Proliferative Myositis of the Breast in a Patient with Contralateral Phyllodes Tumor: A Unique Pseudomalignant Lesion

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AIM: We report a case of proliferative myositis (PM) of the breast, which is the second reported in the English literature.
CASE PRESENTATION: A 49-year-old woman underwent surgery due to a fibroadenoma in the right and phyllodes tumor in the left breast. One month after these surgeries, a right breast mass rapidly grew at the surgical site, and biopsy did not provide a diagnosis. The lesion's rapid growth and high cellularity led to a suspicion of malignancy, and the mass was surgically removed. The immunohistochemical markers used were estrogen receptor (ER), S100, smooth muscle actin (SMA), desmin, pan-cytokeratin, Myoblast Determination Protein 1 (MyoD1), myogenin, caldesmon, calretinin, CD34, Anaplastic Lymphoma Kinase (ALK), P53, P63, and Ki67. A low Ki67 index and mitosis, lack of staining with rhabdomyosarcoma markers, and a typical checkerboard pattern ruled out malignancy. The diagnosis was PM.
CONCLUSIONS: This case emphasizes the importance of recognizing pseudomalignant breast masses to avoid catastrophic overtreatment.

Keywords: proliferative myositis; phyllodes tumor; breast; pseudomalignant lesion

Introduction

Proliferative myositis (PM) and proliferative fasciitis (PF), composed of fibroblasts and ganglion-like giant cells, are lesions with the same pathological features, differing in anatomical origin [1]. Due to robust growth and cellularity, they can be misdiagnosed as malignant, causing detrimental overtreatment. Hence, better recognition of such cases is crucial. PM/PF can originate from the pectoral muscles and the fascia surrounding the breast; one case of breast PF was reported in the literature [2]. This study reports PM in the breast, which developed shortly after the excision of a fibroadenoma in the ipsilateral breast and a breast phyllodes tumor (BPT) in the contralateral breast.

Case Report

This study complies with the Declaration of Helsinki ethical rules and ICMJE Recommendations for scholarly work in medical journals. The patient signed an informed consent form, ethical approval for the study was waived by the local ethics committee (Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul) as the study included only retrospective data analysis. A 49-year-old woman underwent surgery for a fibroadenoma in the right and BPT in the left breast. One month after these operations, a right breast lesion rapidly grew in the surgical site and biopsy could not provide a diagnosis. Laboratory tests excluded an infection. The new lesion was analyzed using markers for estrogen receptor (ER), S100 protein, smooth muscle actin (SMA), desmin, pan-cytokeratin, Myoblast Determination Protein 1 (MyoD1), myogenin, caldesmon, calretinin, CD34, Anaplastic Lymphoma Kinase (ALK), p53, p63 and Ki67.

Pathological reanalysis of the fibroadenoma and BPT confirmed the previous diagnoses. In the last lesion, spindle fibroblast-like and plump ganglion-like myofibroblastic cells invading the muscle fibers formed a checkerboard pattern (Fig. 1A). Mitosis was sparse and without atypia. Myofibroblastic spindle and inflammatory cells infiltrated the collagenous stroma and hyalinized matrix (Fig. 1B). A prominent myxomatous stroma was typical (Fig. 1C). Ganglion-like cells had large vesicular nuclei, eosinophilic macronucleoli and amphophilic cytoplasm (Fig. 1D). Ki67 indices were always below 10% including densely stained areas (Fig. 2A). CD34 stained microcapillaries but not neoplastic cells (Fig. 2B). p53 was focally present (Fig. 2C). Spindle and ganglion-like cells are strongly and weakly SMA-positive, respectively (Fig. 3A). Desmin stained the striated muscle fibers but not neoplastic cells (Fig. 3B). Only adipocytes were SMA-positive (Fig. 3C). Lastly, caldesmon only stained the vessel wall smooth muscles (Fig. 3D). Other immunohistochemical (IHC) markers were negative.

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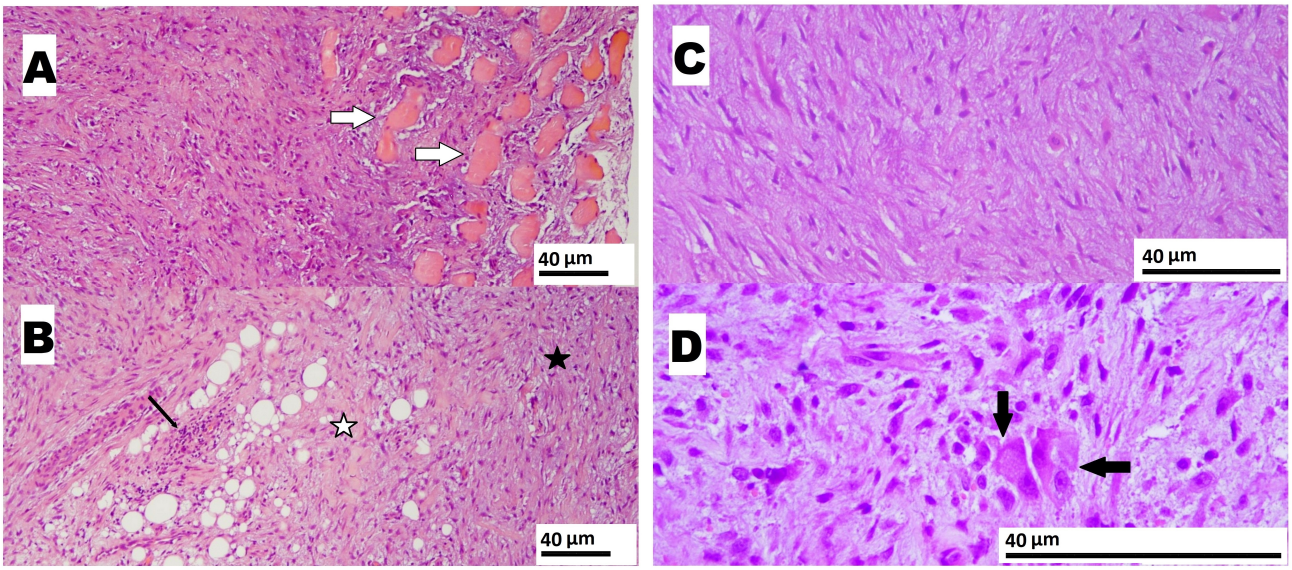

Fig. 1. Micromorphology of proliferative myositis in haemotoxylin-eosin staining. (A) Spindle fibroblastic and ganglion-like myofibroblastic cells between the striated muscle fibers (white arrows) formed the checkerboard pattern. (B) Fibroblastic/myofibroblastic spindle cells infiltrated the collagenous stroma (white star) and the hyalinized matrix (black star) besides focal inflammation (black arrow). (C) Prominent myxomatous stroma, typical for PM. (D) Ganglion-like cells with large vesicular nuclei, eosinophilic macronucleolus and amphophilic cytoplasm (black arrows). Magnifications: ×100 (A,B); ×200 (C); ×400 (D). PM, proliferative myositis.

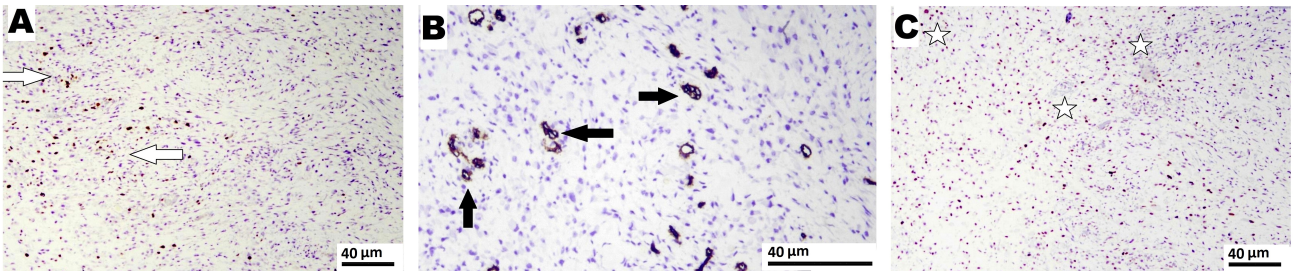

Fig. 2. Proliferation index (Ki67), microangiogenesis (CD34) and tumor suppressor P53 protein in proliferative myositis. (A) Ki67-stained areas (white arrows). (B) CD34-stained microcapillaries (black arrows), but no other cellular structures. (C) Focal p53 positivity (red-brown stained nuclei, white stars demonstrate densely-stained areas). Magnifications: ×100 (A); ×200 (B); ×100 (C).

Discussion

PM/PF lesions are extremely rare, yet distinguishing them from malignancies is crucial to prevent overtreatment. A six-year analysis of the pseudosarcomatous lesions in the Swedish Cancer Registry found only nine PM/PF cases [3]. PM/PF cases generally present with more severe pain and faster lesion growth than malignant or benign soft tissue tumors [4]. PM/PF may develop after trauma, however, they are not reactive but benign. Due to nuclear polymorphism, high cellularity, spindle cells, and infiltrative growth, they mimic malignancies [3]. Many mitotic cells may be present, yet never with atypia [4]. Some consider PF a variant of nodular fasciitis (NF)/nodular myositis (NM), but ganglion-like cells and diffuse muscle infiltration distinguish these lesions from NF/NM [5]. PM/PF may mimic many benign and malignant lesions, including fibromatosis, rhabdomyosarcoma, pleomorphic dermal sarcoma, myxoinflammatory fibroblastic sarcoma, epitheloid sarcoma or angiosarcoma, epitheloid hemangioendothelioma, histiocytoma, Spitz nevus, melanoma, ganglioneuroblastoma and squamous cell carcinoma [5, 6, 7].

In PM/PF, both fibroblast- and ganglion-like cells may express vimentin, actin and SMA [8]. There is only one previous report of a breast PF. The patient was a 62-year-old woman who noticed a palpable mass growing for five days [2]. Pathology revealed plump polygonal cells where myofibroblasts infiltrated fibro adipose tissue. The cells expressed vimentin but not S100, p63, and SOX10. Myofibroblasts expressed SMA and fibronectin but not desmin [2]. In the present case, the specimen had sparse mitotic figures and no atypia. The SMA expression pattern was consistent with previous reports describing PM/PF [2,8]. Yet, a broad antibody panel—the largest for PM/PF lesions reported up to date—was used to ensure a lack of malignancy. Ki67 and p53 antibodies were employed to assess proliferation and biological aggressiveness as many malignancies

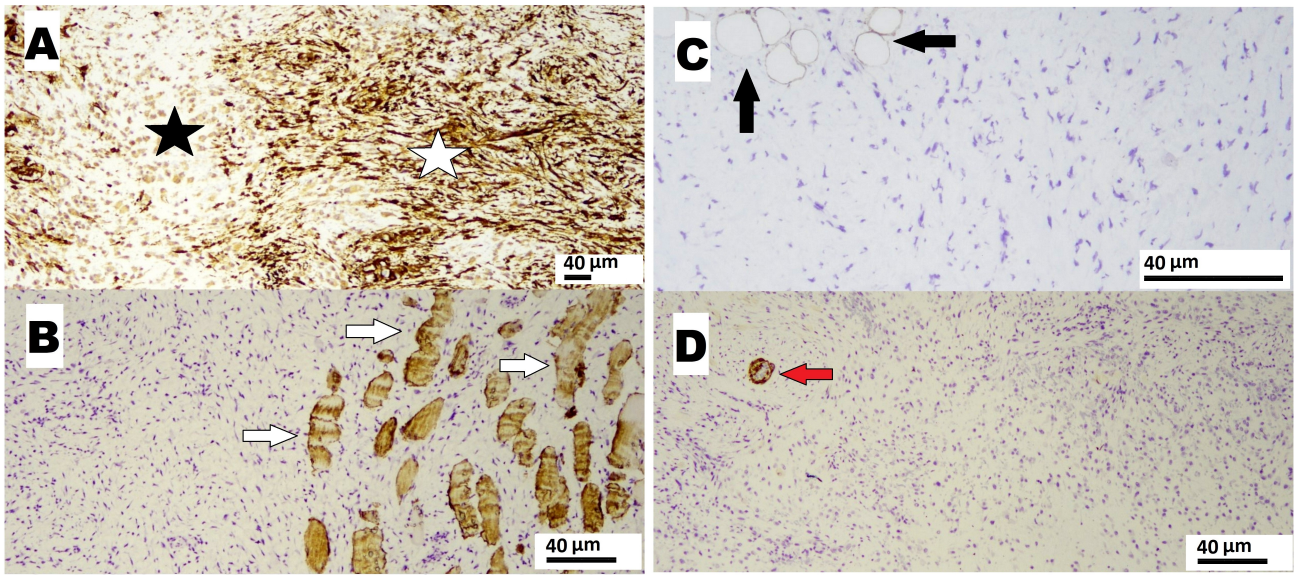

Fig. 3. Immunostaining features of proliferative myositis differentiating from malignant lesions. (A) Strong SMA expression within spindle cell (white star) and weak staining within ganglion-like cells (black star). (B) Desmin stained the muscle fibers (white arrows) but not the neoplastic infiltration. (C) S100 stained only the adipocytes (black arrows). (D) Caldesmon only stained the vessel walls (red arrow). Magnifications: ×40 (A); ×100 (B); ×200 (C); ×100 (D). SMA, smooth muscle actin.

are p53-positive. However, up to 48% of benign soft tissue lesions overexpress p53 at certain levels, causing protein accumulation and positive staining [9]. In this case, p53 was focal, and Ki67 was low. The cells in the tumor specimen did not have an aggressive morphology reminiscent of triple-negative breast cancer, so IHC staining for SOX10 was not necessary. Yet, IHC staining for ER was used to rule out a hormone receptor-expressing breast adenocarcinoma and came out negative.

Besides desmin, myogenin and MyoD1 antibodies were applied, regarded as more sensitive striated muscle markers [10]. Desmin only stained interspersed striated muscle layers, and myogenin and MyoD1 were negative, ruling out a rhabdomyosarcoma. Caldesmon was negative except for the vessel walls, excluding benign or malignant smooth muscle lesions. As mentioned earlier, epitheloid angiosarcomas and hemangioendotheliomas are PM/PF differential diagnoses [6]. Lack of CD34 expression except in the microvessels and central necrosis eliminated these. Calretinin stains desmoid fibromatosis at most, followed in decreasing order by PM/PF, fibrous histiocytoma, NF, and solitary fibrous tumors [11]. It was negative in this case. Anaplastic lymphoma kinase (ALK) stains several neoplasms relevant to the differential diagnosis of PM/PF, including inflammatory myofibroblastic tumor, ganglioneuroblastoma, and Spitz tumor (mainly the amelanotic type), and is in the antibody panel list of the WHO 2018 Classification of Cutaneous Melanocytic Neoplasms [12, 13, 14, 15]. The current case was negative for ALK. Melanocytic tumors, including amelanotic forms, neural crest tumors with a Schwann cell component, and almost all benign peripheral nerve sheath tumors (PNSTs) stain positively with S100, while malignant PNSTs express less or no amounts [16, 17, 18]. Yet, some mesenchymal lesions and myoepithelial cells within certain breast tumors may also express this protein [16, 17]. In this case, S100 only stained adipocytes, and bearing the lack of ALK positivity in mind, ganglioneuroblastoma, melanocytic, or myoepithelial breast lesions were excluded. p63 and PanCK stainings help distinguish PM/PF from metaplastic carcinoma with mesenchymal differentiation (MCMD) and squamous cell carcinoma, as most squamous and basal cell carcinomas express p63 [19]. The lesion's rapid growth and p63 and PanCK negativity confirmed a lack of MCMD and squamous cell carcinoma. Lastly, the absence of a zonal pattern excluded ischemic fasciitis and myositis ossificans, contemplated due to surgical history.

PM/PF and BPTs may have shared pathogenetic features. BPTs are fibroepithelial neoplasia with a morphopathological continuum from benign to malignant. BPTs have mesenchymal components and may mimick sarcoma as the PM/PF do [20]. A PM case exerted a reciprocal 6q23:14q32 translocation, as previously seen in a BPT [21]. The FosB protein is involved in many malignancies, including breast cancer; 10% of PM specimens diffusely express FosB in cell nuclei [22]. PM/PF may also strongly express c-fos with accompanying gene rearrangements [23]. Notably, c-fos expression is present in 53% of BPTs versus 23% of breast fibroadenomas [24]. Hence, fos oncogene may be involved in both BPT and PM in the present case. Lastly, p53 protein immunoexpression is almost absent in breast fibroadenomas but it is expressed in 75% of BPTs [24]. The

lesion was stained focally with p53 protein in this case, yet it is still interesting due to findings in BPTs.

This case study does not present genetic tests. However, this is not a limitation since such tests are not yet available due to the rarity of PM/PF. The study showing c-fos gene rearrangements in PM/PF included only six patients, which cannot be used as a touchstone to compare with the results of a single case [23]. *MYH9* or *USP9* gene arrangements (commonly connected in translocations) occur in NF but not in PF, which may help discern these pathologies [5, 25]. However, analyzing these genes was not deemed necessary as the pathology in the present case was discordant with NF, and 10% of NFs do not harbor *MYH9* rearrangements [5]. The above data is not a sure proof of PM/PF and BPT co-pathogenesis, yet analyzing future cases with the same disease concurrence would pave the way for discoveries.

Conclusions

This unique case emphasizes the importance of recognizing pseudo malignant lesions in the breast to prevent misdiagnoses and catastrophic consequences. Employing a broad antibody panel to facilitate a definitive diagnosis will avoid false pathological decisions for similar lesions.

Availability of Data and Materials

Data can be obtained from the author upon reasonable request. Sending pathological specimens is not possible due to the general policies of Turkish Ministry of Health unless a consulting is required for pathologies without definitive diagnosis.

Author Contributions

ZKS performed all the histochemical and immunohistochemical stainings of the case specimens, reanalyzed previous benign tumors to confirm the pathological diagnosis, searched the relevant literature and interpreted the findings, wrote the manuscript and revised the manuscript critically for important intellectual content. The author read and approved the final manuscript. The author has participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The patient signed an informed consent form. The ethical approval for the study was waived by the local ethics committee (Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul) as the study included only retrospective data analysis. The study adheres to the Declaration of Helsinki.

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Conflict of Interest

The author declares no conflict of interest.

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