



CASE REPORT

PET/CT-Detected myofibroblastoma of the breast with bizarre cells: A potential diagnostic pitfall of malignancy

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Abstract

Myofibroblastoma (MFB) is a rare benign mesenchymal tumor usually occurring in the breast parenchyma. This tumor can present as a palpable nodule or can be incidentally detected as a nonpalpable mass on routine screening mammogram. We first report a rare case of histologically proven MFB of the breast revealed by fluoro-deoxyglucose uptake on PET-CT examination in a patient with a lung nodule. Tumor exhibited an unusual morphology, being predominantly composed of polygonal, epithelioid, and decidual-like cells set in a myxoid stroma. The most striking feature was the multifocal presence of atypical/bizarre, mono/bi-nucleated cells that, in addition to diffuse myxoid stromal changes, were a concern of malignancy, especially on core biopsy. The final diagnosis of MFB was achieved on surgically resected specimen and, similarly to other benign soft tissue tumors (especially leiomyoma and schwannoma/neurofibroma), the term "*bizarre cell MFB of the breast*" is proposed to emphasize the degenerative/reactive nature of the atypia.

KEYWORDS

atypical/bizarre cells, breast, myofibroblastoma, PET/CT, soft tissue tumor

1 | INTRODUCTION

The 18F-Fluorodeoxyglucose (FDG) positron emission tomography with computed tomography (PET/CT) is an anatomic and functional imaging useful for both staging and post-therapeutic surveillance of several malignant tumors¹. In the last years, with the increasing use of FDG PET/CT, there is evidence that unexpected lesions (also known as "*incidentalomas*"), unrelated to tumor spread, are incidentally detected at unusual sites, including the breast². In this regard, breast incidentalomas with focal increased FDG uptake on PET/CT have been found in 0.36%–1.12% of patients³. However, although uncommon, these lesions are often malignant in nature (malignancy rates ranging from 27.3% to 83.3%), being mostly represented by

invasive carcinomas and ductal carcinomas in situ and less frequently by malignant phyllodes tumors and primary breast sarcomas^{4,5}. Benign breast lesions detected by FDG PET/CT are rare, and most of them are histologically represented by fibrocystic disease, stromal fibrosis, fibroadenoma, benign papillary lesions, and benign phyllodes tumors⁵.

We herein report a rare case of mammary myofibroblastoma (MFB) with multifocal degenerative-type atypia, incidentally detected on FDG PET/CT. The presence of large-sized, bizarre mono- and multi-nucleated cells, along with diffuse myxoid stromal changes, were a potential diagnostic pitfall of malignancy, especially on core biopsy. The term "*bizarre cell MFB of the breast*" was proposed.

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2 | MATERIALS AND METHODS

Bioptic and surgical specimens were submitted for histological examination in neutral-buffered 10% formalin, dehydrated using standard techniques, embedded in paraffin, cut to 5 μ m, and stained with hematoxylin and eosin (H&E). Immunohistochemical studies were performed with the labeled streptavidin-biotin peroxidase detection system using the Ventana automated immunostainer (Ventana Medical Systems, Tucson, AZ). The antibodies tested were vimentin, α -smooth muscle actin, desmin, myogenin, h-caldesmon, S-100 protein, CD99, CD34, bcl-2, CD10, cytokeratins (AE1/AE3 clone); epithelial membrane antigen (EMA), p63, HMB45, Melan A, INI-1, estrogen receptor (ER), progesterone receptor (PR), and Ki-67; all from Dako, Glostrup, Denmark. Appropriate positive and negative controls were included.

FISH analysis for the detection of FOX1 (previously FKHR), located on 13q14.11, was performed as previously described in our laboratory⁶. In a normal cell, 2 fusion signals are present; in a cell that lacks one 13q14 region, only 1 fusion signal is observed. All

nonoverlapping interphase neoplastic nuclei with intact morphology were analyzed for each case using hematoxylin- and eosin (H&E)-stained sections as histotopographic reference. The number of nuclei counted was 60, and the case was interpreted as deleted if only 1 fusion signal was detected in more than 22% of the nuclei evaluated (N3 SDs above the average false-positive rate observed in control FISH).

2.1 | Case presentation

An 80 years-old man with a history of thoracic and aortic aneurysms presented to our hospital for a solitary pulmonary 1.4 cm nodular lesion in the left lower lobe detected on follow-up CT scan evaluation. The patient underwent PET-CT scan for staging purposes, which evidenced moderately increased uptake in the lung nodule with a maximum standardized uptake value (SUVmax) of 24. In addition, a nodular solid lesion with faint metabolic uptake value (SUVmax) of 3 was detected in the upper outer quadrant of his left

FIGURE 1 PET-CT findings of the reported case. A) PET-CT scan showed a 2,5 cm nodular solid lesion (circle) in the upper outer quadrant of the left breast; B) 18-FDG PET revealed a faint metabolic uptake value (SUVmax) of 3 (circle)

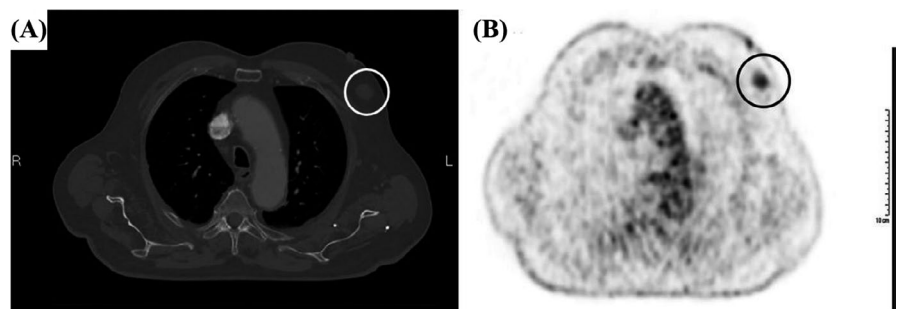
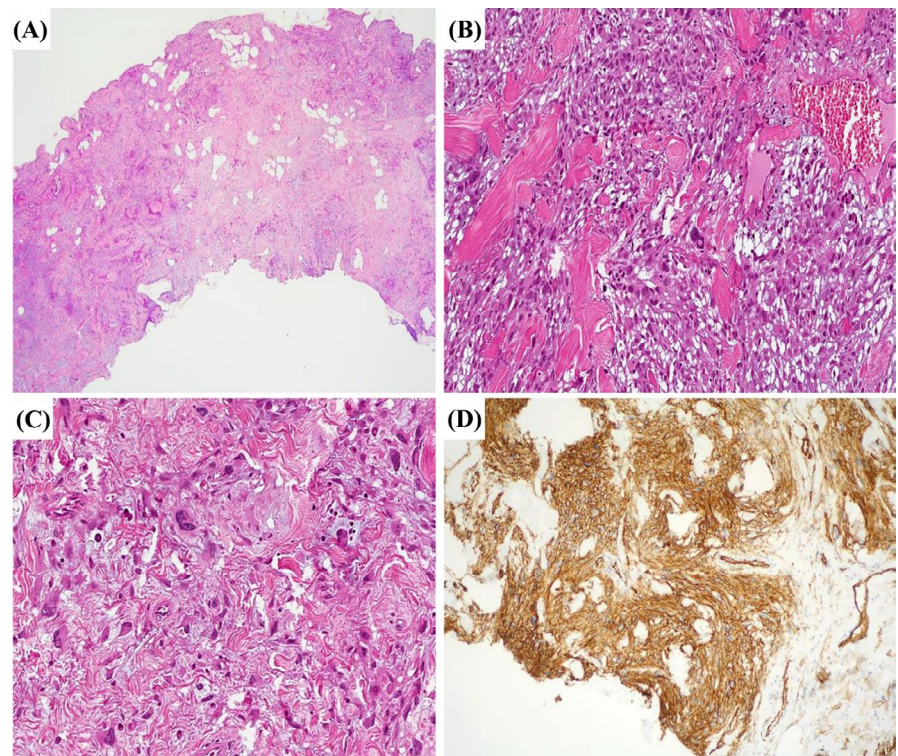


FIGURE 2 Histological and immunohistochemical findings on core needle biopsy. (A) On low power view, a moderately cellular neoplastic proliferation set in a fibro-myxoid stroma with interspersed mature adipocytes was observed. (B) Neoplastic cells were set in a myxoid stroma with interspersed keloid-like collagen fibers; (C) Atypical stromal cells with abundant eosinophilic cytoplasm and nuclear pleomorphism were frequently seen; (D) Immunohistochemically, neoplastic cells were diffusely stained with CD34



breast (Figure 1A,B). Ultrasonography of the breast revealed a well-circumscribed, echogenic nodule, measuring 2.5 cm in its greatest diameter, with heterogeneous echotexture, posterior acoustic shadowing, and with minimal vascularity on Doppler. Tumor calcifications were lacking. To further characterize the breast lesion and its possible relation to the lung nodule (metastasis), an ultrasound-guided core needle biopsy was performed. Histological examination showed a proliferation of polygonal, epithelioid, and decidual-like cells with abundant eosinophilic cytoplasm, set in a myxoid stroma with interspersed keloid-like collagen fibers (Figure 2A,B); although some neoplastic cells exhibited severe nuclear atypia, neither mitoses nor necrosis were seen (Figure 2C). Immunohistochemistry revealed diffuse staining for vimentin, CD34 (Figure 2D), and only focally for desmin. The provisional diagnosis of “*atypical mesenchymal lesion of uncertain malignancy*” was rendered with the recommendation of histological evaluation in the surgically resected sample (diagnostic category: B3). Accordingly, the patient underwent surgical excision of the breast nodule with a rim of normal breast parenchyma. Gross examination revealed a well-circumscribed, unencapsulated nodule of 2.5 cm in its greatest diameter. The cut surface showed a solid nodule, fibro-myxoid in appearance, and whitish in color. Histological examination revealed an

unencapsulated tumor with pushing, lobulated margins, composed predominantly of cells with polygonal, epithelioid, and decidual-like morphology (Figure 3A–C). Only a minority of spindle-shaped cells were seen. Neoplastic cells, mostly arranged haphazardly or in solid nests, were set in an abundant myxoid stroma containing numerous keloid-like collagen fibers (Figure 3D). Focally islands of mature adipocytes were seen within the tumor, but mammary ducts and lobules were lacking. An unexpected finding was the multifocal presence of large-sized, bizarre mono- and multi-nucleated stromal cells (Figure 3E,F). These neoplastic cells exhibited abundant eosinophilic cytoplasm and nuclei with moderate to severe pleomorphism, including prominent nucleoli and pseudoinclusions. Mitotic activity was very low ($\leq 1/50$ HPF). Atypical mitoses and necrosis were absent. Immunohistochemically, neoplastic cells were positive for vimentin, CD34, desmin (Figure 4A), estrogen/progesterone receptors, CD99, CD10, and bcl-2 protein. None of the other markers tested was positive. Ki-67 expression was very low (2%, Figure 4B). FISH analysis revealed the monoallelic deletion of the FOX1 in more than 45% of neoplastic cells population, confirming the monoallelic loss FOXO1/13q14 loci (Figure. 4C).

Based on the morphological, immunohistochemical, and molecular features, a diagnosis of “*bizarre cell myofibroblastoma of breast with*

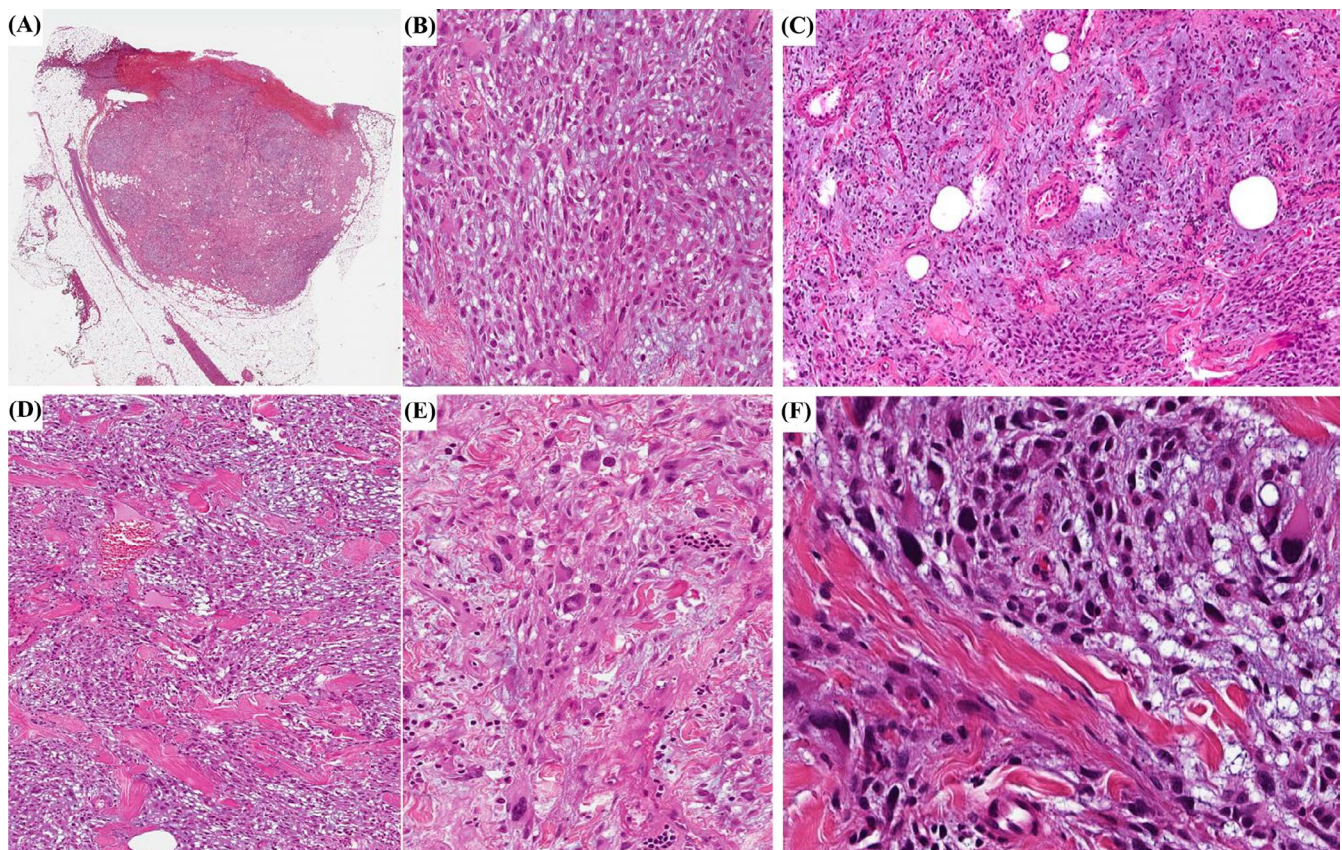


FIGURE 3 Histological findings of the surgically resected specimen. (A) Low magnification showing an unencapsulated tumor with pushing, lobulated margins; (B) Neoplastic cells exhibited a polygonal, epithelioid, decidual-like, and spindled morphology; (C) Neoplastic cells, mostly arranged haphazardly or in solid nests, were set in a fibro-myxoid stroma. (D) Numerous keloid-like collagen fibers were frequently seen within tumor stroma; (E, F) Multiple foci of bizarre neoplastic cells with abundant eosinophilic cytoplasm and nuclei with moderate to severe pleomorphism, including prominent nucleoli and pseudoinclusions, were observed

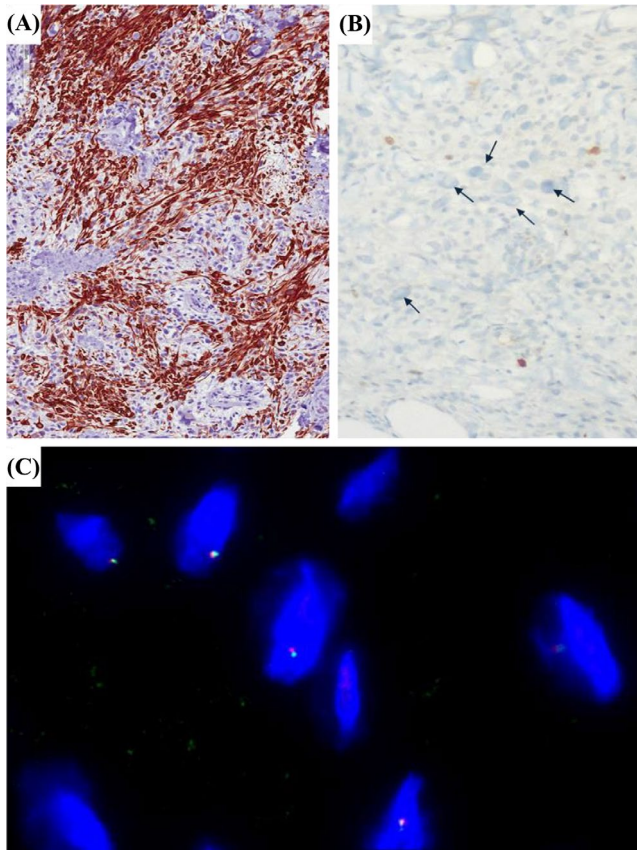


FIGURE 4 Immunohistochemical findings and FISH analysis of the surgically resected specimen. (A) Neoplastic cells were diffusely stained with desmin. (B) Immunohistochemistry for Ki67 revealed a weak proliferative activity with focal and weak staining in 2% of neoplastic cells. Notably, neoplastic cells with bizarre nuclei showed negative staining (arrows). (C) FISH analysis showing monoallelic loss of FOXO1/13q14 loci as indicated by the presence of 1 fusion red/green signal in tumor cells

extensive myxoid stroma” was rendered. The patient is now healthy with no evidence of local recurrence after 3 years of follow-up.

3 | DISCUSSION

With the increasing use of FDG PET/CT in daily practice for staging purposes of patients affected by malignant tumors, there is the possibility to detect unexpected lesions with a variable increased FDG uptake². The breast parenchyma may show focal increased FDG uptake on PET/CT for both malignant and less frequently benign lesions³⁻⁵. We herein report the first case of a histologically proven mammary MFB, incidentally detected by FDG PET/CT. Therefore, radiologists, surgeons, and pathologists must be aware of this possibility when dealing with incidentally detected breast lesions, especially in male patients.

Apart from this uncommon detection, the interest of the present case relies on the unusual morphology of mammary MFB. Diagnosis of classic-type MFB is straightforward if all the morphological features are present⁷⁻⁹: a bland-looking spindle cell

tumor with pushing borders, low mitotic activity (<2 mitoses x 10 HPF), and myofibroblastic immunophenotype. However, potential diagnostic pitfalls may arise when dealing with uncommon morphology, especially in needle core biopsy. The most diagnostically challenging variants are represented by epithelioid/deciduoid cell, myxoid, lipomatous, infiltrating, cellular, fibrous/collagenized, small cell, and palisaded/Schwannian variants, as they could be misinterpreted with several other lesions, including invasive breast carcinoma, desmoid-type fibromatosis, and sarcomas⁷⁻¹³. The presence of mono- or multi-nucleated atypical/bizarre cells has been reported only focally in the context of an otherwise classic-type mammary MFB¹⁴. The present case showed the combination of several unusual morphological features, including polygonal, epithelioid/deciduoid cells, numerous large-sized atypical/bizarre cells, and diffuse myxoid stromal changes. To the best of our knowledge, the combination of all these alarming features, especially the multifocal atypia, has not been reported in mammary MFB so far. We emphasize that such an unusual benign tumor can be misinterpreted as a malignant tumor, especially on core biopsy. In this regard, we rendered a provisional diagnosis of “*atypical mesenchymal tumor of uncertain malignancy*,” emphasizing that the final diagnosis was referred to surgical excision. In the surgical specimen, malignancy could be easily ruled out on the basis of the absence of high mitotic activity, atypical mitoses, and necrosis and the correct diagnosis of MFB was achieved based on the following features: i) tumor with pushing borders; ii) presence of thick, keloid-like collagen fibers interspersed within tumor stroma; (iii) low mitotic activity (<1/50 HPF); and iv) demonstration of fibroblastic/myofibroblastic differentiation (vimentin+, CD34+, desmin+). As commonly observed for other benign soft tissue tumors, such as leiomyoma and schwannoma/neurofibroma, the present case shows that also mammary MFB may exhibit multifocal reactive/degenerative atypia that does not affect prognosis^{15,16}.

4 | CONSENT TO PARTICIPATE

Not applicable.

5 | CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

GA, SS, and AM involved in study design and acquisition of pathological data. GA and GB involved in acquisition of pathological data and writing of the manuscript. GM critically reviewed the manuscript. All authors have read and approved the manuscript.

ETHICS APPROVAL

Not applicable.

DATA AVAILABILITY STATEMENT

All data and material are available.

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REFERENCES

1. El-Galaly TC, Gormsen LC, Hutchings M. PET/CT for Staging; past, present, and future. *Semin Nucl Med*. 2018;48:4-16.
2. Schaaf WE Jr, Patel Z, Retrouvey M, Cunningham TD, Johnson LS. Frequency and clinical relevance of PET/CT incidentalomas. *Abdom Imaging*. 2014;39:657-662.
3. Falomo E, Strigel RM, Bruce R, Munoz Del Rio A, Adejumo C, Kelcz F. Incidence and outcomes of incidental breast lesions detected on cross-sectional imaging examinations. *Breast*. 2018;J24:743-748.
4. Bach AG, Abbas J, Jasaabuu C, Schramm D, Wienke A, Surov A. Comparison between incidental malignant and benign breast lesions detected by computed tomography: a systematic review. *J Med Imaging Radiat Oncol*. 2013;57:529-533.
5. Dunne RM, O'Mahony D, Wilson G, McDermott R, O'Keeffe SA. The role of the breast radiologist in evaluation of breast incidentalomas detected on 18-fluorodeoxyglucose positron emission tomography/CT. *Br J Radiol*. 2013;86:20130034.
6. 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.
7. Howitt BE, Fletcher CD. Mammary-type myofibroblastoma: clinicopathologic characterization in a series of 143 cases. *Am J Surg Pathol*. 2016;40:361-367.
8. Magro G, Salvatorelli L, Puzzo L, et al. Practical approach to diagnosis of bland-looking spindle cell lesions of the breast. *Pathologica*. 2019;111:344-360.
9. Magro G. Mammary myofibroblastoma: an update with emphasis on the most diagnostically challenging variants. *HistolHistopathol*. 2016;31:1-23.
10. Magro G, Salvatorelli L, Spadola S, Angelico G. Mammary myofibroblastoma with extensive myxoedematous stromal changes: a potential diagnostic pitfall. *Pathol Res Pract*. 2014;210:1106-1111.
11. Magro G, Foschini MP, Eusebi V. Palisaded myofibroblastoma of the breast: a tumor closely mimicking schwannoma: report of 2 cases. *Hum Pathol*. 2013;44:1941-1946.
12. Magro G. Epithelioid-cell myofibroblastoma of the breast: expanding the morphologic spectrum. *Am J Surg Pathol*. 2009;33:1085-1092.
13. Magro G, Angelico G, Righi A, Salvatorelli L. Small round cell myofibroblastoma of the oral cavity: a tumor mimicking embryonal rhabdomyosarcoma. *Pathol Res Pract*. 2018;214:463-465.
14. Magro G, Amico P, Gurrera A. Myxoid myofibroblastoma of the breast with atypical cells: a potential diagnostic pitfall. *Virchows Arch*. 2007;450:483-485.
15. Oliva E. Practical issues in uterine pathology from banal to bewildering: the remarkable spectrum of smooth muscle neoplasia. *Mod Pathol*. 2016;29(Suppl. 1):S104-S120.
16. Rodriguez FJ, Folpe AL, Giannini C, Perry A. Pathology of peripheral nerve sheath tumors: diagnostic overview and update on selected diagnostic problems. *Acta Neuropathol*. 2012;123:295-319.

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