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Case Report

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Invasive lobular carcinoma of the breast metastasizing to the lesser pelvis. part I: urinary bladder and uterine cervix

Abstract

Background: The breast malignancy currently termed invasive lobular carcinoma has heterogeneous clinical, imaging and histopathologic features. It frequently metastasizes to the soft tissues of distant organs and has one of the highest fatality rates of all breast cancers.

Case presentation: This report describes two cases of fatal breast cancers representing two separate subtypes of invasive lobular carcinoma that spread to the lesser pelvis. The clinical and mammographic findings were striking in the first case, in which the classic form of the malignancy subsequently metastasized to the urinary bladder and later to the lumbar spine and pleura, but the immunohistochemical biomarkers (ER/PR positive, HER2 negative, Ki67 7%) did not predict the poor patient outcome. In the second case the unexpected microscopic findings from the uterine cervix prompted examination of the breasts, where the disease was occult at imaging. Microscopic examination of the bilaterally pathologic axillary lymph nodes confirmed the diagnosis of the solid form of invasive lobular carcinoma.

Conclusion: These two fatal breast cancer cases represent two different subtypes of extensive malignancies metastasizing to distant organs and having a high fatality rate. These metastases can appear in uncommon locations, as in these two cases, making determination of the true origin of the primary tumour a complex task. Thorough analysis of the histopathology findings of the metastases combined with the IHC biomarkers helped determine the site of the primary tumour. Although necessary for this determination, the same IHC biomarkers fail to predict the poor long-term outcome. Instead, the IHC biomarkers indicate a favourable prognosis and provide deceptive information for management guidance.

Key words: Invasive lobular carcinoma, breast cancer metastases, breast cancer of mesenchymal origin, large format histopathology

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Abbreviations: ILC, Invasive lobular carcinoma; BCMO, breast cancer of mesenchymal stem cell origin (proposed by the authors based on published cell culture studies); MLO, mediolateral oblique projection; CC, craniocaudal projection; H&E, hematoxylin-eosin staining; US, ultrasound; IHC, immunohistochemical biomarkers; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; Ki67, proliferation index

Introduction

The diagnosis of "invasive lobular carcinoma" (ILC) is given to a diverse group of malignancies having a wide range of clinical findings, imaging presentations, histopathology and long-term patient outcome, each with its own subgroup terminology, such as classic, solid, tubulo-lobular, alveolar, and pleomorphic. The World Health Organization (WHO) Classification of tumours specifically lists ILC as an epithelial tumour of the breast, originating from the epithelial cells of the milk-producing terminal ductal-lobular unit, TDLU).[1,2] Our research data from a cell culture study challenges the WHO's assumption and has provided evidence that classic ILC has its origin in the pluripotent hybrid stem cells of the mesenchyme.[3] These data combined with divergent clinical, imaging, histopathologic findings have prompted us to suggest a terminology, indicating a breast cancer of mesenchymal stem cell origin, BCMO.[3-6]

The first case of this report is an example of classic ILC. The breast cancer subtype diagnosed as invasive lobular carcinoma, solid type, has a vastly different histopathological and imaging presentation and may indeed have its site of origin in the epithelial cells of the breast lobule. This breast cancer subtype is the subject of our second case.

First case:

This 62-year-old woman presented with a self-detected diffuse thickening in the lateral half of her left breast. She had not participated in mammography screening during the previous eight years. Clinical breast examination confirmed the presence of extensive, firm thickening with retraction of the nipple-areola complex and numerous palpable axillary nodes. Mammography revealed extensive architectural distortion confirming the clinical findings and demonstrated retraction of the underlying pectoral major muscle (Figures 1,2). Following hand-held ultrasound examination and US-guided 14G-core needle biopsy, mastectomy was performed. The mastectomy slices were examined using large format thin section histopathology. The final histopathology report was a 65x60 mm moderately differentiated classic invasive lobular carcinoma. The tumour-free margin was only one mm from the chest wall. IHC biomarkers: ER/PR positive, HER2 negative, Ki67 7%. There was extensive lymph vessel invasion with five axillary lymph node metastases (pN 5/5) diagnosed (Figure 3).

Follow-up: The patient received chest wall radiation and hormonal therapy. Five years after mastectomy the patient was diagnosed with distant metastases to the urinary bladder, lumbar spine and pleura (Figures 4,5).

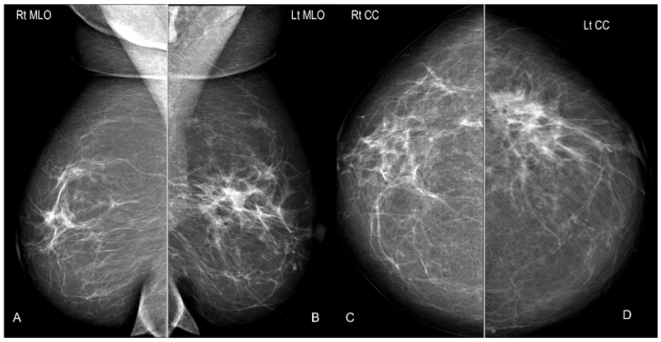


Figure 1 Bilateral MLO (A,B) and CC (C,D) projections. Unusually *extensive architectural distortion* with no associated microcalcifications between the chest wall and the areola of the left breast, the characteristic imaging biomarker of breast cancer of mesenchymal stem cell origin (aka classic ILC).

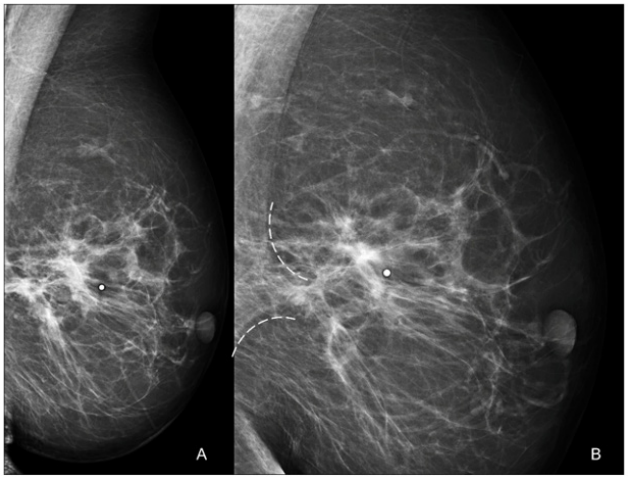
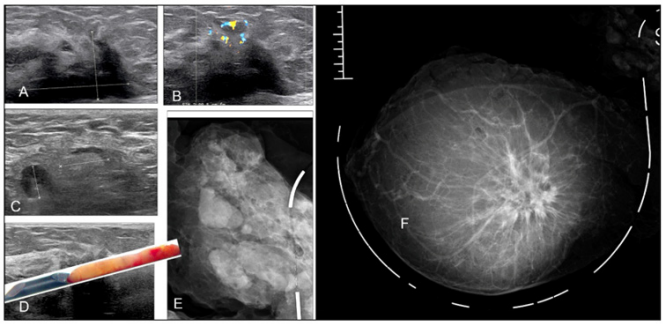
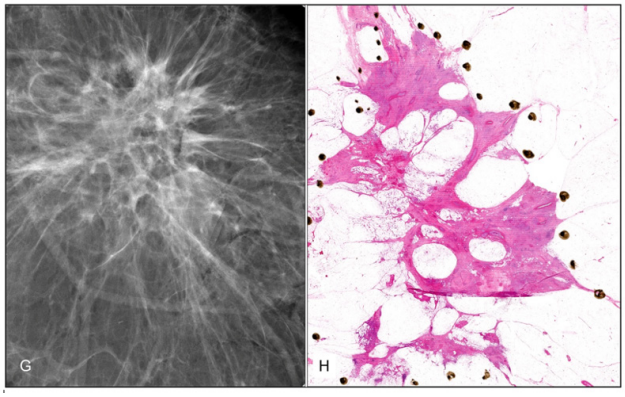
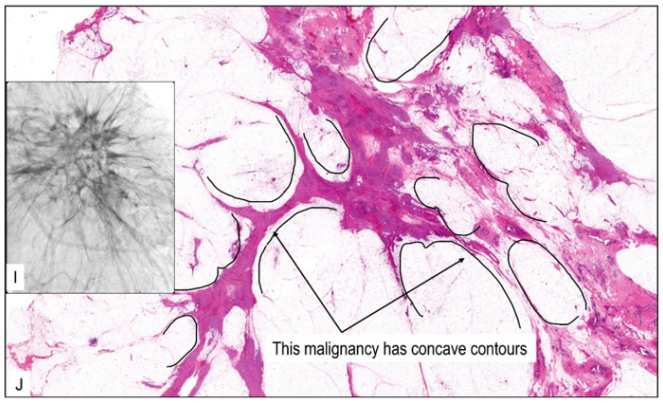
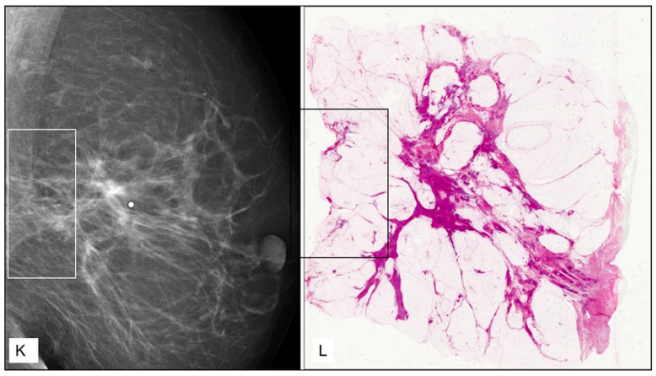


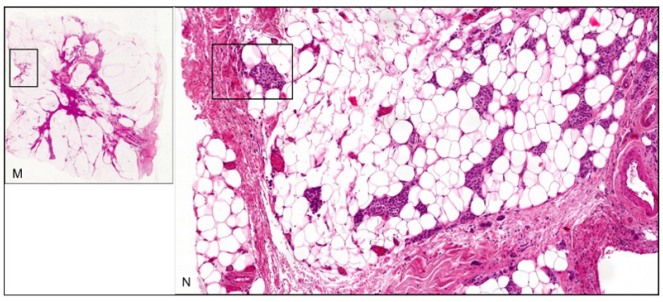
Figure 2 Left latero-medial horizontal projection (A) and with microfocus magnification (B). Extensive malignancy causes a tent-like retraction of the underlying pectoral major muscle, which can also be provoked at clinical examination.

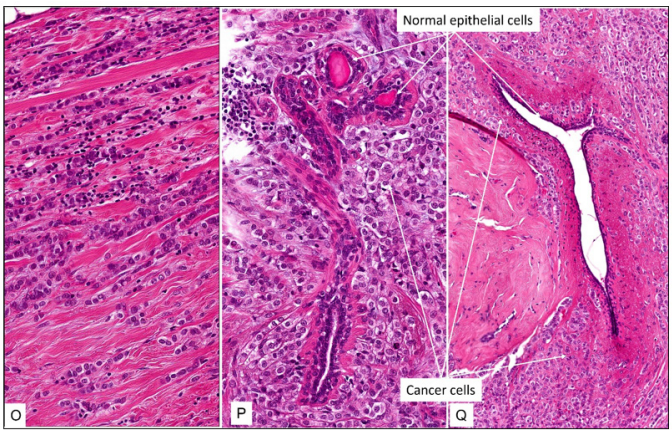












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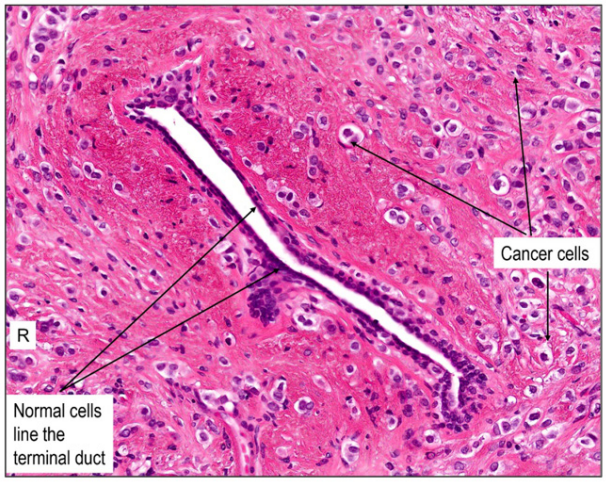

Figure 3 Hand-held ultrasound (A,C), Doppler (B) and US-guided 14G core biopsy (D). Specimen radiograph of the surgically removed pathologic axillary lymph nodes (E). Mastectomy specimen radiograph (F). Microfocus magnification specimen radiographs (G,I) show the imaging biomarker, extensive architectural distortion of this diffusely infiltrating tumour. The large format thin section histopathology images correlated with the sliced specimen radiographs (H,J) show the morphologic basis for the spiderweb-like structure of the mammographic images, including the concave tumour interface with the surrounding adipose tissue. The histopathology report claims a one mm free posterior margin toward the chest wall, although correlation with the mammogram indicates more extensive tumour involvement of the chest wall (K-N). The high-power histopathology image (O) shows tumour cells in single files between the newly formed excess of fibrous tissue. The epithelial cells lining the terminal duct and acini (P) and a subsegmental (Q) and terminal (R) duct are all normal.

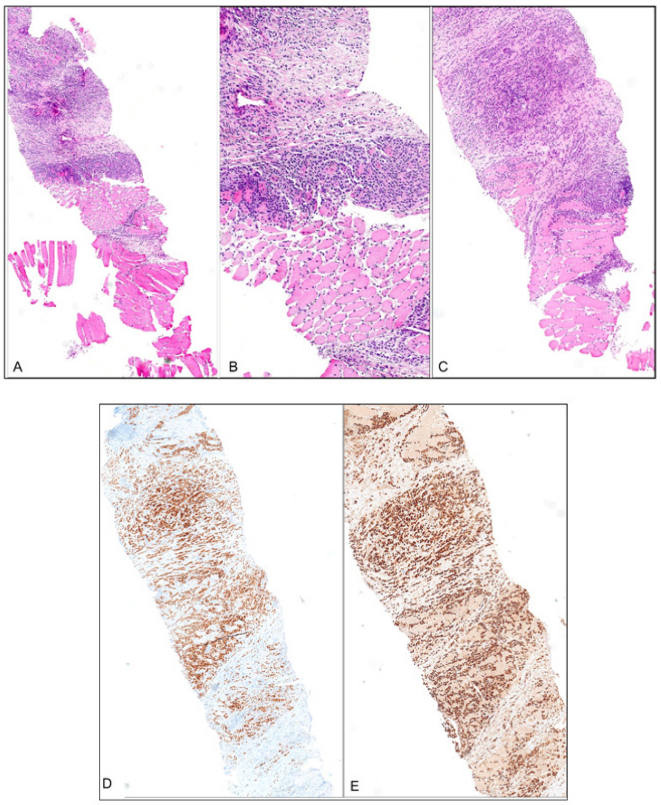

Figure 4 H&E staining of the musculoskeletal metastases in the lumbar spine (A-C). IHC biomarkers: ER positive (D), GATA3 positive (E).

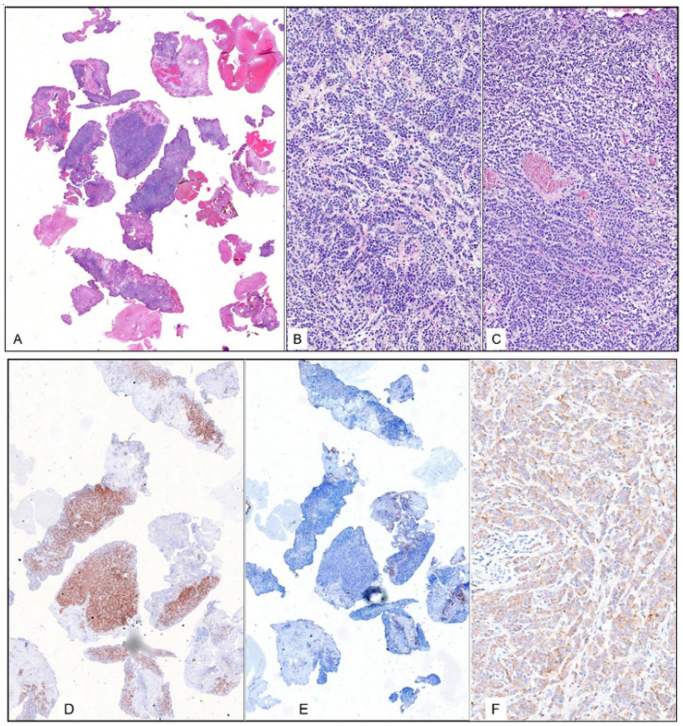

Figure 5 Low- and intermediate power histopathology images of the surgically removed ILC metastases from the urinary bladder (A-C). IHC findings: ER positive (D), PR negative (E) and HER2 negative (F). The histologic and IHC findings confirm the ILC origin of these distant metastases.

Outcome: Six years after diagnosis and treatment for ILC the patient died from disseminated breast cancer of extralobular mesenchymal hybrid stem cell origin (BCMO), officially termed ILC.

Second Case:

A 55-year-old woman presented with abdominal pain and abnormal uterine bleeding. She underwent surgical biopsy of the uterine cervix. Histopathologic examination of the specimen revealed metastases from invasive lobular carcinoma of the breast (Figures 6–10).

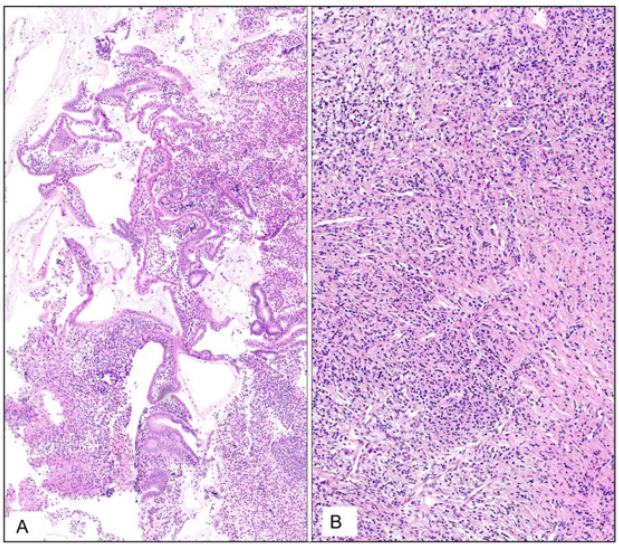

Figure 6 H&E staining of the surgical biopsy tissue specimen from the uterine cervix shows invasive lobular carcinoma of the breast.

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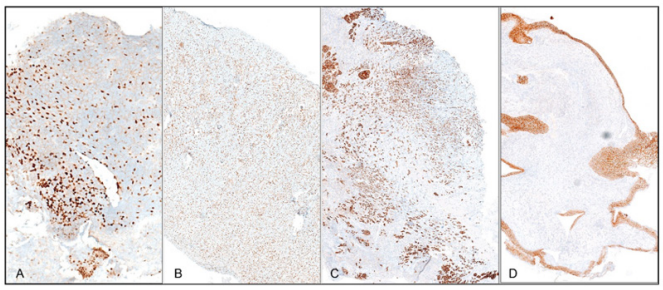

Figure 7 Immunohistochemical biomarkers of the uterine cervix biopsy specimen: ER (A) and PR (B) positive, CAM 5.2 (C) positive, E-cadherin (D) negative.

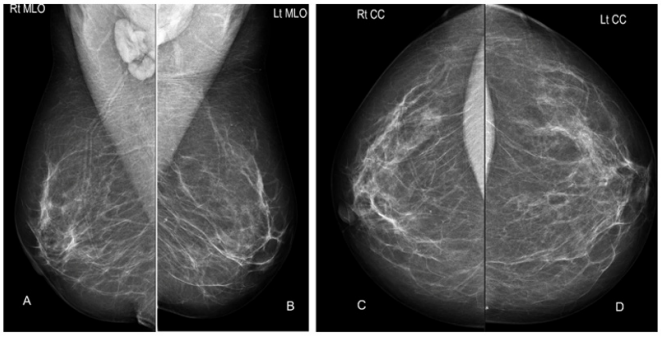

Figure 8 MLO (A,B) and CC (C,D) mammograms: bilateral pathologic axillary lymph nodes. There were no suspicious findings in the breast parenchyma at mammography, nor any change from previous mammograms. Clinical breast examination and breast ultrasound revealed no abnormalities in the breasts.

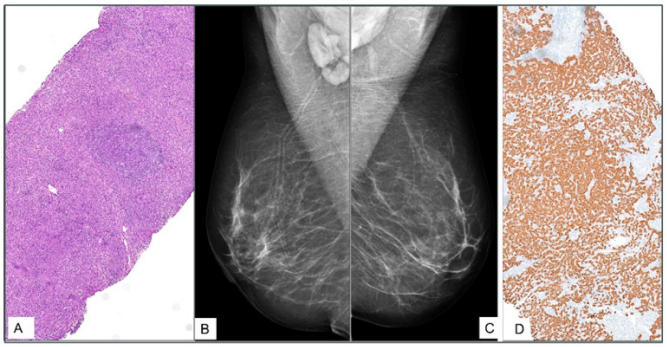

Figure 9 Histopathology of the 14G core needle biopsy from the right axillary node, H&E staining (A). MLO mammograms show the bilateral pathologic axillary lymph nodes (B,C). Histopathology of the 14G core needle biopsy from the left axillary node, ER staining (D). Microscopic examination of the pathologic axillary lymph nodes shows the solid form of invasive lobular carcinoma in both axillae.

Follow-up: No further operative procedures were performed. Thirteen months after diagnosis the patient developed liver metastases.

Discussion

Invasive lobular carcinoma (ILC) of the breast is generally considered to arise from the epithelial cells of lobular acini of the breast.[1,2] This theory has evolved from two speculative articles published by Foote and Stewart during the 1940s, [7,8] and accepted without verification. [9-12] However, this prevailing theory fails to account for the unusually poor, 60% long-term survival of patients with the classic form of ILC, a survival that has not improved during the past half century.[4-6,13,14] Additionally, the imaging presentation is unusual and there is a lack of clear morphologic evidence for a lobular epithelial origin. These contradictions have caused our research group to question the prevailing theory and search for a more evidence-based site of origin.[3,4,15] Our cell culture studies indicated a site of origin in the hybrid-pluripotent mesenchymal stem cells. "… the low proliferative capacity of the cultured cells is in line with the low expression of the Ki67 proliferation marker observed in all the investigated tumour tissues. Our results suggest that this malignancy contains epithelial–mesenchymal hybrid cells capable of initiating a tumour-forming process. In addition to the unusual clinical, imaging, and histopathologic aspects of diffusely infiltrating breast cancer, these cell culture findings also fail to support the current assumption that this breast cancer subtype has its origin in the epithelial cells of the breast lobules".[3]

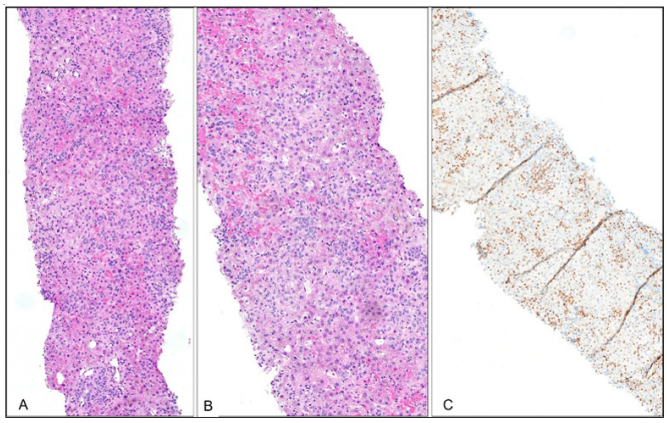

Figure 10 Core needle biopsy (14G) of the liver metastases, H&E staining (A,B), positive ER staining (C).

Outcome: 18 months after diagnosis and initiation of conservative treatment, the patient died from metastases of the solid form of invasive lobular carcinoma.

Conclusion

Mammographic detection of classic invasive lobular carcinoma can be difficult due to the lack of a central tumour mass and microcalcifications. Its structure consists of alternating layers of newly formed fibrous tissue and discohesive cancer cells that appear on pathology slides as single files. It does not form discrete masses and is usually imperceptible at mammography until becoming palpable at a size of several centimetres. There is cell culture evidence that this classic form originates from pluripotent hybrid stem cells of the mesenchyme, for which our suggested terminology is breast cancer of mesenchymal stem cell origin. On the other hand, the solid form of invasive lobular carcinoma forms discrete, often multifocal spherical masses and is generally detectable mammographically before becoming palpable, making our second case unusual in being occult at mammography. These cases represent two of the most challenging breast cancer subtypes. The immunochemical biomarkers, while being very helpful for determining the origin of the distant metastases, provide a deceptively favourable prognosis that may compromise patient management.

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Conflict of interest

The authors declare that they have no competing interests.

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