



Inflammatory Myofibroblastic Tumor of the Breast Coexisting with Pseudoangiomatous Stromal Hyperplasia

Canan Kelten Talu¹, Yasemin Çakır¹, Ezgi Hacıhasanoğlu¹, Cem Leblebici¹, Şefika Aksoy², Mehmet Ali Nazlı³

¹Clinic of Pathology, İstanbul Training and Research Hospital, İstanbul, Turkey

²Clinic of General Surgery, İstanbul Training and Research Hospital, İstanbul, Turkey

³Clinic of Radiology, İstanbul Training and Research Hospital, İstanbul, Turkey

ABSTRACT

Inflammatory myofibroblastic tumors (IMTs) are uncommon breast lesions that consist of spindle cells accompanied by plasma cell-rich inflammatory infiltration, which may mimic breast cancer clinico-radiologically. A woman aged 38 years with a breast mass was referred to our general surgery clinic. The physical examination revealed a mass with irregular borders in the upper outer quadrant of the left breast. In mammography, the lesion was 15 mm in diameter with a spheric form and high density. Ultrasonographically, the mass was solid, heterogeneous, and hypoechoic with posterior enhancement. Histopathologic examination of a core needle biopsy revealed a proliferation of spindle cells with eosinophilic cytoplasm and mild nuclear atypia, which showed negative immunostaining for pancytokeratin, HMWCK, CAM5.2, p63, CD34, β -catenin, and ALK but diffuse positivity for smooth muscle alpha (SMA). The lesion was reported as a "spindle cell lesion" and excision with clear margins was recommended. In the lumpectomy specimen, the lesion consisted of spindle cells that formed fascicles and infiltrated the surrounding breast parenchyma. Lymphocytes and plasmocytes scattered among spindle cells were noted. Necrosis, increased mitotic activity, nuclear pleomorphism and hyperchromasia were not detected. Immunohistochemical findings were the same in the core needle biopsy. The Ki-67 proliferation index was below 5%. With these findings, differential diagnoses were ruled out and the tumor was reported as IMT. In close proximity to this lesion, areas of columnar cell lesion with atypia and surrounding pseudoangiomatous stromal hyperplasia were seen. Patient has a follow-up of 16 months without recurrence.

Keywords: Inflammatory myofibroblastic tumor, PASH, spindle cell, breast

Introduction

Inflammatory myofibroblastic tumors (IMTs) are commonly seen in the lungs, respiratory tract, gastrointestinal system, urinary system, and deep soft tissues in children and young adults. Local recurrence is not uncommon (1). Histopathologically, the lesions consist of bundles formed by benign-looking spindle cells, accompanied by plasma cell-rich inflammatory infiltration. Depending on the density of the components forming the lesion, variants such as fasciitis-like, compact-spindle cell, and hypocellular-fibrous IMT have been described (2). IMTs were formerly thought to be reactive lesions; however, currently there is a tendency to accept them as borderline neoplasia, owing to the detection of repetitive anaplastic lymphoma kinase (ALK) gene rearrangements (1). IMT of the breast is very rare in the literature. To date, 27 cases have been reported in the literature. This lesion is especially important for ruling out differential diagnoses in breast (1, 3). Pseudoangiomatous stromal hyperplasia (PASH) is usually an incidental microscopic lesion characterized by anastomosing slit-like, non-endothelialized spaces in breast stroma (4). The common feature of IMT and PASH is that they both comprise myofibroblastic cells.

Case Presentation

A woman aged 38 years with a mass in her left breast was referred to our general surgery clinic. No features were determined either in her past medical history or family history. A physical examination revealed a 15-mm spherical mass with indistinct borders and high density. Ultrasonographically, the mass was solid, heterogeneous, hypoechoic, peripherally vasculated, and showed posterior enhancement (Figure 1).

The core needle biopsy specimen demonstrated spindle cell proliferation with bundle formation, in which cells showing eosinophilic cytoplasm with mild nuclear atypia were seen (Figure 2a). Immunohistochemically, spindle cells were positive for SMA, negative for pancyto-

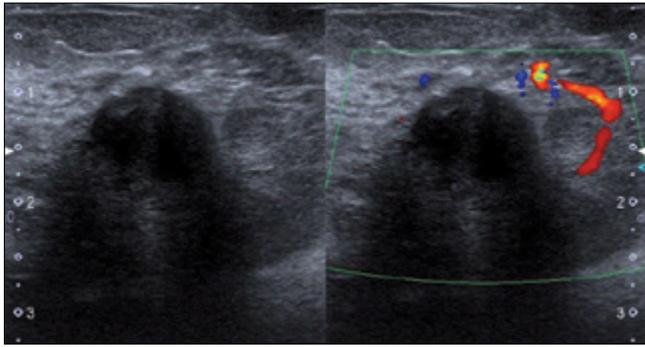


Figure 1. Ultrasonographically-solid, heterogeneous, hypoechoic, peripherally-vascularized mass with posterior enhancement

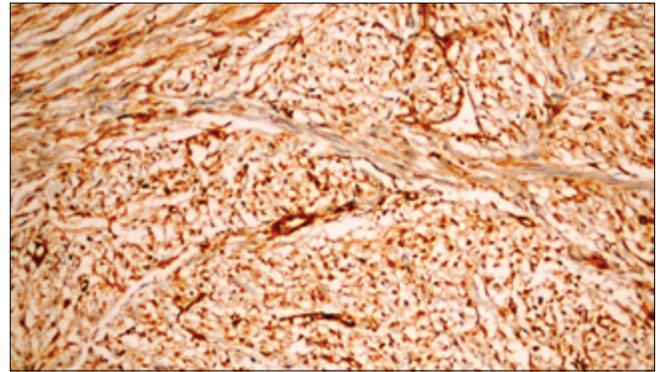


Figure 3. Smooth muscle alpha positivity in tumor cells

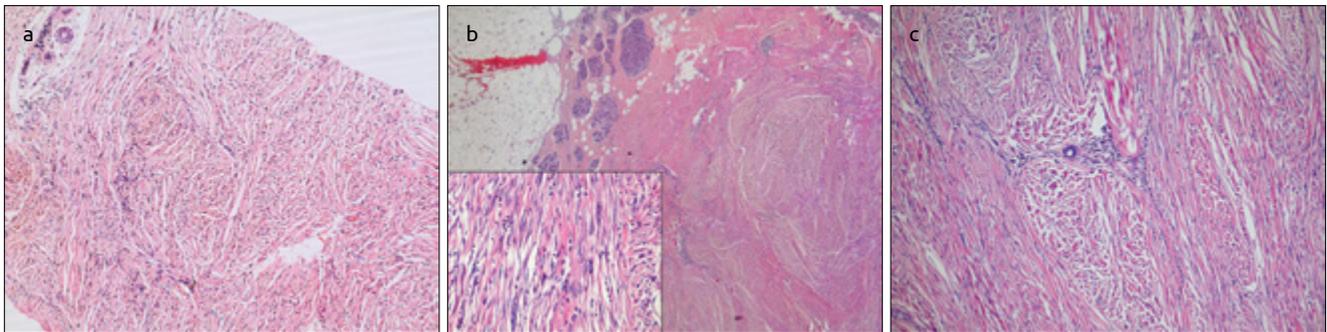


Figure 2. a-c. Core needle biopsy specimen showing spindle cell proliferation with eosinophilic cytoplasm and mild nuclear atypia (a) Spindle cell proliferation with eosinophilic cytoplasm and low-grade nuclear features in the lumpectomy specimen (b) Inflammatory infiltration scattered among the spindle cells, primarily composed of lymphocytes and plasmacytes (c)

keratin, CK5/6, CK14, CAM5.2, p63, CD34, desmin, and β -catenin. The tumor was reported as ‘spindle cell lesion’ and excision with clear margins was recommended for a definitive diagnosis.

In the macroscopic examination of the lumpectomy specimen, the lesion was solid and white-tan colored with irregular borders (1.3 x 1.3 x 1 cm). Microscopically, the lesion comprised spindle cells that formed fascicles and infiltrated the surrounding breast parenchyma. The spindle cells had eosinophilic cytoplasm with low-grade nuclear features (Figure 2b). There was also inflammatory infiltration scattered among spindle cells, primarily composed of lymphocytes and plasmacytes (Figure 2c). Necrosis, increased mitotic activity (0/10 HPF), nuclear pleomorphism and hyperchromasia were not detected. Immunohistochemically, tumor cells stained positive for vimentin and smooth muscle alpha (SMA) (Figure 3), and negative for pancytokeratin, HMWCK, CAM5.2, p63, CD34, β -catenin, ALK, and estrogen (ER) and progesterone receptors (PR). The Ki-67 proliferation index was found below 5%. With these histopathologic and immunohistochemical findings, lesions in the differential diagnosis were ruled out and the tumor was reported as IMT. In close proximity to the lesion, areas of columnar cell change (CCC) with atypia (flat epithelial atypia) and surrounding PASH were seen. The patient has a follow-up of 16 months without recurrence. Written consent was taken from the patient for this case report.

Discussion and Conclusion

It is important to recognize low-grade spindle cell lesions of the breast and distinguish one from another, because of the differences in treatment. Definitive diagnosis requires histopathologic examination, and the differential diagnosis consists of a spectrum of lesions, including reactive lesions as well as benign and malignant neoplasms.

The differential diagnosis includes: fibromatosis, nodular fasciitis, reactive spindle cell nodule, leiomyoma/leiomyosarcoma, myofibroblastoma, dermatofibrosarcoma protuberans (DFSP), phylloides tumor, low-grade fibromatosis-like metaplastic carcinoma (LGFLMC), low-grade myofibroblastic sarcoma (LGMFS), and spindle cell sarcoma (primary or metastatic) (1, 2, 5-9). In our case, the excision specimen demonstrated spindle cell proliferation with mild nuclear atypia, bundle formation, and irregular-infiltrative borders; therefore, fibromatosis, LGFLMC, and LGMFS primarily considered in the differential diagnosis.

Fibromatosis (desmoid-type) usually arises from the pectoral fascia and extends into the breast. Most cases (80%) show nuclear β -catenin expression and lymphocytes, if there are any, at the periphery of the lesion (5). In this case, the lesion was localized in breast parenchyma, distant from the pectoral fascia. Additionally, the presence of lymphoplasmocytic infiltration scattered among spindle cells and β -catenin negativity helped to eliminate fibromatosis. The lesion consisted of monotonous-spindle cells with low-grade nuclear features, had no epitheloid areas dispersed among spindle cells, and did not show positive staining with any of the high- and low-molecular-weight cytokeratins. LGFLMC was excluded owing to these features (6). LGMFS is a cellular malignant neoplasia that consists of myofibroblasts. It has rarely been reported in breast. The gold standard in the diagnosis of LGMFS is to show fibronexus junctions and fibronectin fibrils that connect myofibroblasts to extracellular matrix using electron-microscopy (7). ALK protein expression and gene rearrangement have not been reported in LGMFS. In this current case, ALK was found immunohistochemically negative. However; the presence of lymphoplasmocytic infiltration dispersed throughout the lesion and absence of high cellularity, nuclear hyperchromasia, and high mitotic activity were more

consistent with IMT than LGMFS. ALK gene rearrangement can be detected in half of IMT cases, especially in older patients (1). Nodular fasciitis presents as a rapidly enlarging, painful or tender subcutaneous nodule, usually in the upper extremities and trunk (2). It consists of spindle cell proliferation and collagen fibrils, set in a loose-myxoid stroma that contains capillaries, and extravasated erythrocytes and inflammatory cells. The spindle cells have prominent nucleoli and high mitotic activity; however, most cases are well-demarcated and do not infiltrate the surrounding breast parenchyma.

Phylloides tumor has biphasic component consisting of clefts lined by epithelial cells and cellular stromal proliferation (2). Primary breast sarcoma is extremely rare; it is good practice to exclude phylloides tumor first. Patient history and clinical information are important for the diagnosis of metastatic breast sarcoma. DFSPs form well-demarcated nodules located superficially in the dermis and subcutaneous tissue. Microscopically, DFSPs consist of CD34-positive innocent-looking spindle cells with a storiform pattern. Myofibroblastoma and nodular PASH present as well-circumscribed masses, similar to fibroadenoma (4, 8). Leiomyoma and leiomyosarcoma of the breast are usually seen as well-demarcated nodular masses in the nipple-areolar complex (2, 9). History of former biopsy is crucial in the diagnosis of reactive spindle cell nodules. These lesions demonstrate hemosiderin-laden macrophages and chronic inflammatory cells, which reflect the former procedure.

The etiology of PASH is still controversial. It is usually seen in premenopausal period, has high frequency in gynecomastia materials, and can have hormone receptor positivity. Hormone-dependent etiology is mostly considered because of these characteristics (4). PASH is not a true vascular proliferation (CD31 negative). The myofibroblast-lined spaces among collagen fibers in the stroma give the lesion its characteristic appearance. PASH is encountered frequently in the stroma surrounding CCC areas, which are accepted as preneoplastic lesions for low-grade breast carcinomas. Dabbs et al. stated that the coexistence of CCC and PASH could be an example of epithelial-stromal interaction (10). In this current case, the vicinity of the tumor demonstrated flat epithelial atypia in lobular units and PASH in the surrounding stroma. There are only a few case reports in the literature with ER and PR receptor expression in IMT (11, 12). Banet et al. (11) reported 2 IMT cases within the placenta, one of which showed patchy expression for PR receptor without ALK immunoreactivity, as well as gene rearrangement (11). Satomi *et al.* (12) reported an IMT of the mandible in a 14-year-old girl. No immunopositivity for ER, PR or ALK-1 was shown in that tumor. Similarly, we could not demonstrate positivity for either ER or PR in the current case.

In this case, both IMT and PASH areas were observed in close proximity to the lesion. Marked flat epithelial atypia was detected in PASH areas in the stroma. The vicinity of these two lesions, PASH areas mainly surrounding flat epithelial atypia, and young age of the patient made us consider whether a special group of IMT cases, such as ALK-negative IMT, could in fact be reactive proliferative lesions resulting from endocrine stimulation, or that the coexistence of these lesions was just a coincidence. However, we could not determine ER or PR nuclear expression either in IMT or PASH areas to support our hypotheses in this case.

As a result, we aimed to present a rare breast lesion, IMT, which can also mimic malignancy, and discuss the differential diagnosis. With this case, IMT with stromal PASH in close proximity, which also originates from myofibroblastic cells, has been described for the first time in the literature.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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References

- Gleason BC, Hornick JL. Inflammatory myofibroblastic tumors: where are we now? *J Clin Pathol* 2008; 61: 428-437. (PMID: 17938159) [\[CrossRef\]](#)
- Lakhani SR, Ellis IO, Schnitt SJ, Tan PH, van Vinver MJ. WHO Classification of Tumors of the Breast. Lyon 2012.
- Khanafshar E, Phillipson J, Schammel DP, Minobe L, Cymerman J, Weidner N. Inflammatory myofibroblastic tumor of the breast. *Ann Diagn Pathol* 2005; 9:123-129. (PMID: 15944952) [\[CrossRef\]](#)
- Virk RK, Khan A. Pseudoangiomatous stromal hyperplasia: an overview. *Arch Pathol Lab Med* 2010; 134:1070-1074. (PMID: 20586640)
- Devouassoux-Shisheboran M, Schammel MD, Man YG, Tavassoli FA. Fibromatosis of the breast: age-correlated morphofunctional features of 33 cases. *Arch Pathol Lab Med* 2000; 124:276-280. (PMID: 10656738)
- Dwyer JB, Clark BZ. Low-grade fibromatosis-like spindle cell carcinoma of the breast. *Arch Pathol Lab Med* 2015; 139:552-557. (PMID: 25822766) [\[CrossRef\]](#)
- Morgan PB, Chundru S, Hatch SS, Hawkins HK, Adegboyega PA, Eltorkey MA. Uncommon malignancies: case 1. Low-grade myofibroblastic sarcoma of the breast. *J Clin Oncol* 2005;23:6249-6251. (PMID: 16135491) [\[CrossRef\]](#)
- Magro G Mammary myofibroblastoma: a tumor with a wide morphologic spectrum. *Arch Pathol Lab Med*. 2008; 132:1813-1820. (PMID: 18976021)
- Virchow's Arch. 2002 Mar;440(3):249-6012. Vecchio GM, Cavaliere A, Cartagine F, Lucaccioni A, Lombardi T, Parenti R, Salvatorelli L, Magro G. Intraparenchymal leiomyoma of the breast: report of a case with emphasis on needle core biopsy-based diagnosis. *Pathologica* 2013; 105: 122-127. (PMID: 24466762)
- Recavarren RA, Chivukula M, Carter G, Dabbs DJ Columnar cell lesions and pseudoangiomatous hyperplasia like stroma: is there an epithelial-stromal interaction? *Int J Clin Exp Pathol* 2009; 3:87-97. (PMID: 19918332)
- Banet N, Ning Y, Montgomery EA. Inflammatory Myofibroblastic Tumor of the Placenta: A Report of a Novel Lesion in 2 Patients. *Int J Gynecol Pathol* 2015; 34: 419-423. (PMID: 26262452) [\[CrossRef\]](#)
- Satomi T, Watanabe M, Matsubayashi J, Nagao T, Chiba H. A successfully treated inflammatory myofibroblastic tumor of the mandible with long-term follow-up and review of the literature. *Med Mol Morphol* 2010; 43:185-191. (PMID: 20857269) [\[CrossRef\]](#)