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Malignant Fibrous Histiocytoma of the Breast. Report of Two Cases and Review of the Literature

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Abstract. *Sarcomas of the breast are uncommon, accounting for less than 1% of all primary malignancies. Among these tumors, malignant fibrous histiocytoma (MFH) is very rare. Two cases of this neoplasm are reported, with histological findings and surgical treatment. The issue of radiation-induced lesions after surgery for carcinoma and the necessity for a correct preoperative diagnosis is examined. A review of the available literature evaluates the histopathological and biological features of MFH of the breast, for which there are no prospective trials, owing to the rarity of this kind of neoplasm. The extent of surgery or role of axillary lymph nodes dissection and multimodality therapy are discussed.*

Non-epithelial tumors of the breast are rare, accounting for less than 1% of all primary breast malignancies, both in our experience and in the literature (1-3). These lesions can be generically defined as "sarcomas", comprising all malignancies arising from the connective tissue of the gland, however, cases of cystosarcoma phylloides are believed by Pollard to be excluded from soft tissue sarcomas of the breast because it is a distinct clinicopathological entity (4, 5).

Malignant fibrous histiocytoma (MFH) of the breast primarily arises from the gland or following adjuvant radiation treatment after surgery for carcinoma (6-8). The rarity of these tumors is the reason why the optimal treatment is unclear.

Two cases of MFH of the breast are here reported, with the purpose of examining the main clinical and pathological features of this neoplasm. A review of the available literature is presented.

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Case Report 1

B.A., a 79-year-old female nun, was admitted to our Department with a nodular mass in the upper outer quadrant of her right breast, discovered at mammography. The lesion presented cystic echographic features.

On physical examination, a firm but painless oval mass, with distinct margins, 1.5 cm in diameter, was palpated in the upper outer quadrant of the breast and a non-specific lymphadenopathy was noted in the ipsilateral axilla. The left breast was unremarkable.

Based on these findings, a wide local excision (WLE) was made under local anaesthesia and the diagnosis of MFH was histologically established. The surgical specimen contained a well-circumscribed, oval mass with a diameter of 2.5x2 cm.

Histological examination revealed a diffuse myxoid background, with perivasal hypercellular areas composed of a variable population of both fibroblast-like nuclei and pleomorphic or multiple nuclei (Figures 1-2). The eosinophilic cytoplasm had ill-defined, irregular margins. The cells showed an irregular arrangement, with a high mitotic rate. An inflammatory infiltrate of lymphomonocytes was observed throughout the myxoid areas.

The immunostains of the cellular population were positive for vimentin and negative for cytokeratin, CD45 (PanLeu), desmin and CD68. The tumor reached the deep surgical resection margin.

Currently, 4 years following surgery, the patient is free from local recurrence or metastasis on physical examination, as well as on imaging studies.

Case Report 2

C.M., a 42-year-old unmarried female, with no known significant previous medical or familial history, presented with a mass in her left breast, discovered by the patient 3 years previously and enlarging from 6 months.

Upon examination, a 1-cm skin area of retraction was identified in the upper external quadrant of her left breast

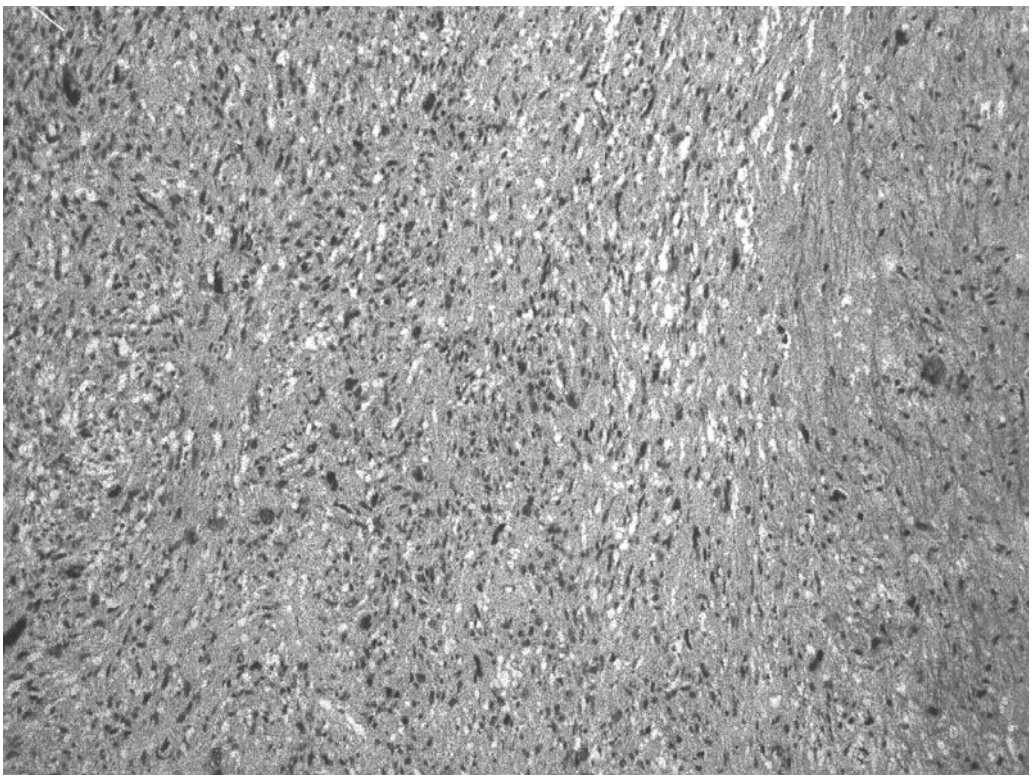

Figure 1. *Histological picture of MFH of the breast. Area of low cellular density with bizarre nuclei and collagenous stroma (H&E, 100 x).*

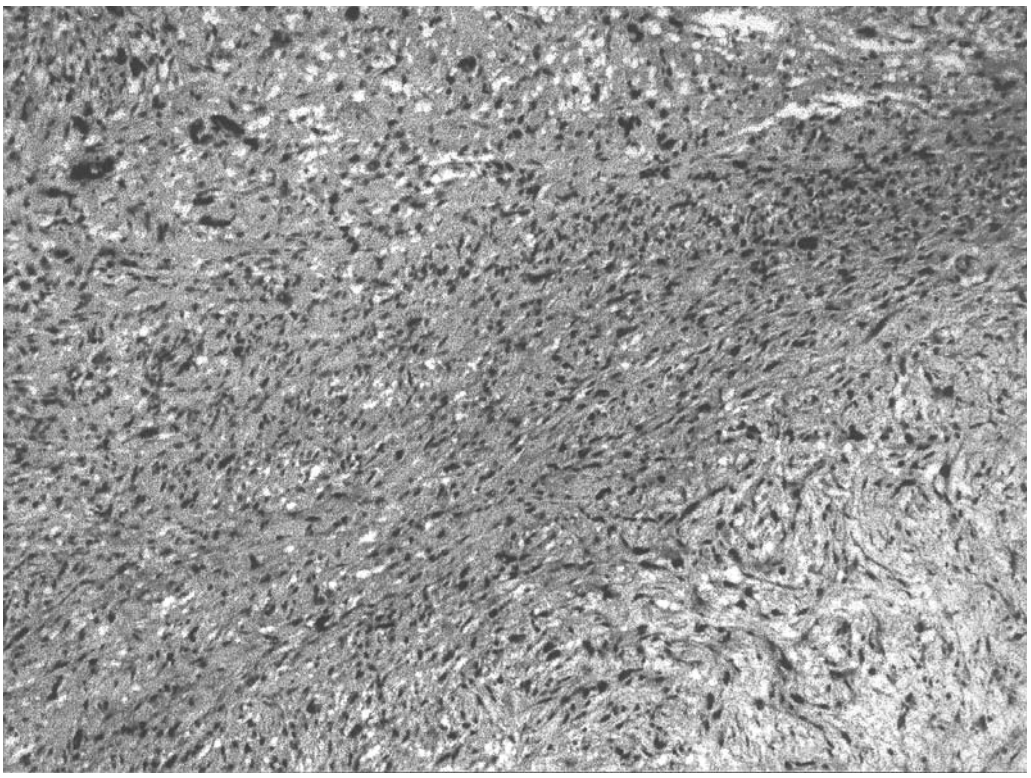

Figure 2. *Histological picture of MFH of the breast. Area of more dense cellularity and fibrous stroma alternating with area of myxoid stroma (H&E, 100 x).*

corresponding to an ill-defined, solid mass, 1.5 cm in diameter, clearly painful at palpation. The mass appeared to be movable and not fixed to the chest wall, while the palpation of the loco-regional lymph nodes did not reveal other pathological findings. The right breast was unremarkable.

Mammographic studies showed a retro-areolar, dense, small-sized (about 1.5 cm in diameter) mass, with indistinct margins and the absence of microcalcifications. A simple mastectomy was therefore accomplished with excision of the underlying pectoral fascia and ipsilateral axillary lymph nodes dissection.

The histological sections showed a mesenchymal neoplasm composed primarily of spindle or rounded cells corresponding to fibroblasts arranged in a storiform or herringbone pattern. The nuclei were oval to spindle-shaped and the cytoplasm had, in some cases, vacuolar appearance and PAS-positive reaction. Occasionally associated with this pattern were other cellular areas containing giant cells, larger binucleated fibroblasts and foamy PAS-positive histiocytes. Additionally, plasma cells and lymphocytes were seen uniformly dispersed throughout the stroma. The mitotic rate ranged from two to four per 10 hpf.

All axillary lymph nodes removed were free from metastasis and the pathological findings were consistent with "Malignant fibrous histiocytoma, fibrous variant". The patient is alive and free from local recurrence or metastasis 24 years after surgery.

Discussion

The concept of MFH, first introduced in 1964 by O'Brien and Stout, concerns a soft tissue sarcoma composed of fibroblast-like and histiocytic-like cells, mixed with pleomorphic giant and inflammatory cells (9-11). MFH is a fairly common tumor in the deep soft tissues: the most frequent primary sites are the lower (49%) and upper (19%) limbs, but it has been reported even in the retroperitoneum and abdomen (16%), while localization in the breast is extremely rare (11, 12).

The precise histogenesis of the tumor remains a matter of some debate. Although it probably arises from the tissue histiocyte that is capable of acting as a facultative fibroblast, it has also been suggested that it is a primitive mesenchymal tumor showing a capability of dual differentiation towards fibroblast or histiocyte (1, 4).

MFH of the breast can arise "*de novo*" from the connective tissue of the gland, or be associated with a cystosarcoma phylloides, or develop in a breast after irradiation for carcinoma. In the last case, the term "post-radiation sarcoma" of extraglandular origin may be more appropriate (1, 2, 6). The potential for the development of these sarcomas is increasing because of the growing popularity of breast-sparing surgery followed by irradiation in the treatment of carcinoma (13). Moreover, Inoshita and Youngberg report 2 cases of MFH arising from surgical scars, thus suggesting a close relationship between surgery or radiation injury and tumorigenesis (14, 15). According to Sheppard, most sarcomas are now related to radiation for soft tissue neoplasms, particularly breast cancer (6, 7): these tumors are characterized by long latency periods ranging from 3 to 34 years (8, 16) and a poor prognosis (8).

MFH shows features spanning a wide spectrum of histological patterns, falling essentially into 4 principal variants on the basis of the criteria assessed by Weiss-Enzinger and Kearney: the fibrous type (the most frequent), the giant-cell type (pleomorphic), the myxoid type and the inflammatory type (5, 10, 17-19).

Although the role of fine-needle aspirate cytology (FNA) in diagnosing epithelial lesions of the breast is nowadays well-established, the importance of this procedure in the evaluation of mesenchymal lesions is less clear (15, 20-22). Nevertheless, Pollard asserts that a preoperative diagnosis can be made reliably by tru-cut biopsy or FNA in the same way as for carcinoma, which is likely to have been the initial working diagnosis in most cases (23).

Immunohistochemical studies performed with the immunoperoxidase technique show that cells stain positive for vimentine and negative for cytokeratin, these being intermediate proteins known to be specific markers of cellular differentiation toward mesenchymal and epithelial type, respectively (2, 24). Tetu *et al.* have assessed, by immuno-histochemistry, the prognostic value of the expression of a member of the stress polypeptides family, the heat-shock protein of 27 KDa (HSP-27), showing a more favorable outcome in all patients in which the immunostaining for HSP-27 is positive (58% of the patients affected by MFH) (25).

Nakanishi *et al.* report a high incidence of genetic changes in the tumorigenesis of human post-radiation sarcomas by polymerase chain reaction-single-strand conformation polymorphism (PCR-SSCP). This study reveals the aberrant mobility shifts of bands in 24 cases, 21 shifts in exon 5, 18 in exon 7 and 12 in exon 8, with a total of 58 mutations in 21 (88%) out of 24 cases. Moreover, the evaluation of p53 gene alterations reveals a low frequency of mutation in sporadic soft tissue sarcomas (20%), in contrast to the high frequency of p53 gene mutations in post-radiation sarcomas (58%) (16).

MFH of the breast may be a very aggressive tumor, fast-growing with a high rate of local recurrence (44%) and distant metastases (42%), particularly to the lungs (82%), bony skeleton, pleura and liver; regional lymph nodes involvement ranges from 12% to 32% (2, 26). The studies available in the literature report occasional skin and subcutaneous soft tissue metastases due to MFH, usually as a terminal event (17, 19, 27).

The treatment of choice for MFH of the breast, as well as that of sarcoma, is surgery. There are several current options in the treatment of this disease, because the rarity of the tumor precludes prospective trials. The standard therapy is mastectomy, which, according to Pollard, should include the excision of both underlying pectoral muscles, in order to reduce the rate of local recurrence (4). Other approaches

include a breast-preserving WLE with adequate negative margins, particularly for smaller tumors (less than 5 cm according to Gutman) (12, 28).

The staging or therapeutic role of routine axillary dissection has not been defined. Some authors (3, 4) believe that the incidence of regional lymph node involvement is low (12-29%), representing a late step in the natural history of the disease. Accordingly, axillary lymph node dissection in MFH of the breast seems to be unjustified. However, other authors, who have found metastases in the axillary lymph nodes in 12% to 32% of their patients, strongly recommend the procedure (2,11,28).

In the absence of prospective randomized trials, there is still uncertainty as to the correct role of adjuvant therapy (4, 24). Radiotherapy could be considered for patients in whom surgical margins are not adequate or microscopically involved (2, 3). Chemotherapy has been disappointing in the treatment of these lesions (3, 4) and hormone manipulations currently have no place in clinical practice (4, 26). Pollard *et al.* describe their experience with breast sarcomas, reporting high rates of local recurrence after WLE and simple mastectomy (67% and 54%, respectively) (4).

Little is known about the prognosis of MFH of the breast, because in most studies only a short follow-up period is reported (1, 2, 23). The percentages of survival reported in the literature range from 40 to 60% after 2 years, and from 20 to 35% after 5 years (1).

In conclusion, evaluation of our cases, as well as those reported previously, leads us to assert that MFH of the breast is a rare entity, nevertheless posing remarkable concerns about the correct therapeutic approach.

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