Virchows Arch (2003) 443:222–224
DOI 10.1007/s00428-003-0853-8

LETTER TO THE EDITOR

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Breast sarcoma showing myofibroblastic differentiation

Received: 12 March 2002 / Accepted: 21 April 2003 / Published online: 3 July 2003

Sir,
Myofibroblasts were originally described as a part of granulation tissue and healing wounds 30 years ago and were extensively studied in the past 20 years. However, the precise definition of myofibroblast as a distinctive cell type is still controversial as well as the concept of myofibroblast being neoplastic. Irrespective of that, it cannot be denied that tumors composed mainly of myofibroblasts do exist. Most of them are benign, i.e., myofibroblastomas [2, 4, 9], some with borderline biological course, i.e., inflammatory myofibroblastic tumor [1], and, rarely, they pursue a malignant biological behavior [2]. Among them, a distinctive form of low-grade myofibroblastic sarcoma was recognized [5, 7, 8], while high-grade lesions have not yet been well characterized. Here, we present the case of unusual high-grade breast sarcoma, which is showing myofibroblastic differentiation.

A 51-year-old woman presented with left-side breast enlargement of 3-months duration and hemorrhagic mammillar discharge. The ultrasound examination revealed a huge tumor replacing almost the entire breast tissue. During the surgery, an intraoperative biopsy was performed, showing malignant spindle-cell tumor. The patient underwent radical mastectomy, followed by chemo- and radiotherapy. Two years after the diagnosis she is still alive.

Macroscopically, the tumor tissue was grayish-white in color, mainly soft and gelatinous, with large foci of hemorrhage and necrosis. It was partially well demarcated from the surrounding breast tissue, but extended through and penetrated overlying skin (Fig. 1A), and measured 22×20×15 cm. On histological examination, the tumor was composed of spindle-shaped cells with poorly defined, pale cytoplasms and fusiform nuclei with small, inconspicuous nucleoli (Fig. 1B). Nuclei were mainly tapering and wavy; some became plumper, but with only mild nuclear atypia. The tumor showed various growth patterns; in most parts cells were arranged in a fascicular pattern (Fig. 1D) and set in a faintly fibrillar, partly mucoid stroma. In those parts, a striking nuclear palisading was the dominant feature (Fig. 1C). Somewhere, a storiform (Fig. 1E) or herringbone pattern (Fig. 1F) was seen. Cellularity varied from high to low in those parts where the stroma became more collagenized and hyalinized. Mitotic activity ranged from 8 to 35 per 10 HPF. Immunostaining showed strong and diffuse vimentin and α-smooth muscle actin (SMA) positivity (Fig. 1G), while stains for pan-cytokeratin, S-100 protein, CD34, desmin and h-caldesmon (Fig. 1H) were all negative. Axillary lymph nodes were negative for metastases.

Among various growth patterns, the most prominent was the fascicular pattern with marked nuclear palisading. This feature made the possibility of spindle cell sarcomatoid carcinoma—which, regarding the site of origin, would be the most likely diagnosis—much less probable. Indeed, tumor cells were negative for pan-cytokeratin, while positive for vimentin, and the surrounding breast tissue showed neither the signs of in situ or invasive carcinoma, nor the signs of epithelial proliferation. Among the malignant tumors described to contain nuclear palisading we considered MPNST, leiomyosarcoma, sinovial sarcoma and dermatofibrosarcoma protuberans. The results of immunostaining, i.e., strong and consistent positivity for SMA and negativity for all the other markers, narrowed our differential diagnosis to sarcomas with myoid differentiation. We included the h-caldesmon and desmin into the immunostaining panel and found tumor cells completely negative. H-caldesmon is a protein combined with actin and tropomyosin that regulates cellular contraction. It is a specific marker of both smooth-muscle cells and its neoplasms, while myofibroblasts and tumors with myofibroblastic differentiation are negative for this protein [10]. Thus, it can facilitate the differential diagnosis between leiomyosarcomas and other tumors with smooth-muscle cell-like differentiation,

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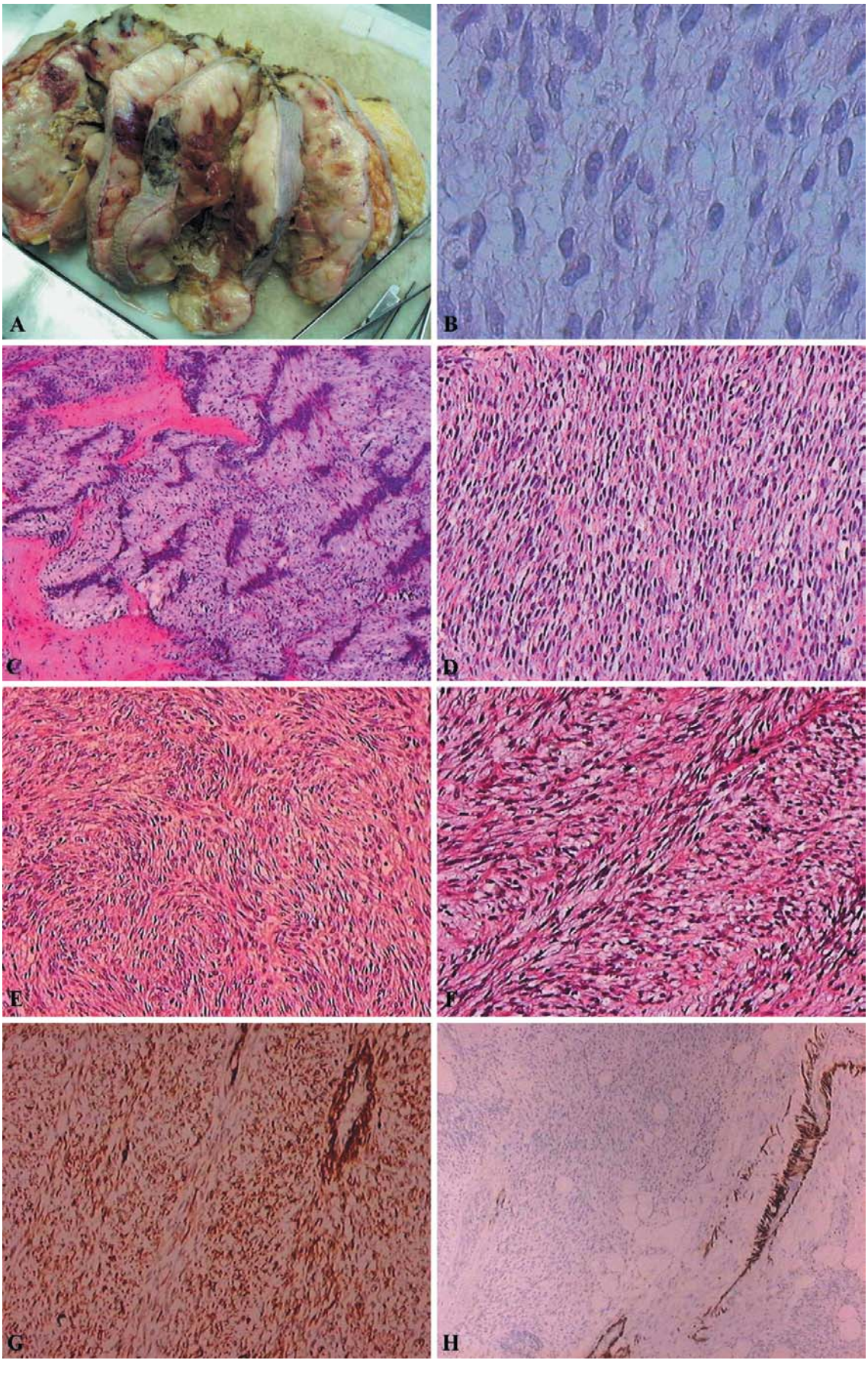
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Fig. 1A–H The gross and histological features of breast sarcoma. **A** Tumor tissue is grayish-white with large foci of hemorrhage and necrosis. Cytological features in breast sarcoma: nuclei are tapering and wavy or vesicular with small nucleoli (**B**, ×400), and showing marked nuclear palisading (**C**, ×40). Growth patterns in breast sarcoma are either fascicular (**D**, ×100), storiform (**E**, ×100) or herring bone (**F**, ×100). The immunophenotype of breast sarcoma: tumor cells are strongly positive for SMA (**G**, ×100), while negative for h-caldesmon (**H**, ×100)

including myofibroblastic tumors. In some parts, mainly those with storiform architecture, the tumor closely resembled malignant fibrous histiocytoma (MFH). It is well known that myofibroblastic differentiation can be found in MFH. Montgomery et al. found the ultrastructural evidence of myofibroblastic differentiation in 29% of MFH [6]. Some of them expressed myoid markers on immunohistochemistry, but this expression was always focal, as well as in tumors without myofibroblastic ultrastructural morphology. The tumors they examined all had pleomorphic morphology, without recognizable myofibroblastic features. Our case demonstrated recognizable myofibroblastic morphology throughout the whole tumor, regardless of architectural pattern, as defined in low-grade myofibrosarcomas [8]. The tumor cells were not focal, but strongly and diffusely positive for SMA, while negative for caldesmon. If we consider these features as a signs of myofibroblastic differentiation, the diagnosis of high-grade myofibrosarcoma would be the most appropriate.

Although myofibrosarcoma has not yet been defined as a separate entity, a category of low-grade malignant myofibroblastic tumors were recently recognized and described in the article of Mentzel et al. [5]. The authors suggest the designation of this lesions as low-grade myofibroblastic sarcomas. Montgomery et al. also reported the series of soft-tissue sarcomas composed predominantly of myofibroblasts, which were of low- or intermediate-grade malignancy. The selection of their cases was based on recognizable and consistent morphology and was confirmed by immunohistochemical expression of myoid antigens, and, in some of the cases, with electron microscopy [7]. Our case demonstrates all these morphological and phenotypical features, except high-grade morphology expressed by high proliferative activity and broad areas of hemorrhage and necrosis.

The aim of this letter was to describe a type of breast sarcoma that needs further studies with a large number of cases to be better understood.

Acknowledgements We thank Professor Christofer D.M. Fletcher for his contribution in establishing the diagnosis.

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