Doyle et al.¹² showed that MUC4

Table 2 – Immunohistochemical panel used in the revision

Antigen	Result	Antigen	Result
BCL 2	Positive	CK7	Negative
CD99	Positive	p63	Positive
ER	Positive	S100	Negative
PR	Negative	HER-2	Negative
AE1AE3	Negative	CD34	Negative
35BH11	Negative	CK5	Negative
MUC4	Positive	34BE12	Negative

MUC4 = mucin 4.

expression was present in 78% of SEFs, including 100% of hybrid LGFMS-SEF and 69% in “pure-SEFs.” Although MUC4 is a sensitive and relatively specific marker for LGFMS and SEF, its expression is also observed focally among cases of synovial carcinoma, ossifying fibromyxoid tumors, epithelioid gastrointestinal stromal tumors and myoepithelial carcinoma.^{5,12}

The treatment of these tumors is challenging. The standard treatment for low-grade sarcomas is surgical removal without adjuvant therapy since the recurrence, if any, is usually local. Maretty-Nielsen et al.³ published a case series with 14 patients treated in Denmark between 1979 and 2010. The treatment strategies were variable according to clinical presentation. Twelve patients were diagnosed with localized tumors and were treated with surgery. Four cases presented local relapse, without evidence of distant metastasis, and were treated with surgery without adjuvant therapy-similar treatment to the primary tumor. The patients that developed distant metastasis were treated with different strategies, including ifosfamide, doxorubicin hydrochloride, imatinib mesylate, trabectedin, gemcitabine, docetaxel, and palliative radiotherapy. The better response to chemotherapy was observed with trabectedin and resulted in short-term control of disease progression.³

Herein, we report the case of a 53-year old woman with a relapsing tumor in the axillary fossa. After three years of the initial diagnosis, she presented metastases to the lung and pleura. At this time, the histologic diagnosis was fibromatosis-like metaplastic carcinoma, which encouraged us to initiate chemotherapy with carboplatin and paclitaxel. At the end of the fourth cycle the disease unexpectedly progressed, setting the tumor as chemo-resistant. A new histological revision added to the unfavorable clinical course led to the final diagnosis of a hybrid low-grade fibromyxoid sarcoma/sclerosing epithelioid fibrosarcoma. Therapeutic planning involves a surgical debulking attempt, with the intention of an improved quality of life.

The positivity of the immunophenotype for p63 and hormonal receptors was reasonable for the diagnosis of fibromatosis-like metaplastic carcinoma (FMC). Metaplastic carcinoma encompasses a group of neoplasms characterized by differentiation of the neoplastic epithelium into squamous cells and/or mesenchymal-looking elements.¹⁴ FMC was formerly called monophasic spindle cell carcinoma, and is a rare entity characterized solely by the sarcomatoid element.¹⁵ The latter has a better prognosis compared with the classical form of metaplastic carcinoma, presenting local recurrence and low metastatic potential.¹⁶ Histologically, FMC is characterized by bland spindle cells, with mild or absent nuclear atypia, arranged in wavy, interlacing fascicles. Sometimes, cords and clusters of plump spindle and more epithelioid cells are found.¹⁴ Immunohistochemical analysis, with a broad panel of cytokeratins, is required for the diagnosis, since

no specific cytokeratin is expressed in all tumors. Among the cytokeratins, the most useful are CK5/6, CK14, 34 β E12, and AE1-AE3.^{16,17} In addition to cytokeratins, p63 is almost invariably positive in the spindle cells, but not in the ductal carcinomatous component.^{14,15,17} The majority of these tumors are negative for hormone receptors and HER 2.^{15,17}

The immunohistochemical reaction for p63 has several diagnostic uses, particularly in the evaluation of epithelial neoplasms, like squamous differentiation in poorly differentiated or spindle cell lesions.¹⁸ Although there is a virtual absence of expression of p63 in soft tissue tumors, Jo and Fletcher¹⁹ reported the expression of this antigen in 9.1% in a series of 650 cases of soft tissue tumors. Among these, 10% of the LGFMS showed multifocal staining. Focal or weak p63 positivity, in the absence of cytokeratin expression, does not allow the diagnosis of spindle cell squamous cell carcinoma.

Although an estrogen/progesterone receptor is found in only a subset of breast carcinomas and carcinomas of the ovary and endometrium, it may also be observed in other carcinomas, for example, of the lung, stomach, and thyroid.²⁰ This aberrant positivity is reported to be related to the antibody clone. The estrogen receptor antibody clone 6F11 (Ventana, Tucson, AZ) gives more false-positive results compared with other clones.²¹ Some authors have advised that weak/moderate expression should be judged more carefully, taking into account the clinical presentation and results of other immunohistochemical reactions.²⁰ The expression of estrogen and progesterone receptors in soft tissue tumors is poorly defined and their significance is uncertain. Valkov et al.²² observed the occurrence, distribution and prognostic value of these hormonal receptors in non-gastrointestinal stromal tumor soft tissue sarcomas. Estrogen receptor was a positive prognosticator in women, while progesterone receptor was a negative prognosticator in men. The estrogen receptor negative/ progesterone receptor positive profile was a negative prognosticator for the whole patient cohort

The results of a disappointing clinical response to the chemotherapy, and the morphological aspects associated with MUC4 expression, the diagnosis of hybrid LGFMS-SEF tumor is strongly supported. The authors call attention to the positive immunophenotype for p63 and estrogen receptor as a pitfall.

Fibrosarcoma has always been considered a diagnosis of exclusion. Recent advances in molecular

biology with the detection of *FUS* gene rearrangement and the expression of MUC4, have contributed greatly to the accurate diagnosis of this entity.

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