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Case study

Myositis ossificans mimicking metaplastic breast cancer on core needle biopsy☆

Klaus Jürgen Schmitz MD[a,*], Matthias Losch MD[b], Abbas Agaimy MD[c]

[a]*Institut of Pathology Recklinghausen, Mühlenstrasse 31, 45659, Recklinghausen, Germany*
[b]*Department of Senology, Prosper Hospital Recklinghausen, Mühlenstrasse 27, 45659, Recklinghausen, Germany*
[c]*Institute of Pathology Recklinghausen, University Hospital, Friedrich-Alexander University Erlangen-Nürnberg, 91054 Erlangen, Germany*

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Summary Myositis ossificans (MO) is an uncommon myofibroblastic proliferation that may closely mimic sarcoma. A 33-year old woman presented with a 2-cm breast mass. A core needle biopsy showed highly cellular spindle cell proliferations with atypia and high proliferation activity. Focal areas of immature osteoid-like matrix were seen. After immunohistochemical analysis, a diagnosis of metaplastic breast cancer was made. Because of the proximity of the tumor to the rib, resection of the tumor including partial resection of the rib was carried out. Complete examination of the excised lesion allowed the correct diagnosis of MO. Only the resection specimens contained a predominance of mature organoid bone tissue admixed with variably cellular myofibroblastic proliferations with the typical zonal pattern, characteristic of MO. The diagnosis of MO was not possible on the initially performed core needle biopsy because biopsy material reflected only the central proliferative portion of the lesion showing increased pleomorphism and early osteoid formation. This case highlights the pitfall related to this unusual presentation of a benign lesion and points to the necessity to include MO in the differential diagnosis of triple-negative metaplastic breast cancer.

1. Introduction

Myositis ossificans (MO) is an uncommon benign tumor-like myofibroblastic proliferation which characteristically presents as a rapidly growing mass within skeletal muscle [1]. Histologically, MO displays a cellular fibromyxoid myofibroblastic proliferation arranged into loose but occasionally highly cellular proliferation that generally recapitulates the appearance of nodular fasciitis. A variable component of bone tissue (the name-giving component) is invariably present and usually shows mature lamellar bone with characteristic zonal maturation. MO is most commonly observed as a solitary lesion in high-risk sites of injury in muscle tissue following trauma. It may also be observed in any types of soft tissue including subcutaneous fat, tendons, nerves, and fascia. It occurs in all ages and in different atypical locations such as hands, feet, and head and neck. Rare examples of MO may occur at such unexpected anatomic sites such as the breast, representing a diagnostic challenge and resulting into misdiagnoses with the risk of inappropriate treatment [2,3].

2. Case description

A 32-year-old woman complained of pain in the left breast. She has no history of trauma or previous surgery. Sonography revealed a hypodense nodule measuring 1.9 cm within the breast. Magnetic resonance imaging mammography showed

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* Corresponding author.
E-mail address: kjschmitz@pathologie-re.de (K. J. Schmitz).

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a tumor measuring 3.3 cm with wide contact to the rib. Imaging did not allow discrimination between tumorous infiltration of the chest wall and peritumoral reaction imitating rib infiltration. The tumor was not captured in the mammography because of its location near the chest wall. Calcification or bone formation was not visible in the mammography because the tumor was outside the mammography field. Bone scintigraphy depicted a nodular uptake of tracer near the fifth rib suggesting an increased uptake of the radiotracer due to increased osteoblastic activity, raising the possibility of rib infiltration. No evidence of tracer uptake in other locations was seen. Computed tomography (CT) confirmed the presence of a tumor in the left breast, measuring 2.7 cm with direct contact to the rib. Infiltration of the rib could not be ruled out. There were no evidence of multifocality and no suspicion of lymph node metastasis. Fig. 1 demonstrates the results of breast sonography, CT, MRT, and scintigraphy.

A core needle biopsy was performed, and histological examination based on hematoxylin and eosin (H&E)–stained sections demonstrated a tumor composed of spindle cells with nuclear atypia embedded in a cellular stroma (Fig. 2). The myofibroblastic-like spindle cells were arranged into a storiform and fascicular pattern and occasionally showed an epithelioid cell pattern. In addition, the stromal matrix demonstrated immature early stage osteocartilaginous matrix without mature cartilage or osseous tissue. Mitotic activity was increased with up to 2 mitoses per high-power field. The proliferation fraction as demonstrated by Ki67 was 40%. The tumor cells lacked any epithelial differentiation (negative for pancytokeratin, CK8-18, CK5/6, and high–molecular weight cytokeratins and negative immunoreaction for GATA-3, estrogen and progesterone receptor, HER-2, and p63). The tumor cells showed variable focal nuclear expression of β-catenin and prominent reactivity with SATB2.

Based on these results, the diagnosis of fibromatosis-like metaplastic breast carcinoma with focal osteoblastic differentiation was favored. As a differential diagnosis, a stromal overgrowth of a malignant phylloides tumor was discussed.

A breast-conserving surgery was performed together with resection of the neighboring rib due to the proximity of the tumor to the chest wall. Although the tumor was classified as "triple-negative," no neoadjuvant therapy was performed because metaplastic breast cancers tend to be less sensitive to neoadjuvant therapy regimens. In addition, the breast surgeon was concerned about further tumor growth under neoadjuvant therapy resulting in possible inoperability. Gross specimen showed an oval and rather sharply demarcated tumor with a gray and gritty cutting surface (Fig. 3). The tumor seems to be located within the fat tissue of the breast with contact to the dorsal fascia. The lesion compressed the neighboring muscle tissue. There was no infiltration of the ribs. Histologically, the complete surgical specimen allowed the identification of the typical zonal pattern of MO with a peripheral rim of mature bone formation (Fig. 4) and the central portion with a highly cellular fibroblastic spindle cell population. The bone showed the pathognomonic zonal maturation characteristic of MO.

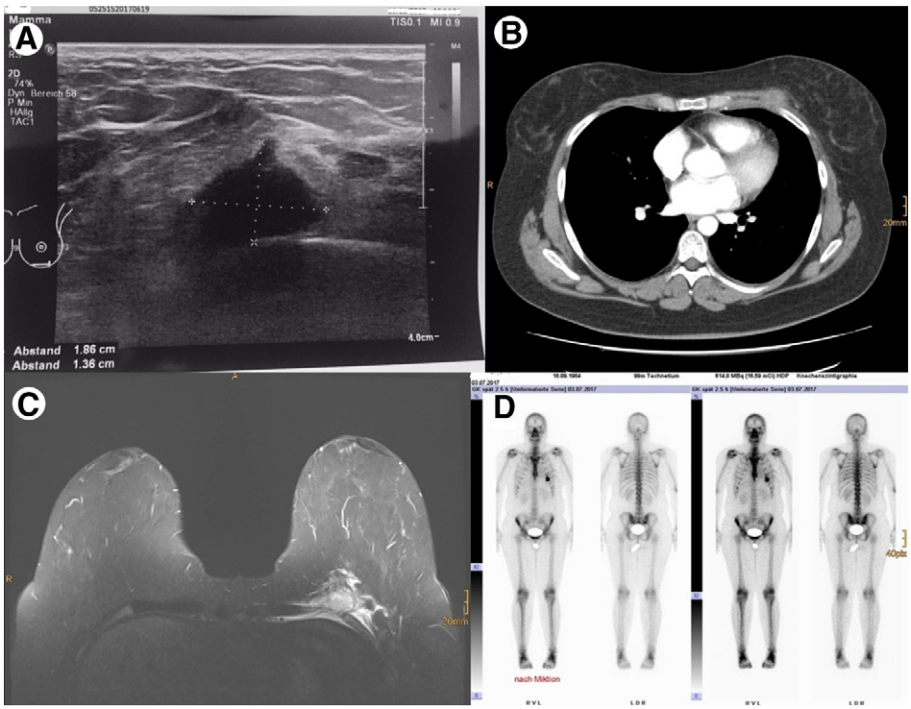

Fig. 1 A, sonography with breast mass. B, CT showing the mass close to the rib. C, MRT depicting the mass. D, bone scintigraphy with increased tracer uptake projected to the rib.

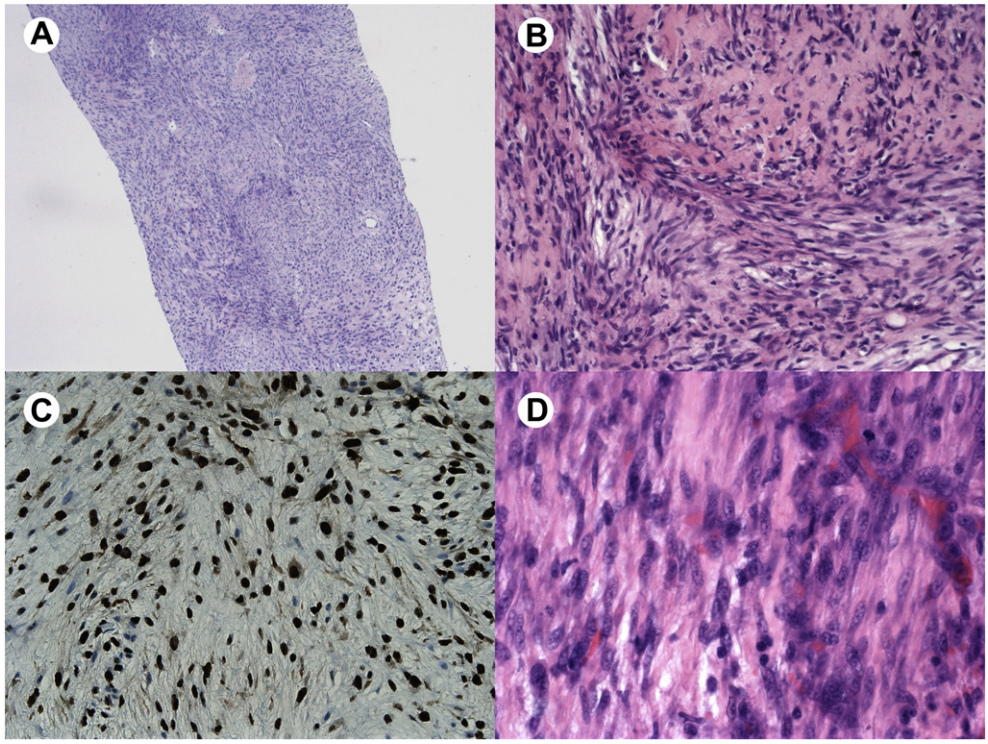

Fig. 2 A, Low magnification demonstrating a highly cellular spindle cell lesion (H&E, original magnification ×40). B, Spindle cell lesion with increased nuclear atypia and initial formation of osteoid (H&E, ×200). C, Ki-67 immunostaining with strongly increased tumor cell proliferation with a Ki-67 index up to 40% (×200). D, High magnification demonstrating the nuclear features of the spindle cells with hyperchromatic and pleomorphic tumor cells (H&E, ×400).

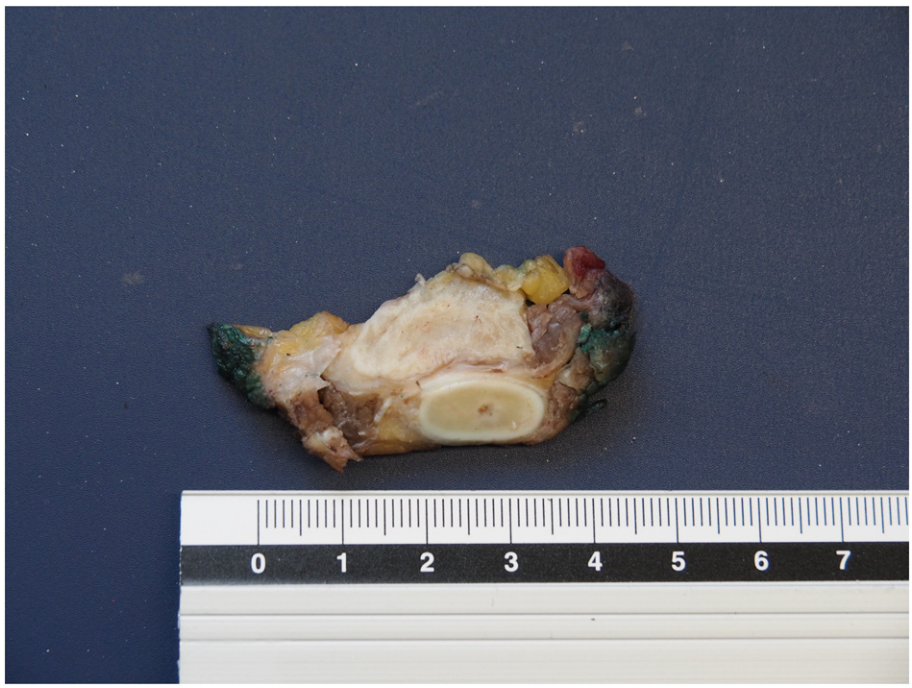

Fig. 3 Gross specimen with the sharply demarcated grayish tumor was located in the posterior portion of the breast near the rib, pushing muscle tissue aside.

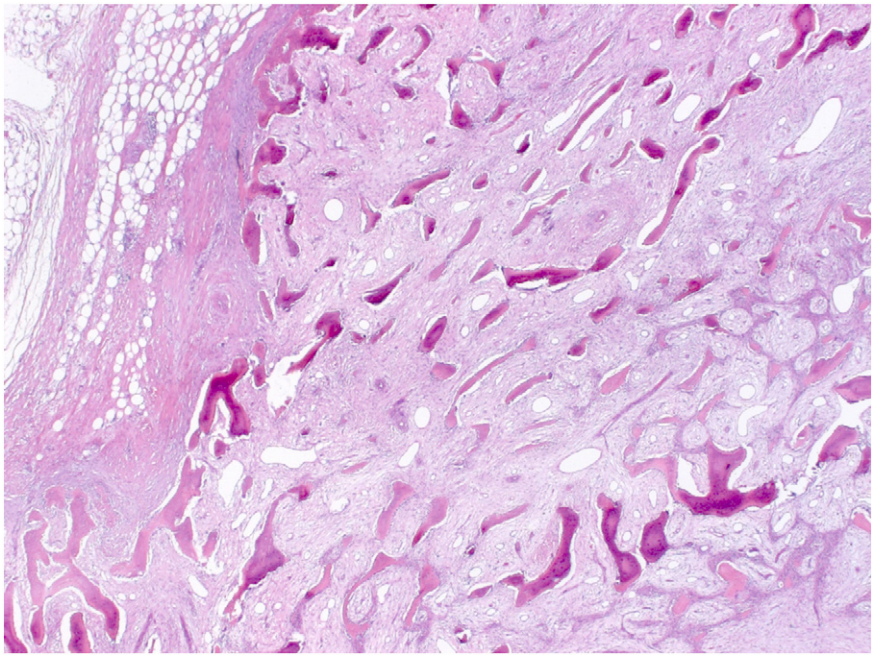

Fig. 4 Light microscopic view showing a peripheral rim of mature bone that was missing in the initial needle core biopsy (H&E, ×20).

The center of the lesion showed a highly cellular proliferation with spindle-shaped cells and formation of immature osteoid. The fibroblasts and myofibroblasts displayed a mild to moderate nuclear polymorphism. Immunohistochemical analysis was repeated, and there was no epithelial differentiation nor was there a phylloides component.

To further confirm the diagnosis of MO, fluorescent in situ hybridization (FISH) analysis for ubiquitin specific peptidase (*USP6*) gene rearrangement was performed with a commercially available break-apart probe (Zytovision, Bremerhaven, Germany) as reported previously [4]. FISH identified typically breaks in 48 of 50 analyzed spindle cells, confirming *USP6* translocation (Fig. 5).

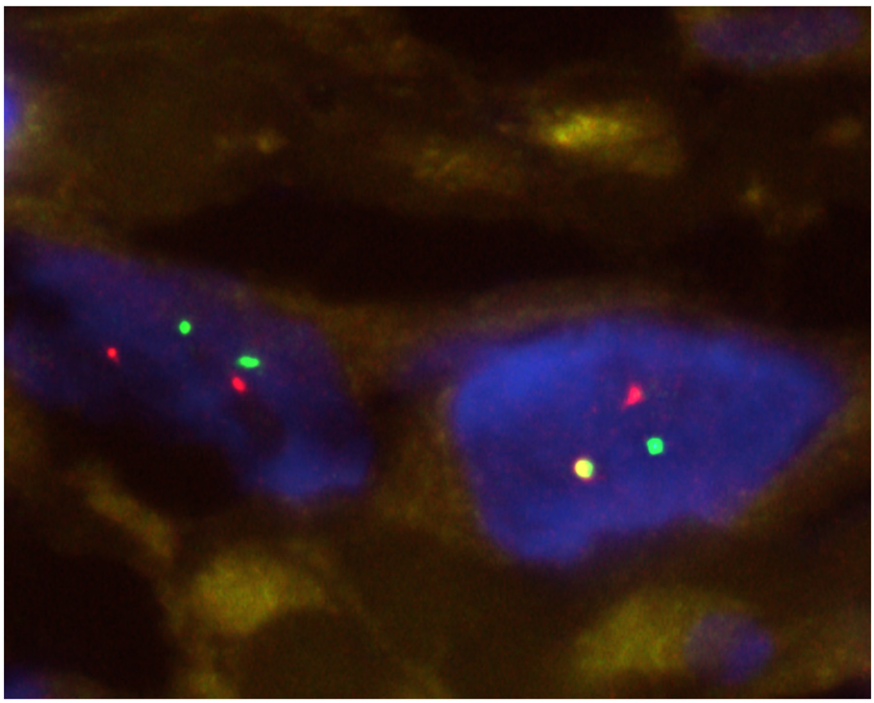

Fig. 5 FISH analysis using the *USP6* probe demonstrating 2 tumor interphase nuclei with 1 fused signal (orange) and 2 split-apart signals each indicating translocation.

3. Discussion

The present case illustrates a very unusual manifestation of nontraumatic MO of the breast. After extensive immunohistochemical workup, the benign lesion was misdiagnosed as triple-negative metaplastic breast cancer on core needle biopsy. Correct diagnosis of MO was only possible after pathological examination of the complete gross specimen. The initial core needle biopsy lacked the pathognomonic features of zonal maturation and was composed exclusively of the immature tumor component harboring early osteoid. Only the gross macroscopic and microscopic evaluation of the whole resection specimen allowed identification of the typical bone formation in the periphery of the tumor, thus facilitating the diagnosis of MO.

Besides the histopathological pitfall presented in this case, the clinical presentation of the tumor was also suggestive of malignancy. The patient reported no history of trauma. CT and MRT suggested possible infiltration of the rib. In addition, the intratumoral peripheral accentuated ossification was not depicted on mammography, and last but not least, the increased radiotracer uptake pictured in the bone scintigraphy was suspicious of bone infiltration.

The present tumor was located near the rib in the posterior portion of the breast. Detailed macroscopic examination rules out an origin in the muscle tissue. The nodule was well demarcated and extended into adjacent fascial tissue. Thus, fasciitis ossificans might be considered as a differential diagnosis. Fasciitis ossificans is thought to be a bone-forming subtype of nodular fasciitis first described in 1969 [4] and histologically looks quite similar to MO; however, fasciitis ossificans usually lacks the typical zonal pattern of osteoid in the middle zone and mature bone in the periphery [5]. Therefore, the present case is best diagnosed as an MO and not as fasciitis ossificans.

The tumor presented in this study was investigated for *USP6* translocation by FISH. The *USP6* gene, also known as *TRE17,* encodes the enzyme ubiquitin carboxyl-terminal hydrolase 6. The translocation results in the fusion of the promoter region of *MYH9* located on 22q 12.3 to the entire coding sequence of *USP6*, with the result of upregulation of *USP6* expression. The analysis of *USP6* gene arrangement is helpful in the differential diagnosis of spindle cell lesions and especially helps to differentiate nodular fasciitis from its malignant mimickers such as low- and high-grade sarcomas in small biopsies. We recently analyzed a wide panel of cases with nodular fasciitis and morphologically related myofibroblastic proliferations with emphasis on frequency of *USP6* gene rearrangements [6]. FISH analysis revealed *USP6* translocation in 74.4% (32/43) of nodular fasciitis. None of the reparative/reactive myofibroblastic lesions revealed *USP6* translocation (0/15).

MO is a benign and often self-limiting lesion that was recently shown to exhibit *USP6* rearrangement suggesting close relationship to nodular fasciitis [7]. In the present case, we were able to confirm *USP6* rearrangement verifying the relationship of MO with nodular fasciitis and aneurysmal bone cyst. In a recent study on 11 cases, Bekers et al [7] demonstrated a *USP6* rearrangement in 8 of 9 cases. Before that study, only 2 cases of MO with *USP6* rearrangement have been published. *USP6* rearrangement may be useful as a diagnostic tool to identify MO/nodular fasciitis in diagnostic challenging cases like the one presented in this report.

We initially performed β-catenin immunochemistry to discriminate the tumor from fibromatosis, metaplastic breast cancer, and malignant phylloides tumor, which are known to express β-catenin [8]. Rather surprisingly, the present case exhibited a focal nuclear β-catenin staining. A recent study demonstrated that *USP6* fusion may activate the Wnt signaling pathway; thus, it is not surprising to observe focal nuclear catenin expression in *USP6*-rearranged MO [9]. However, the relevance and the frequency of this finding in MO remain unknown and need to be addressed in future studies.

4. Conclusion

Correct preoperative diagnosis of MO is problematic on histological ground alone, and careful correlation with imaging findings is mandatory. A well-oriented biopsy would facilitate diagnosis or at least would suggest MO as a possibility when the characteristic zonal maturation is seen on the biopsy. However, as in the current case, it may happen incidentally that the core biopsy contains only the highly active proliferating cellular area of the tumor with variable degree of atypia and high proliferation index. This would then be complicated by the presence of early stage (immature looking) osteoid which, based on the site of origin, would suggest a diagnosis of extraskeletal osteosarcoma (in soft tissue sites) or metaplastic sarcomatoid carcinoma (such as in the breast as in the current case).

Contributions

K. J. S. and A. A. established the diagnosis. K. J. S. wrote the manuscript. A. A. performed additional immunohistochemical analysis and *USP6* rearrangement analysis and has made substantial contribution to conception and design of the manuscript. M. L. provided clinical data and has given final approval of the version to be published.

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