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Case Report

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The association of classic invasive lobular carcinoma of the breast with gastrointestinal malignancies

Abstract

Background: Classic invasive lobular carcinoma is one of the most poorly understood breast malignancies. Many features make it an outlier among other breast cancers. The characteristic physical examination finding is diffuse thickening rather than a focal tumour mass. Deformation can be extreme, including shrinkage of the breast. This malignancy is usually occult at mammography until it reaches the size of several centimetres. Breast ultrasound is more sensitive due to the excessive, newly formed fibrous connective tissue. The dissemination pattern is variable, and metastases may be found in unusual sites. The efficacy of treatment has not improved during the past decades despite the development of new therapeutic agents, with long-term patient survival remaining in the range of 60-70%. The long-held assumption that this malignancy arises from the epithelial cells of the breast lobules has hindered progress in our understanding of this complex disease.

Case presentation: The chosen cases describe diffusely invasive lobular carcinoma associated with gastrointestinal malignancies that may be synchronous or asynchronous in random order of appearance. Patients with bilateral classic invasive lobular carcinoma are at risk of developing linitis plastica in the stomach, and correspondingly, patients with linitis plastica are at risk of developing classic invasive lobular carcinoma of the breast.

Conclusion: Close cooperation among the organ-based cancer teams is necessary when bilateral classic invasive lobular carcinoma develops in the breasts, either synchronously or asynchronously, or when linitis plastica of the stomach is diagnosed. These patients should receive CDH1 gene testing, and cases testing positive should undergo annual surveillance using multimodal diagnostic methods. Most importantly, the mesenchymal pluripotential stem cell aspects of this breast disease, combined with cell culture results, should question the accepted assumption that it has a lobular epithelial origin.

Key words: breast cancer, invasive lobular carcinoma, BCMO (breast cancer of mesenchymal pluripotent hybrid stem cell origin), linitis plastica, gastrointestinal cancer, gene damage, MET (mesenchymal-epithelial transition), CDH1 gene mutations

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Abbreviations: AI, artificial intelligence; ILC, invasive lobular carcinoma; BCMO, breast cancer of mesenchymal pluripotent hybrid stem cell origin; MLO, mediolateral oblique projection; CC, craniocaudal projection; IHC, immunohistochemical; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; Ki67, proliferation index; LVI, lymph vessel invasion; TDLU, terminal ductal lobular unit; MET, mesenchymal-epithelial transition; CDH1 (Cadherin 1) gene

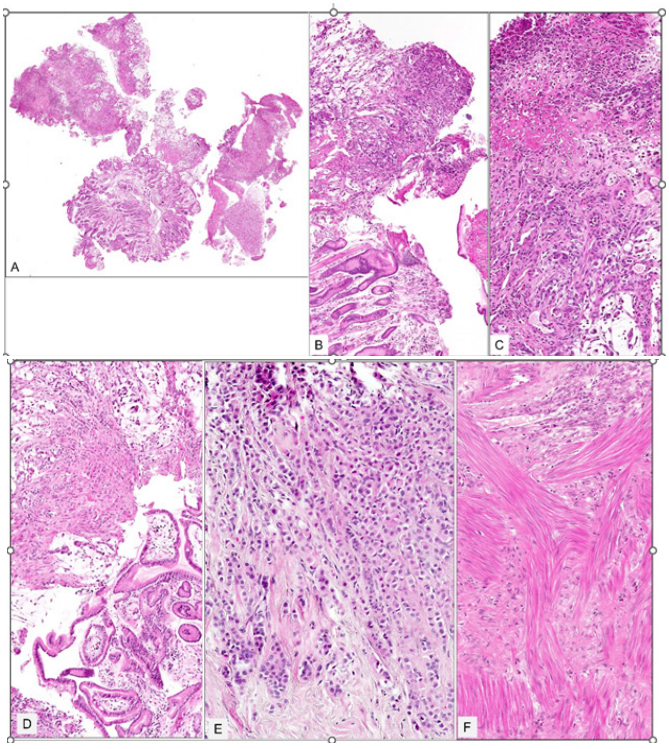
Introduction

The diagnosis and treatment of classic invasive lobular carcinoma of the breast is considerably challenging,[1] becoming further exacerbated if a second or third associated malignancy develops. Contrary to its diagnostic terminology, cell culture evidence has indicated a mesenchymal stem cell origin of this pseudo-epithelial malignancy, accounting for its unusual clinical, imaging, histopathologic, immunohistochemical and outcome characteristics. The results of our cell culture study suggest replacing the term classic invasive lobular carcinoma with the term breast cancer of mesenchymal stem cell origin (BCMO).[2–4]

Case presentations

Case 1

This patient had surgery for stomach cancer (linitis plastica) at the age of 60 (Figure 1).



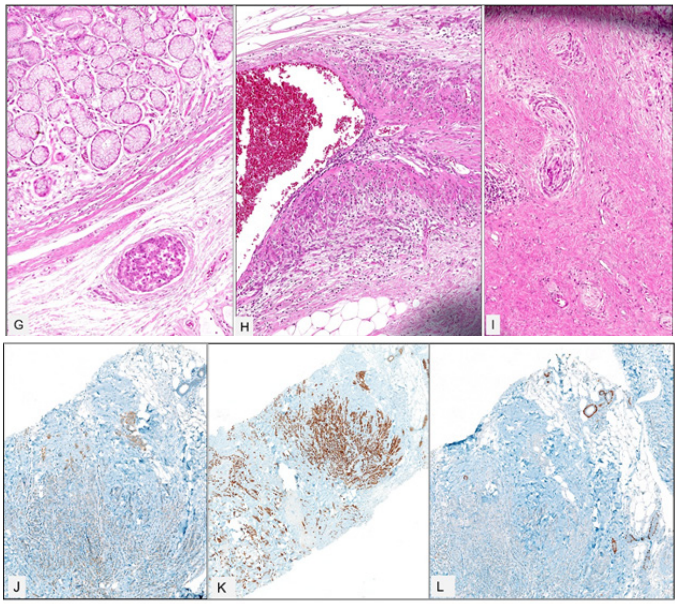


Figure 1 Low-power (A-D,F) and higher-power (E) histopathology images of the stomach cancer diagnosed two years before the diagnosis of her breast malignancy. Muscle invasion (F), vascular invasion (G,H) and perineural invasion (I). Immunohistochemical biomarkers: HER2 (J), CAM 5.2 (K), p63 (L).

Two years later, she felt a thickening in the upper-inner quadrant of her left breast. Corresponding to the palpatory finding the mammograms showed extensive non-calcified architectural distortion. Hand-held ultrasound (US) examination and breast magnetic resonance imaging (MRI) confirmed the palpatory findings and the imaging diagnosis of a malignant breast disease. Her screening mammograms 16 months earlier did not show any abnormal lesion (Figures 2-7).

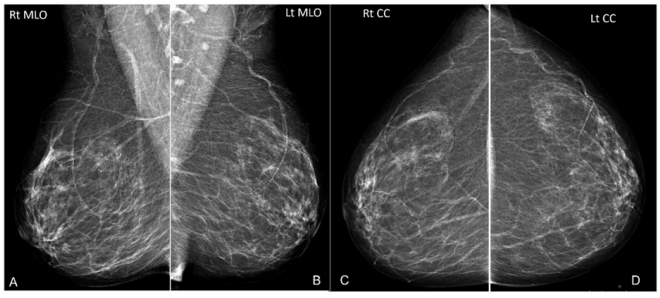


Figure 2 Medio-lateral oblique (MLO) projections (A,B) and cranio-caudal (CC) projections (C,D) at the first examination: nearly entirely fatty replaced breasts, normal mammograms.

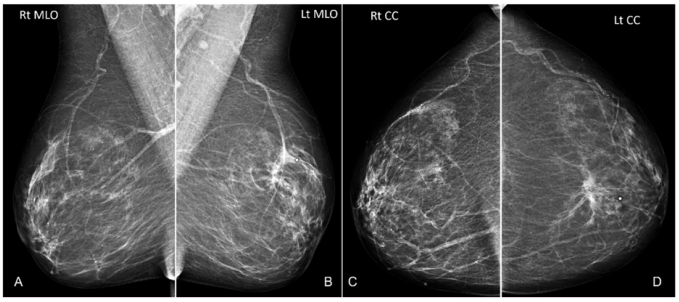


Figure 3 MLO (A,B) and CC projections (C,D) sixteen months later. There is non-calcified architectural distortion measuring several cm in extent corresponding to the palpable thickening in the upper-inner quadrant of the left breast.

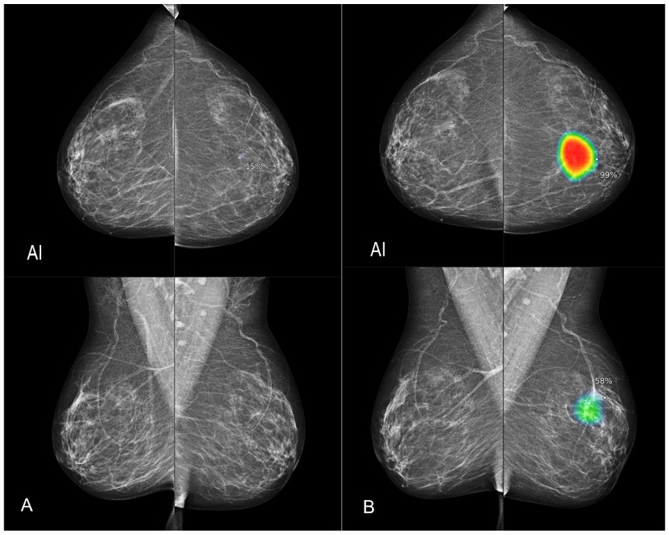


Figure 4 An artificial intelligence algorithm did not detect any abnormality on the previous mammograms (A) but flagged the extensive abnormality sixteen months later (B).

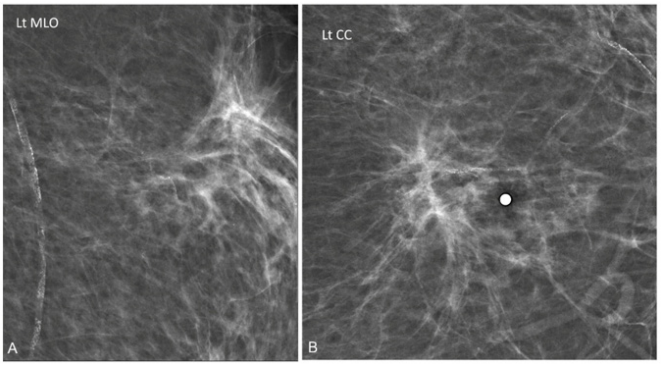


Figure 5 Microfocus magnification mammograms, MLO (A) and CC projections (B) show the spider web-like architectural distortion with no central tumour mass or microcalcifications, a characteristic imaging biomarker of diffuse breast cancers of mesenchymal stem cell origin (BCMO).

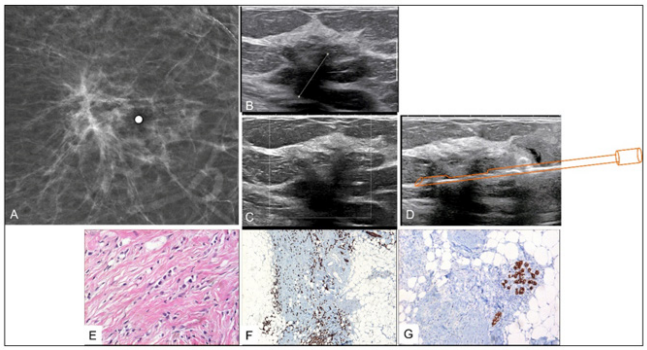


Figure 6 Microfocus magnification image, CC projection (A). Hand-held US images (B,C) and 14G core biopsy (D). Histologic examination of the 14G core biopsy specimen (E) shows breast cancer of mesenchymal stem cell origin (BCMO, aka ILC), ER positive (F) and E-cadherin negative (G).

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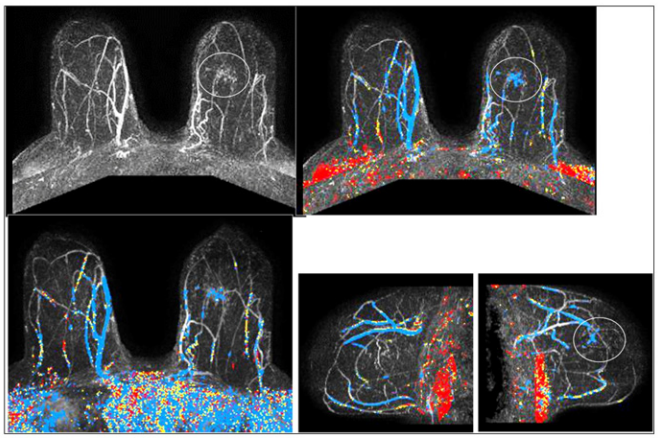
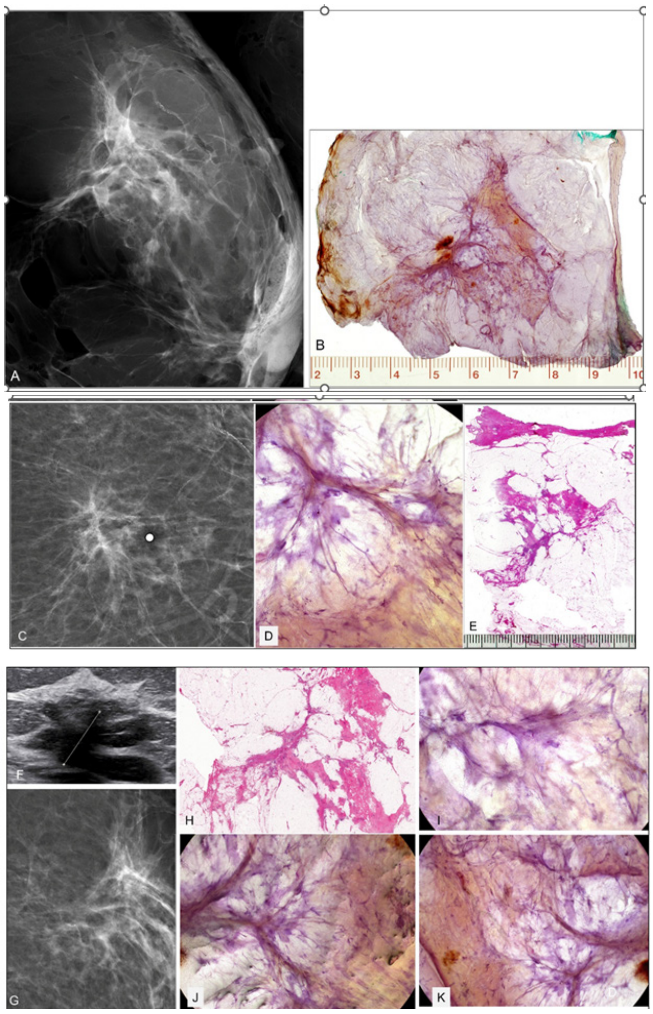


Figure 7 Breast MRI examination demonstrates the presence of the pathologic lesion, but the MRI extent of the tumour is smaller than on the mammograms or on ultrasound examination.

The patient's breast malignancy was resected with a 25 mm clear margin. The histopathology report described a 62x42 mm moderately differentiated diffusely infiltrating breast cancer of mesenchymal stem cell origin (BCMO, aka ILC) associated with lobular carcinoma in situ (LCIS). IHC biomarkers: ER/PR positive, Her-2 negative, Ki67 16 %. No LVI. pN: one sentinel node with isolated cancer cells. See Figure 8.



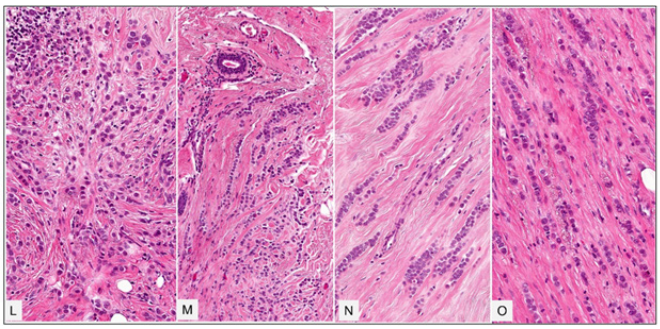


Figure 8 Breast imaging (A,C,F,G), large format thick (B,D,I-K) and thin (E,H) section histopathologic image collage of this diffusely infiltrating breast cancer of mesenchymal stem cell origin. Cellular details of the microscopic examination findings show single files of the malignant cells and the excess amount of fibrous connective tissue (L-O).

Outcome: Two years after her breast cancer diagnosis and initiation of treatment, the patient died from her disseminated gastrointestinal malignancy, linitus plastica.

Case 2

An 88-year-old woman presented with a self-detected tumour in the upper portion of her left breast. Clinical breast examination confirmed the presence of a 2-3 cm firm tumour mass, shown at mammography as a non-calcified asymmetric density. Clinical and US examination of the left axilla showed no abnormal axillary lymph nodes (Figures 9,).

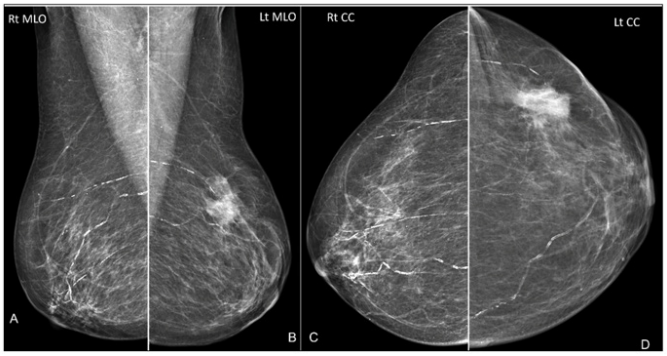


Figure 9 MLO (A,B) and CC (C,D) mammograms. Non-calcified asymmetric density with slight architectural distortion is seen in the upper-outer quadrant of the left breast. The overlying skin is retracted and thickened.

The patient underwent mastectomy (Figure 11). **Histopathologic diagnosis:** There was a 25x15 mm unifocal, moderately differentiated invasive breast malignancy of intralobular mesenchymal stem cell origin. Perineural infiltration. IHC biomarkers: ER/PR positive, HER2-negative, E-cadherin negative, Ki67 12%. No LVI. pN 0/8.

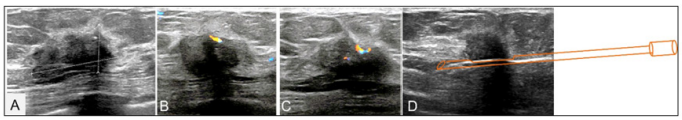


Figure 10 Hand-held US and Doppler (A-C) support the diagnosis of a malignant tumour. Ultrasound guided 14G core biopsy (D). The histologic diagnosis of the 14G core specimen was breast cancer of mesenchymal stem cell origin (BCMO, aka ILC).

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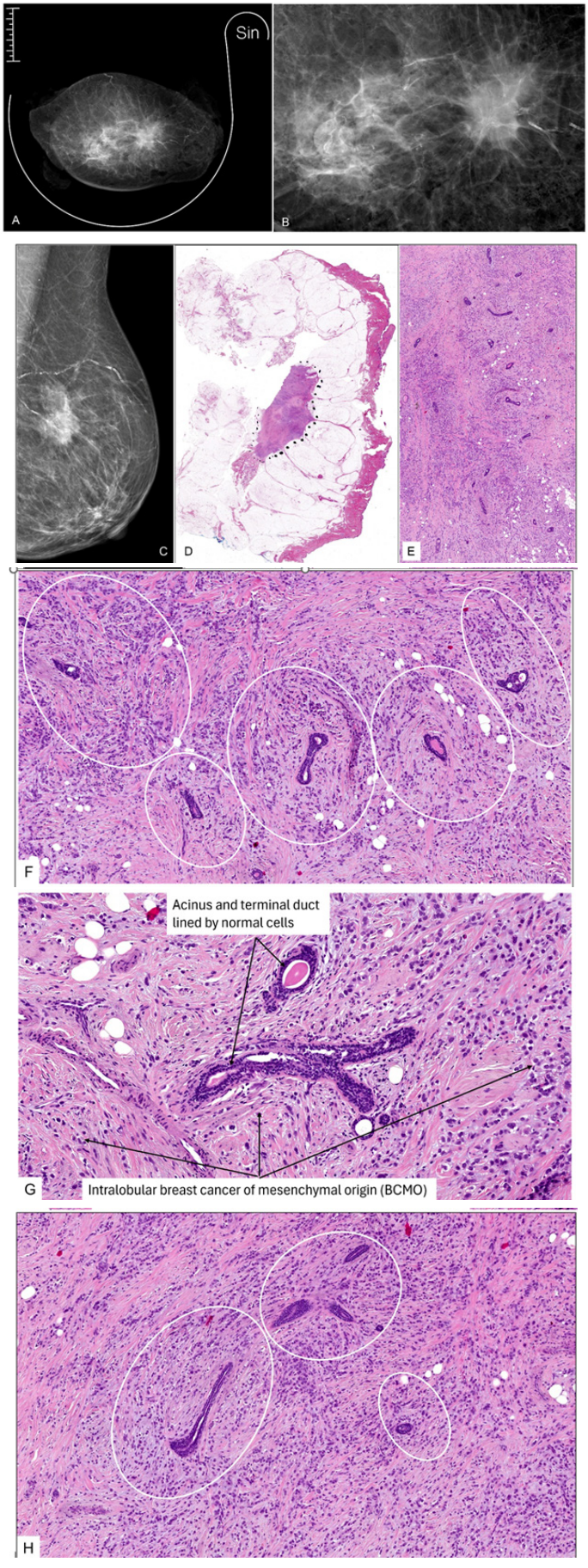


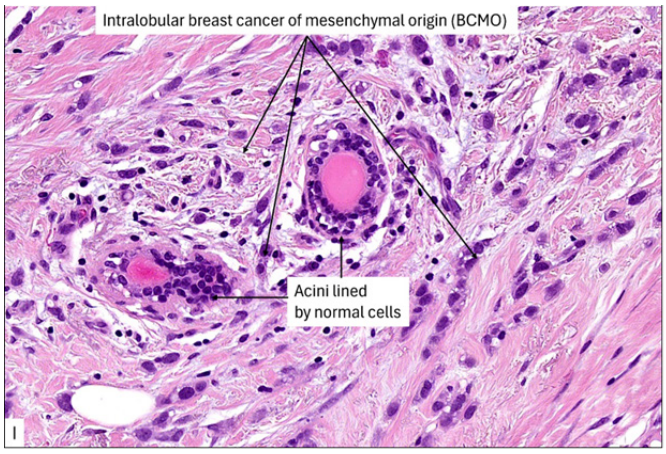


Figure 11 Mastectomy specimen radiograph without (A) and with microfocus magnification (B). The non-calcified tumour mass appears to be unifocal. Left breast, latero-medial horizontal mammogram (C) compared with the low-power large format histopathologic image (D). Intermediate-power histopathology reveals numerous foci of intralobular breast cancer of mesenchymal stem cell origin (intralobular BCMO) (E). Higher-power histology images (F-I) illustrate the characteristic features of intralobular BCMO colonies: normal epithelial cells line the acini and the terminal ducts, surrounded by cancer cells of mesenchymal stem cell origin.

Follow-up

Seventeen months after mastectomy, the patient was diagnosed with a stomach malignancy, which infiltrated diffusely with a dense fibrous stroma. The IHC biomarkers showed values identical to those seen in her breast cancer (Figures 12,13).

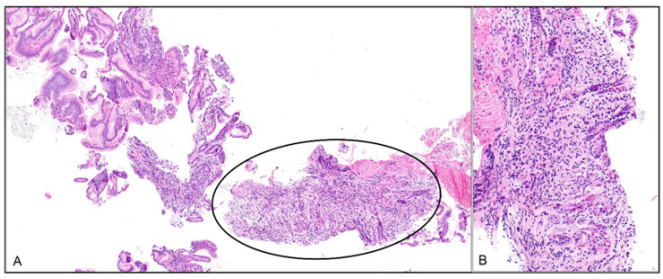
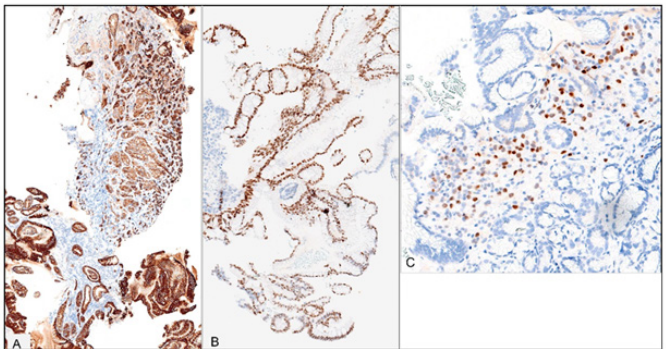


Figure 12 Normal stomach mucosa (left) associated with malignant cells (encircled) (A). Intermediate-power image (B) of the encircled region on Fig.A.



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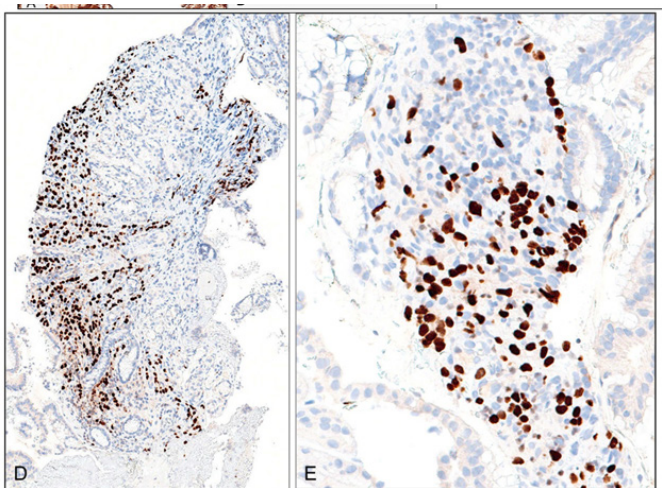

Figure 13 A collage of immunohistochemical biomarkers from the stomach. CAM2 staining (A), CDX2 staining (B), ER staining (C) and GATA3 staining (D,E) demonstrate a breast cancer origin.

Patient outcome

Nineteen months after her breast cancer diagnosis and treatment and two months after diagnosis of breast cancer metastases to the stomach, the patient died from breast cancer of intralobular mesenchymal stem cell origin (BCMO).

Discussion

Analysis of the histopathologic images of ILC challenges the assumption that the disease called "classic invasive lobular carcinoma" has its origin in the luminal epithelial cells of the acini of the TDLU.[1–7] In intralobular BCMO cases the E-cadherin negative malignant cells encircle the normal, E-cadherin positive epithelial cells lining the terminal ducts and acini in a targetoid pattern, indicating that these are two distinct cell populations with separate developmental origins.[6] The normal, pre-existing luminal epithelial cells remain distinctly separate from the surrounding malignant BCMO cells, which remain in the intralobular mesenchyme and appear to have originated from the pluripotent mesenchymal stem cells through the process of mesenchymal-epithelial transition (MET). During this transition they acquire pseudo-epithelial morphology, while remaining fundamentally mesenchymal.[6,8] Our cell-culture study demonstrated the transition of pluripotent hybrid stem cells to epithelial-like E-cadherin negative cells.[2] The E-cadherin negativity could be related to a mesenchymal stem cell origin, rather than to a purported "loss" of the CDH1 gene expression. However, approximately 1/3 of the diffuse invasive lobular carcinoma cases lack the CDH1 gene damage,[9] indicating that CDH1 gene suppression cannot be an obligate precursor of ILC/BCMO. According to the literature, the E-cadherin loss is a tumour suppressor defect in the epithelial cells.[1] Our research results suggest that the cancer cells did not originate from the preexisting epithelial cells; instead, the transformation of the pluripotential stem cells of mesenchymal origin results in pseudo-epithelial cells, consequently the E-cadherin positivity should not be expected. Further information concerning the cellular site of origin could be obtained through spatial transcriptomics.

Extensive research has been carried out on the hereditary stomach and invasive lobular breast cancer cases, focusing on the CDH1 damage in the affected families. In these hereditary cases the strikingly similar microscopic images in both breast and stomach cancer raises the suspicion that CDH1 gene damage can be responsible for the similar multiorgan malignancies. The CDH1 gene damage and the E-cadherin negativity are not necessarily involved in tumorigenesis but are related to the metastatic potential of this malignancy. To draw attention to the evidence supporting a mesenchymal origin of this disease, and the lack of evidence supporting a lobular epithelial origin, we have proposed the terminology of intralobular breast cancer of mesenchymal stem cell origin, intralobular BCMO.[4]

Conclusion

Stem cells are resistant to chemotherapy and radiation, and the current research efforts try to view the BCMO resistance as a problem to be solved. So long as the classic invasive lobular carcinoma (BCMO) is considered an epithelial malignancy,[1] current therapy is not going to result in improved survival, since a high fatality is exactly what one might expect when a malignancy of stem cell origin is treated with therapeutic regimens developed for treating epithelial malignancies. The unchanged poor survival during the past decades provides evidence that the oncologists have been treating a misunderstood cell type with the wrong therapeutic strategy. This is not a treatment challenge; instead, it is a sign that the disease classification itself was wrong.

Acknowledgments

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Conflict of interest

The authors declare that they have no competing interests.

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