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CASE REPORT – OPEN ACCESS

Superficial CD34-positive Fibroblastic Breast Tumor: A Case Report

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ABSTRACT

Background: CD34 is a transmembrane phosphoglycoprotein that plays a role in modulating cell adhesion and myofibroblastic differentiation. A superficial CD34-positive fibroblastic tumor was first identified as a clinical and pathological entity in 2014; it is a rare mesenchymal neoplasm of borderline malignancy that can occur in the superficial adipose tissue anywhere on the body.

Case Report: This is a case of a female patient aged 38 years who was referred to a surgeon due to tumefaction in the left paraxial region. The tumor was excised in toto and pathohistological analysis confirmed a superficial CD34-positive fibroblastic tumor. Immunohistochemical staining was positive for CD34 and additional analysis for signal transducer and activator of transcription and mouse double minute 2 proteins revealed negative staining. It was decided that no additional therapy was needed; however, regular follow-ups were recommended.

Conclusion: This case posed an additional diagnostic and therapeutic challenge due to the localization of the tumor in the breast of a female patient. Special care was needed to exclude a possible breast neoplasm as well as dermal or soft tissue neoplasm. Diagnosis of a superficial CD34-positive fibroblastic tumor should be considered in all CD34-positive tumors with bizarre, irregular nuclei and no proliferative activity.

Keywords: Antigens, breast neoplasm, CD34, mesenchymal neoplasm, surgery

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INTRODUCTION

A superficial CD34-positive fibroblastic tumor was first defined as a clinical and pathological entity in 2014 (1). It is defined as a rare mesenchymal neoplasm of borderline malignancy that can occur in the superficial adipose tissue anywhere on the body. Cases reported in the literature thus far most often relate successful treatment with surgical excision (2). The incidence of this type of tumor is low. The published accounts are usually a case report or a review of a small number of individual cases. Given the small number of superficial CD34-positive fibroblastic breast tumors reported in the literature, there are no standard diagnostic or treatment protocols.

CD34 is a transmembrane phosphoglycoprotein that plays a role in modulating cell adhesion and myofibroblastic differentiation (3). In tissue sections, CD34 is expressed in several places, including mesenchymal stroma and normal breast stroma. Reduced CD34 expression has been noted in malignant phyllodes breast tumors (4). There appears to be a connection between decreased or a lack of CD34 expression and malignancy, regardless of the histological type (4).

CASE REPORT

A 38-year-old female patient was referred to a surgeon due to a finding of tumefaction in the left paraxial region. The tumefaction measured approximately 10×5 cm, and had smooth edges, a hard consistency on palpation, and was non-movable in relation to the surrounding tissue. The patient noted that the tumefaction had been growing steadily for 3 years.

Mammography and ultrasound were performed at an outpatient clinic. The mammography results revealed a prepectoral, oval-shaped, soft-tissue shadow of about 93 mm in diameter situated in the upper left quadrant of the left breast (Fig. 1a). A breast ultrasound showed a heterogeneous, hypoechoic tumor in the upper left quadrant of left breast with multiple vascular structures within the tumor and several axillary lymph nodes with a thickened cortex of some 6 mm in diameter.

The patient was admitted and prepared for surgery. A tumor with well-defined borders located subcutaneously in the suprafascial plane was resected. The excised tumor was well-circumscribed and capsulated. The cut surface was homogenous and brown-red in color. The specimen, measuring about 10×15 cm, was sent for intraoperative frozen section pathological analysis. Since no cancer cells were found in the specimen, a decision was made to

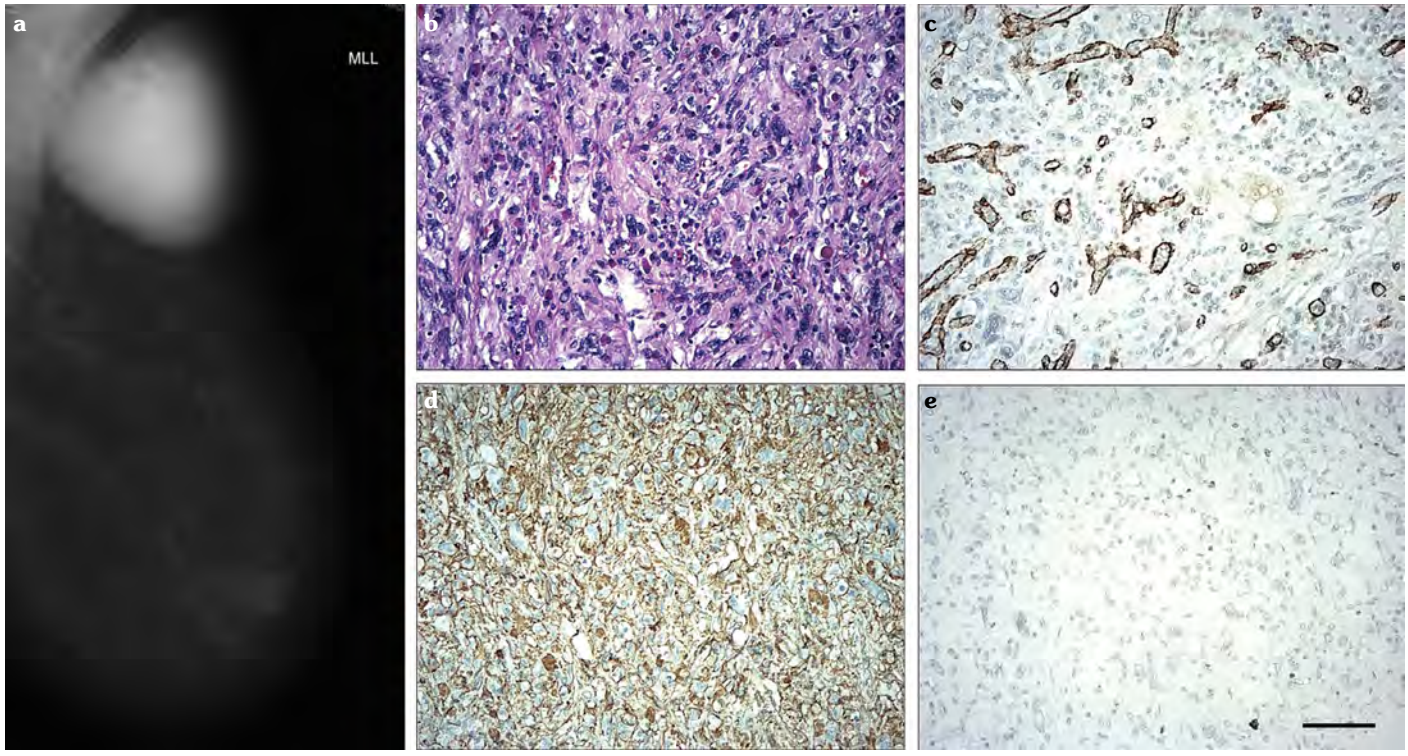

Figure 1. (a) Mammography image of the left breast in the mediolateral view illustrating a soft tissue shadow with a diameter of 93 mm. (b) Hematoxylin and eosin stain image showing a discohesive growth pattern of round to elongated tumor cells, eosinophilic cytoplasm with small to medium vesicular nuclei, and a focally prominent nucleolus. (c) Positive cytoplasmatic staining of smooth muscle cells of blood vessels in tumor; tumor cells were negative for actin staining. ×200 magnification. (d) CD34 results reveal diffuse cytoplasmatic positive staining of tumor cells. ×200 magnification. (e) Ki67 results showing a very low proliferation index. ×200 magnification. Scale bar form B-E is 50 μm

wait for a definitive pathological diagnosis before pursuing further treatment. The postoperative course was not remarkable. The patient was released on the third postoperative day and the sutures were removed after 9 days.

Pathohistological Diagnosis

A definitive diagnosis remained unclear after a routine hematoxylin and eosin staining of the samples and immunohistochemical analysis. Microscopically, a relatively well-defined border was apparent with diffuse nuclear polymorphism and without mitotic activity or necrosis. Multiple multinuclear giant cells with bizarre, irregular nuclei were seen mixed with spindle-shaped fibroblasts and chronic inflammation cell infiltrate (Fig. 1b).

The samples were sent to the pathology department of the University Hospital Center Split, Croatia, for additional immunohistochemical analysis with actin, h-caldesmon, CD34, factor VIII, S100, anaplastic lymphoma receptor tyrosine kinase gene (ALK), cytokeratin (CK) 5/6, p63, CK14, B-cell lymphoma/leukemia-2 (BCL-2), CD99, CD0, estrogen receptor, progesterone receptor, KI67, and histochemistry analysis using periodic acid-Schiff (PAS) and diastase (PAS-D) (Fig. 1c–e).

Tissue Procurement and Processing

The tumor tissue was fixed in 4% paraformaldehyde in phosphate buffer and dehydrated in graded ethanol. The samples were embedded in paraffin wax, serially sectioned in the sagittal plane at 7 μm, and mounted on glass slides. Immunohistochemical staining was performed and the samples were analyzed using an Olympus BX40 light microscope (Olympus Corp., Tokyo, Japan).

The sections were deparaffinized in xylene and rehydrated in ethanol and water. In order to quench endogenous peroxidase activity, the sections were incubated in 0.1% hydrogen peroxide for 30 minutes and washed in distilled water. For antigen retrieval, the sections were heated in a microwave oven at 95°C for 15 minutes in sodium citrate buffer (pH 6.0), cooled to room temperature, and washed in phosphate buffer saline (PBS). The sections were then incubated with anti-goat serum (XO907; Dako, Agilent Technologies, Inc., Santa Clara, CA, USA) for 20 minutes in the dark and washed in PBS.

Immunohistochemical Staining

The sections were separately incubated for 1 hour with the following primary antibodies (all Dako, Agilent Technologies, Inc., Santa Clara, CA, USA): monoclonal mouse anti-human actin (muscle) primary antibody (dilution 1:100, clone HHF35), monoclonal mouse anti-human caldesmon primary antibody (dilution 1:100, clone h-CD), monoclonal mouse anti-human CD34 class II primary antibody (dilution 1:100, clone QBEnd 10), monoclonal mouse anti-human von Willebrand factor (FV III) primary antibody (dilution 1:100, clone F8/86), polyclonal rabbit anti-human S100 primary antibody (dilution 1:100), monoclonal mouse anti-human CD246, ALK protein primary antibody (dilution 1:100, clone ALK1),

Table 1. Antibodies used in the immunohistochemical analysis of tumor tissue

Immunohistochemical stain	Type of primary antibody	Results
Actin (muscle)	Monoclonal mouse anti-human	Negative
Caldesmon	Monoclonal mouse anti-human	Negative
CD34 Class II	Monoclonal mouse anti-human	Positive
Von Willebrand factor (FVIII)	Monoclonal mouse anti-human	Negative
S100	Polyclonal rabbit anti-human	Negative
CD246, ALK protein	Monoclonal mouse anti-human	Negative
Cytokeratin 5/6	Monoclonal mouse anti-human	Negative
Cytokeratin 18	Monoclonal mouse anti-human	Negative
BCL2 oncoprotein	Monoclonal mouse anti-human	Negative
CD99, MIC2	Monoclonal mouse anti-human	Negative
CD10	Monoclonal mouse anti-human	Negative
Estrogen receptor alpha	Monoclonal mouse anti-human	Negative
Progesterone receptor	Monoclonal mouse anti-human	Negative
Ki-67 antigen	Monoclonal mouse anti-human	Proliferative activity very low

ALK: Anaplastic lymphoma receptor tyrosine kinase; BCL: B-cell lymphoma/leukemia

monoclonal mouse anti-human CK5/6 primary antibody (dilution 1:100, clone D5/16 B4), monoclonal mouse anti-human CK18 primary antibody (dilution 1:100, clone DC 10), monoclonal mouse anti-human BCL2 oncoprotein primary antibody (dilution 1:100, clone 124), monoclonal mouse anti-human CD99, MIC2 primary antibody (dilution 1:100, clone 12E7), monoclonal mouse anti-human CD10 primary antibody (dilution 1:100, clone 56C6), monoclonal mouse anti-human estrogen receptor alpha primary antibody (dilution 1:100, clone 1D5), monoclonal mouse anti-human progesterone receptor primary antibody (dilution 1:100, clone PgR 636), and monoclonal mouse anti-human Ki-67 antigen primary antibody (dilution 1:100, clone MIB1) (Table 1).

Primary antibody binding was detected using peroxidase/diaminobenzidine (DAB) and the rabbit/mouse EnVision detection system (K5007; Dako, Agilent Technologies, Inc., Santa Clara, CA, USA) as recommended by the manufacturer. All of the sections were subsequently washed in PBS and visualized with DAB solution. Finally, the sections were rinsed in distilled water, counterstained with hematoxylin, and dehydrated in ethanol and xylene. Analysis was performed using an Olympus BX51 microscope equipped with a digital camera and using Olympus DP-SOFT Version 3.1 software (Olympus Corp., Tokyo, Japan). Three observers analyzed the staining to account for inter-observer variation.

Controls

In order to perform negative controls, sections were incubated without primary antibodies. Positive controls demonstrated meningeal structures or other targets in known locations for the primary antibodies. All of the antibodies used were obtained from major commercial companies and the antibody data sheets revealed no reports of specific cross-reactivity.

Histochemical Staining

PAS and PAS-D histochemical staining were performed using a standard staining protocol (5).

Results of Immunohistochemical Staining

To determine a definitive diagnosis, tissue samples were sent for additional consultation to the Dana Farber Cancer Institute in Boston, MA, USA. Further immunohistochemical analysis for STAT and MDM2 proteins was performed and revealed negative staining. A diagnosis of superficial CD34-positive fibroblastic tumor was established.

The STAT family of proteins includes intracellular transcription factors involved in cell proliferation and immune regulation. Recent studies have confirmed that gene changes, most notably, NAB2-STAT6 gene fusions, are hallmarks of solitary fibrous tumors/hemangiopericytomas (6). The MDM2 protein is a negative regulator of p53 tumor suppressor. It is commonly used to distinguish lipomatous tumors (7).

Given that a superficial CD34-positive fibroblastic tumor rarely demonstrates an aggressive clinical course according to the available data, it was decided in this case that no additional therapy was needed, but regular follow-up was suggested. The first-year follow-up showed no recurrence of disease.

DISCUSSION

Due to the small number of superficial CD34-positive fibroblastic tumor cases in the published literature, there are still no standard protocols for diagnosis or treatment. According to the current World Health Organization classification and published cases, the malignancy is thought to be limited, due to the fact that this mesenchymal tumor rarely metastasizes (1). Prior to the description and reporting of the particular pathohistological characteristics, this tumor was often diagnosed as undifferentiated pleomorphic sarcoma or myxofibrosarcoma. A report of 2 cases and a review of the literature published in January of 2020 discussed a total of 44 cases (8). Only 1 patient had distant lymph node metastasis, and there was no recurrence after complete resection. The remaining cases

showed no recurrence of the tumor in follow-up (8). This seems to confirm limited malignancy and excision in toto as a treatment method of choice.

Because of the limited malignancy potential of superficial CD34 positive fibroblastic tumors, special care should be taken during differential diagnosis and should include a hypercellular spindle cell neoplasm with scattered pleomorphic epithelioid cells presenting as a soft tissue mass include synovial sarcoma, leiomyosarcoma, nerve sheath tumor, solitary fibrous tumor, dermatofibrosarcoma protuberans, fibrohistiocytic tumor, and fibrosarcoma (8).

CONCLUSION

The case presented in this report posed an additional diagnostic and therapeutic challenge because of the localization of the tumor in the breast. CD34-positive staining in breast tumors commonly occurs in fibroadenomas of the breast and may be found in phyllodes tumors of the breast (4). As a recently defined entity, a superficial CD34-positive fibroblastic tumor presents a considerable challenge for both the surgeon and the pathologist because of its rarity and overlapping features with other pathological entities; however, the limited malignancy of these tumors is important. The localization, age, and sex of the patient require special care to determine a definitive diagnosis in cases of CD34-positive tumors with bizarre, irregular nuclei and no proliferative activity.

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