Case report

Fibroma of the breast: a rare tumour in the spectrum of the benign spindle cell tumours of the mammary stroma

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Benign spindle cell tumours of the mammary stroma comprises different lesions that show a variable degree of fibroblastic/myofibroblastic differentiation. We herein report a previously under-recognised hypocellular fibrocollagenous tumour of the breast, for which the term "fibroma" is proposed. The tumour was composed of CD34-positive bland-looking spindle cells embedded in an abundant hyalinised stroma. Fluorescence *in situ* hybridisation (FISH) showed 13q14 deletion in most neoplastic cells, a chromosomal alteration typically found in mammary myofibroblastoma. Based on morphological, immunohistochemical, and cytogenetic features, we suggest that fibroma belongs to the group of the benign spindle cell tumours of the mammary stroma.

Key words: breast, mammary stroma, fibroma, benign spindle cell tumour, 13q14 deletion.

Introduction

Benign spindle cell tumours of the mammary stroma are an uncommon group of lesions, which share several morphological and immunohistochemical features [1, 2, 3]. Although myofibroblastoma is the most known and well-defined lesion [4, 5], the boundaries of the tumours with fibroblastic differentiation are poorly delineated. This is the main reason why different names, such as "benign spindle cell tumour" [1, 6, 7, 8, 9], "fibroma" [9], "spindle cell lipoma" [10, 11], "myogenic stromal tumour" [12], "solitary fibrous tumour" [13, 14, 15], and myofibroblastoma" [13, 14] have been used, often interchangeably, for the same tumour. There is increasing evidence that the group of "benign spindle cell tumours of the mammary stroma" comprise a wide spectrum of CD34-positive lesions ranging from tumours with fibroblastic differentiation ("benign fibroblastic spindle cell tumour"; "benign fibroblastic spindle cell tumour with fatty component"; spindle cell lipoma) to tumours with clear-cut myofibroblastic differentiation (classic-type myofibroblastoma and its morphological variants) [1, 3]. Solitary fibrous tumour, originally included in this group [2, 3], shows a different molecular profile [16, 17, 18, 19] and it is actually better classified as a soft tissue

tumour occurring in the breast rather than a tumour specific to mammary stroma [1].

We herein report a previously unrecognised, hypocellular, benign mesenchymal spindle cell tumour of the breast with hyalinised collagenous stroma, closely reminiscent of tendon sheath fibroma, for which the descriptive term "fibroma of the breast" is proposed. Because this tumour shares the 13q14 deletion with myofibroblastoma of the breast, we speculate that it belongs to the group of the benign spindle cell tumours of the mammary stroma.

Material and methods

A 58-year-old female presented a painless, well-circumscribed supra-areolar nodule at her right breast. Physical examination revealed a firm, mobile mass, measuring 2 cm in its greatest dimension. There was no associated skin retraction, and axillary lymph nodes were not appreciable on palpation. Ultrasonography revealed a hypoechoic, well-circumscribed tumour without microcalcifications, and thus a fibroadenoma was suspected. The patient underwent fine-needle core aspiration biopsy (FNCAB), but the material was not diagnostic. A lumpectomy was performed, accordingly.

Surgical specimen was submitted for histological examination in neutral-buffered 10% formalin, dehydrated using standard techniques, and embedded in paraffin. Five-micrometre sections were cut and stained with haematoxylin and eosin (HE). Immunohistochemical studies were performed with the labelled streptavidin-biotin peroxidase detection system using a Ventana automated immunostainer (Ventana Medical Systems, Tucson, AZ). The following antibodies were applied: vimentin, CD34, α-smooth muscle actin, desmin, h-caldesmon, wide spectrum cytokeratins (CKMNF116), epithelial membrane antigen (EMA), S-100, myogenin, and oestrogen and progesterone receptors (all from DakoCytomation, Glostrup, Denmark). Polyclonal rabbit antibody (s20-S621, Santa Cruz Biotechnologies, Santa Cruz, CA, USA) against the STAT6 C-terminal was used at a dilution of 1 : 200, after antigen retrieval (96°C EDTA for 30 min).

FISH analysis for the detection of *FOX1* (previously *FKHR*), located on 13q14.11, was performed on 4- to 6-μm paraffin-embedded tissue sections, deparaffinised with xylene and subsequently enzymatically digested with a commercial kit (Paraffin Pretreatment Reagent Kit; Vysis-Abbott Molecular, Downers Grove, IL). Sample DNA was denatured at 75°C for five minutes. The Locus-Specific Identifier *FOX1* Break Apart Probe (Vysis-Abbott), which hybridises to band 13q14, was used. The Locus-Specific Identifier *FOX1* consists of a mixture of 2 DNA probes: the first (720 kilobase) is labelled with Spectrum Green and lies proximal to the *FOX1* gene, and the second one (650 kilobase) is labelled with Spectrum Orange that extends distally from the *FOX1* gene. The probe mix (10 μl), previously denatured for five minutes at 75°C, was applied on each slide. The slides, covered with a glass cover slip, were incubated for 5 minutes at 79°C for codenaturation and placed in a humidified chamber at 37°C overnight to allow hybridisation to occur. After post-hybridisation washes, carried out according to the manufacturer's protocols, tissue sections were counterstained with DAPI I (Vysis-Abbott) and examined with a fluorescence microscope (Olympus, Tokyo, Japan). In a normal cell, two fusion signals are present; in a cell that lacks one 13q14 region, only one fusion signal is observed. All non-overlapping interphase neoplastic nuclei with intact morphology were analysed for each case using haematoxylin and eosin (HE)–stained sections as histotopographic reference. The number of nuclei counted was 60. A specimen was interpreted as deleted if only one fusion signal was detected in more than 22% of the nuclei evaluated (N3 SDs above the average false-positive rate observed in control FISH experiments on normal paraffin-embedded tissue). One positive (spindle cell lipoma) and one negative control (normal tissue) were included in FISH analyses.

Results

Grossly tumor presented as an unencapsulated, well-circumscribed, 2-cm nodule surrounded by a peripheral rim of normal-appearing breast tissue. The cut surface revealed a homogeneous, nodular mass, whitish in colour and firm in consistency. No areas of haemorrhage or necrosis were seen. Histological examination revealed an unencapsulated, hypocellular tumour with pushing margins (Fig. 1A, B). It was predominantly composed of bland-looking spindle cells with a minority of rounded cells, set in an abundant fibrocollagenous stroma containing only rarely capillary-like blood vessels (Fig. 2A, B). Some tumour areas were relatively more cellular and the spindle cells exhibited wavy nuclei (Fig. 3A). Mitoses, nuclear atypia, haemorrhage, and necrosis were absent. Only a few mammary ducts/lobules were entrapped within the tumour (Fig. 1B, 2B). Immunohistochemically neoplastic cells were diffusely stained with vimentin and CD34 (Fig. 3B). No immunostaining was obtained with all the other antibodies tested. Notably, FISH analyses revealed monoallelic deletion of the *FOX1* gene in 67.3% of the cell population (Fig. 3C). Based on the morphological, immunohistochemical, and cytogenetic features, the term "fibroma of the breast" was coined for such an uncommon lesion.

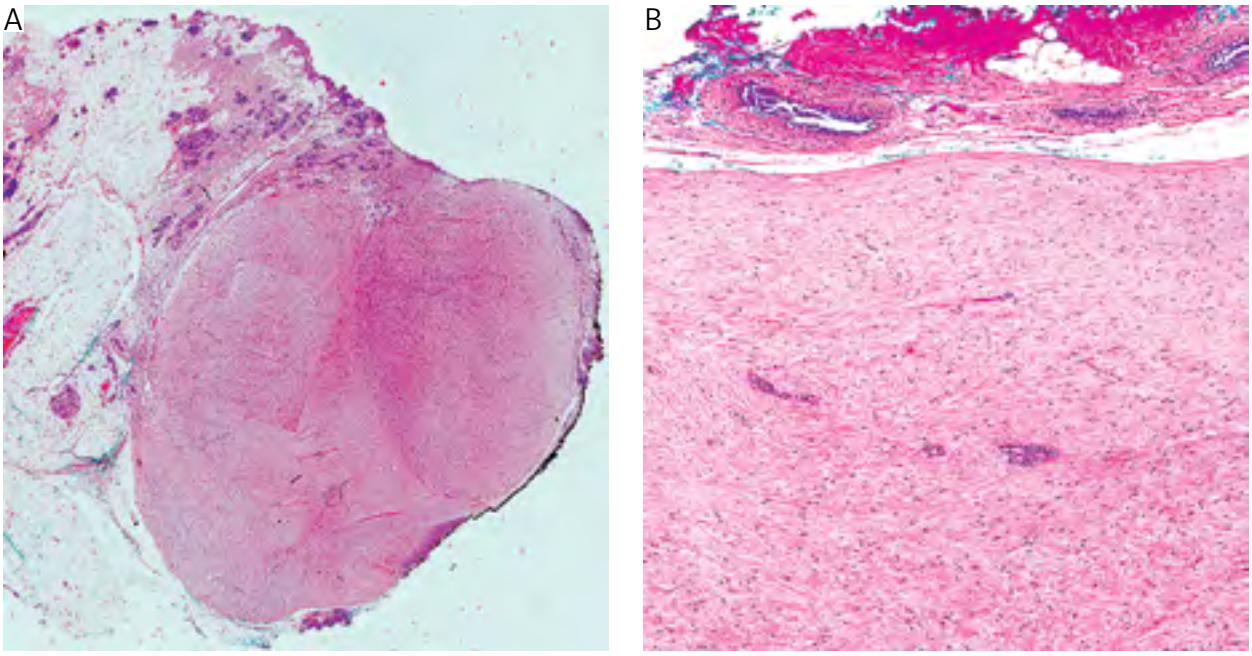

Fig. 1. A) Low-magnification showing a fibrocollagenous tumour with pushing borders. B) Higher magnification showing a hypocellular fibrotic tumour with interspersed mammary ducts

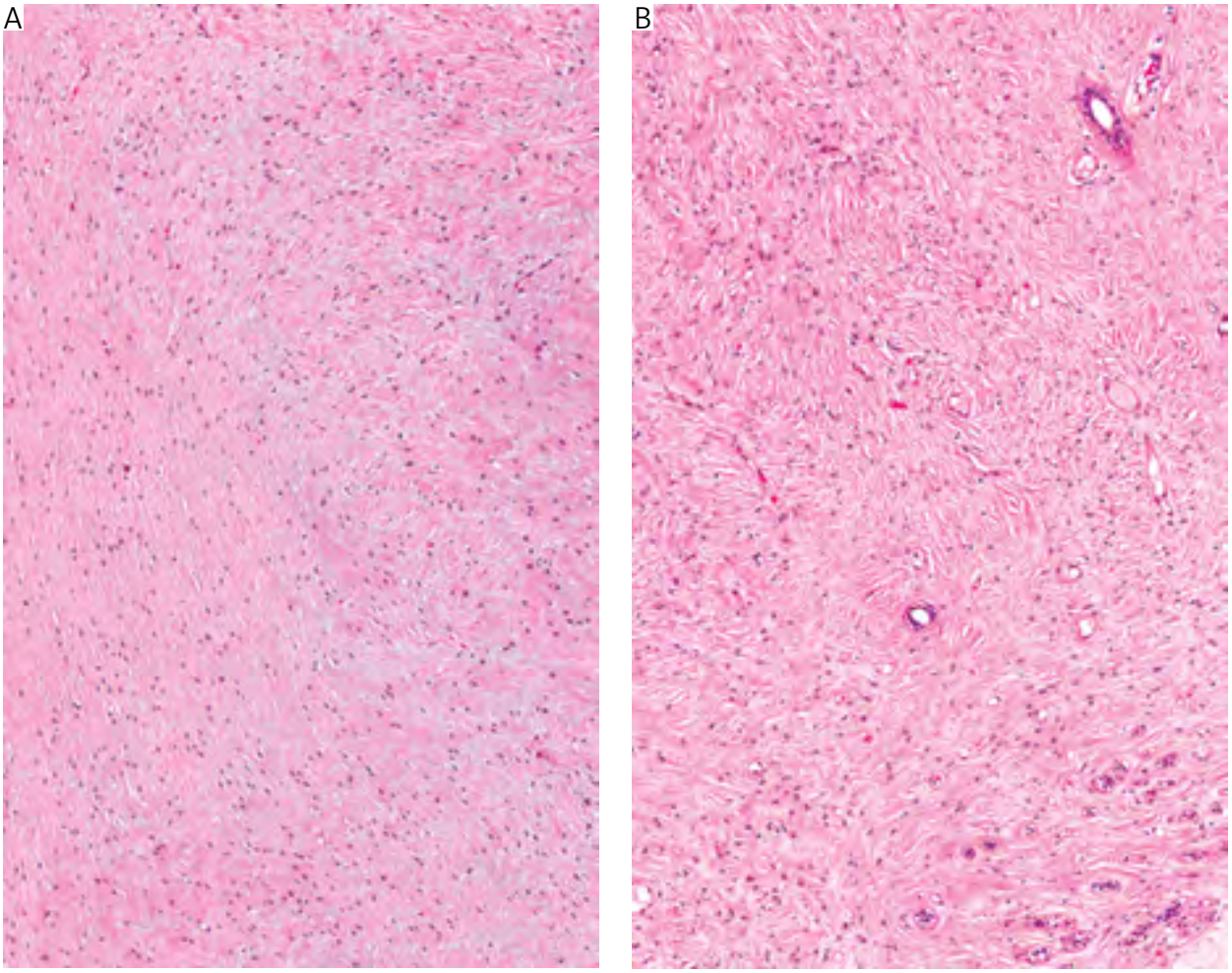

Fig. 2. Tumour is composed of bland-looking spindle cells set in an abundant hyalinised stroma (A) containing mammary ducts and rare capillary-like blood vessels (B)

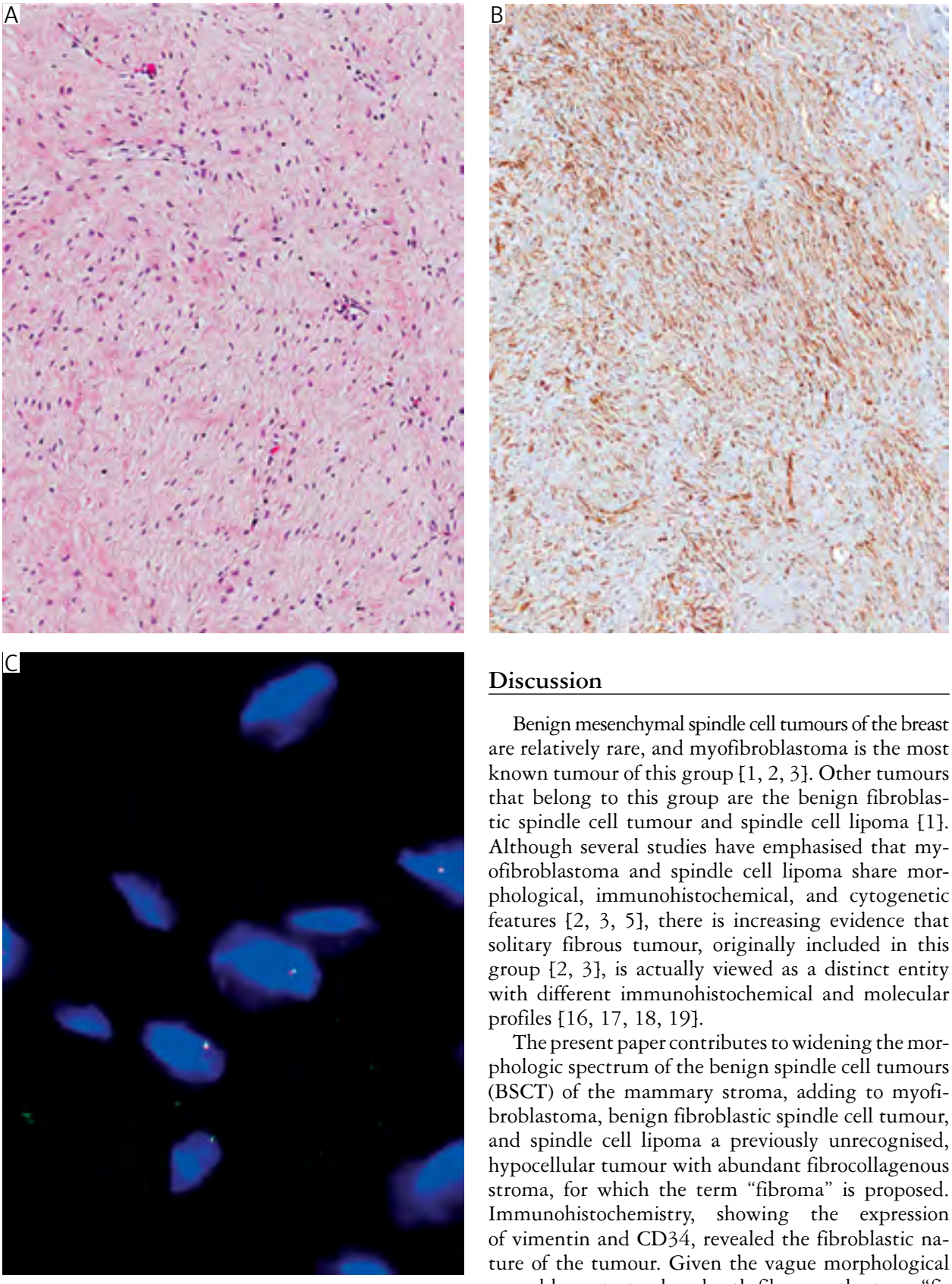

Fig. 3. A) In this tumour area the spindle cells exhibit wavy nuclei. B) The spindle cells are stained with CD34. C) FISH analysis showing monoallelic loss of *FOXO1*/13q14 *loci* as indicated by the presence of one fusion red/green signal in most tumour cells

Discussion

Benign mesenchymal spindle cell tumours of the breast are relatively rare, and myofibroblastoma is the most known tumour of this group [1, 2, 3]. Other tumours that belong to this group are the benign fibroblastic spindle cell tumour and spindle cell lipoma [1]. Although several studies have emphasised that myofibroblastoma and spindle cell lipoma share morphological, immunohistochemical, and cytogenetic features [2, 3, 5], there is increasing evidence that solitary fibrous tumour, originally included in this group [2, 3], is actually viewed as a distinct entity with different immunohistochemical and molecular profiles [16, 17, 18, 19].

The present paper contributes to widening the morphologic spectrum of the benign spindle cell tumours (BSCT) of the mammary stroma, adding to myofibroblastoma, benign fibroblastic spindle cell tumour, and spindle cell lipoma a previously unrecognised, hypocellular tumour with abundant fibrocollagenous stroma, for which the term "fibroma" is proposed. Immunohistochemistry, showing the expression of vimentin and CD34, revealed the fibroblastic nature of the tumour. Given the vague morphological resemblance to tendon sheath fibroma, the term "fibroma of the breast" is proposed. Although the term "fibroma" has already been used for two spindle cell tumours of the breast, based on the illustrations provided by the authors, one case should be best regard-

ed as recurrent phyllodes tumour [20] and the other case as a benign fibroblastic spindle cell tumour [9]. Our case could be confused with fibrous masses of the breast that have been reported in the literature under different names including "fibrous tumour", "fibrous disease", "fibrosis of the breast", "focal fibrous disease", and "fibrous mastopathy" [21]. These uncommon lesions present as discrete breast mass composed of acellular collagenised stroma with admixed atrophic mammary ducts and lobules. As previously suggested [21], some of these lesions could be better classified as examples of pseudoangiomatous stromal hyperplasia. Unlike these lesions, our case contains a distinct CD34/CD10-positive fibroblastic spindle cell component with 13q14 deletion, which imparts to the tumour mass a "fibroma-like" appearance.

The histological diagnosis of fibroma of the breast is usually straightforward due to its typical morphological features (hypocellular, spindle cell tumour with extensive fibrocollagenous stroma), but this tumour needs to be distinguished from other potential mimics. Differential diagnosis mainly includes pseudoangiomatous stromal hyperplasia (cellular variant), fibroadenoma with fibrotic stroma, nodular fasciitis, fibromatosis, myofibroblastoma (collagenised variant), benign fibroblastic spindle cell tumour, solitary fibrous tumour, and neurofibroma. The diagnosis of pseudoangiomatous stromal hyperplasia is straightforward if anastomosing, slit-like pseudovascular spaces are present. When these features are lacking (fascicular variant), the diagnosis can be challenging [1]. Unlike our case, however, the fascicular variant of pseudoangiomatous stromal hyperplasia shows a proliferation of spindle cells arranged in distinct fascicles with interspersed keloid-like collagen fibres, resulting in a myofibroblastoma-like appearance [1].

Although rare ducts/lobules were entrapped throughout the tumour, the classic biphasic pattern of fibroadenoma, namely spindle cell proliferation around tubular/ductal structures, was lacking in our case. Desmoid-type fibromatosis of the breast is a potentially locally-recurring tumour composed of spindle cells set in a fibrous stroma [22, 23]. Unlike fibroma, desmoid-type fibromatosis exhibits infiltrative margins, arrangement of neoplastic cells into long fascicles and immunohistochemical expression of both α-smooth muscle actin and β-catenin [1]. Nodular fasciitis is a spindle cell proliferation that can be composed predominantly of collagenous stroma. However, unlike, fibroma, nodular fasciitis has, at least focally, infiltrative margins, short and not well-formed fascicles, a tissue culture-like appearance, and immunoreactivity for α-smooth muscle actin [1]. The collagenised variant of myofibroblastoma can be confused with fibroma due to its well-circumscribed margins [1]. However, the spindle cells of this myofibroblastoma variant are myofibroblastic in nature, with the expression, apart from CD34, of myogenic markers (desmin; α-smooth muscle actin) [1].

Although fibroma and benign fibroblastic spindle cell tumour share vimentin and CD34 expression, the latter is more cellular and is composed of fibroblast-like cells arranged haphazardly or into short fascicles, closely intermingling with thick collagen fibres [1]. However, the possibility that the present case may represent the collagenised variant of the benign fibroblastic spindle cell tumour cannot be completely ruled out. Solitary fibrous tumour may show extensive fibrocollagenous stroma, posing differential diagnostic problems with fibroma. However, the diagnosis of solitary fibrous tumour is especially based on the presence of medium-sized blood vessels with hyalinised walls and branching configuration and the diffuse nuclear staining for STAT6 [19, 24]. In addition, our case showed the 13q14 deletion, a cytogenetic alteration that is lacking in solitary fibrous tumours [25]. Although in our case there were focal areas with spindle cell exhibiting wavy nuclei, neurofibroma was excluded on the basis of the absence of S-100 expression.

Notably, our case exhibited the 13q14 deletion by means of FISH. This finding is very intriguing in that the same chromosomal abnormality is shared with mammary myofibroblastoma [26, 27], suggesting that these tumours are histogenetically-related. Accordingly, we speculate that the fibroma described herein belongs to the spectrum of the benign spindle cell tumours of the mammary stroma, which comprises myofibroblastoma, benign fibroblastic spindle cell tumour, and spindle cell lipoma. As previously suggested, it is likely that these tumours represent subtle variations of the same entity, probably arising from the uncommitted vimentin+/CD34+ fibroblasts of the mammary stroma, capable of both fibroblastic and myofibroblastic differentiation [1].

The authors declare no conflict of interest.

References

1. Magro G. Differential Diagnosis of Benign Spindle Cell Lesions. Surg Pathol Clin 2018; 11: 91-121.
2. Magro G, Michal M, Bisceglia M. Benign spindle cell tumors of the mammary stroma: diagnostic criteria, classification, and histogenesis. Pathol Res Pract 2001; 197: 453-466.
3. Magro G, Bisceglia M, Michal M, et al. Spindle cell lipoma-like tumor, solitary fibrous tumor and myofibroblastoma of the breast: a clinicopathological analysis of 13 cases in favor of a unifying histologic concept. Virchows Arch 2002; 440: 249-260.
4. Magro M, Fletcher CDM, Eusebi. Myofibroblastoma. In: WHO classification of tumours of the breast. Lakhani S, Ellis IO, Schnitt SJ, et al. (eds). 4th ed. IARC press, Lyon 2012; 130-131.

5. Magro G. Mammary myofibroblastoma: an update with emphasis on the most diagnostically challenging variants. Histol Histopathol 2016; 31: 1-23.
6. Toker C, Tang CK, Whitely JF, et al. Benign spindle cell breast tumor. Cancer 1981;48: 1615-1622.
7. Böger A.. Benign spindle cell tumor of the male breast. Path Res Pract 1984; 178: 395 398.
8. Magro G, Bisceglia M, Pasquinelli G. Benign spindle cell tumor of the breast with prominent adipocytic component. Ann Diagn Pathol 1998; 2: 306-311.
9. Chan KW, Ghadially FN, Alagaratnam. Benign spindle cell tumour of breast-a variant of spindle cell lipoma or fibroma of breast? Pathology 1984;16: 331-337.
10. Smith DN, Denison CM, Lester SC. Spindle cell lipoma of the breast. A case report. Acta Radiol 1996; 37: 893-895.
11. Mulvany NJ, Silvester AC, Collins JP. Spindle cell lipoma of the breast. Pathology 1999; 31: 288-291.
12. Bégin LR. Myogenic stromal tumor of the male breast (socalled myofibroblastoma). Ultrastruct Pathol 1991; 15: 613-622.
13. Damiani S, Miettinen M, Peterse JL, et al, Solitary fibrous tumor (myofibroblastoma) of the breast. Virchows Arch 1994; 425: 89-92.
14. Meguerditchian AN, Malik DA, Hicks DG, et.al. Solitary fibrous tumor of the breast and mammary myofibroblastoma: the same lesion? Breast J 2008; 14: 287-292.
15. Magro G, Sidoni A, Bisceglia M. Solitary fibrous tumour of the breast: distinction from myofibroblastoma. Histopathology 2000; 3: 189-190.
16. Robinson DR, Wu YM, Kalyana-Sundaram S, et al. Identification of recurrent NAB2–STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. Nat Genet 2013; 5: 180-185.
17. Doyle LA, Vivero M, Fletcher CD, et al. Nuclear expression o1f STAT6 distinguishes solitary fibrous tumor from histologic mimics. Mol Pathol 2014; 27: 390-395.
18. Yoshida A, Tsuta K, Ohno M, et al. STAT6 immunohistochemistry is helpful in the diagnosis of solitary fibrous tumors. Am J Surg Pathol 2014; 38: 552-559.
19. Magro G, Angelico G, Leone G, et al. Solitary fibrous tumor of the breast: report of a case with emphasis on diagnostic role of STAT6 immunostaining. Pathol Res Pract 2016; 212: 463-467.
20. Halpert B, Dial DL. Fibroma of the Breast. Am J Pathol 1933; 9: 905-907.
21. Rosen PP. Rosen's Breast Pathology. Lippincott Williams & Wilkins, Philadelphia 2009.
22. Devouassoux-Shisheboran M, Schammel MD, Man YG, et al. Fibromatosis of the breast: age-correlated morphofunctional features of 33 cases. Arch Pathol Lab Med 2000; 124: 276-280.
23. Magro G, Gurrera A, Scavo N, et al. Fibromatosis of the breast: a clinical, radiological and pathological study of 6 cases. Pathologica 2002; 94: 238-246.
24. Falconieri G, Lamovec J, Mirra M, et al. Solitary fibrous tumor of the mammary gland: a potential pitfall in breast pathology. Ann Diagn Pathol 2004; 8: 121-125.
25. Fritchie KJ, Carver P, Sun Y, et al. Solitary fibrous tumor: is there a molecular relationship with cellular angiofibroma, spindle cell lipoma, and mammary-type myofibroblastoma? Am J Clin Pathol 2012; 137: 963-970.
26. Magro G. Mammary myofibroblastoma: a tumor with a wide morphologic spectrum. Arch Pathol Lab Med 2008; 132: 1813-1820.
27. Magro G, Righi A, Casorzo L, et al. Mammary and vaginal myofibroblastomas are genetically related lesions: fluorescence in situ hybridization analysis shows deletion of 13q14 region. Hum Pathol 2012; 43:1887-1893.

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