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Case Report

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Invasive lobular carcinoma of the breast metastasizing to the lesser pelvis. part II: mesenteric, skeletal, perianal and appendiceal metastase

Abstract

Background: The classic invasive lobular carcinoma often spreads to distant organs, causing high disease specific fatality. We have published case reports where this special subtype of breast malignancy gave metastases to the urinary bladder and to the uterine cervix. This case report is a description of widespread dissemination of classic invasive lobular carcinoma of the breast to the perianal region and to the appendix.

Case presentation: This Case report describes multimodality imaging and detailed histopathologic workup of the diffusely disseminating classic invasive lobular carcinoma in a 67-year-old woman. CT examination of the thorax and abdomen revealed extensive metastases to the abdomen and skeleton with the primary tumour subsequently discovered in the left breast. Two years after diagnosis the dissemination continued to unusual sites such as the perianal region and, an additional seventeen months later, the appendix. The comprehensive workup of this unfortunate case has valuable teaching points.

Conclusion: Classic invasive lobular carcinoma is a breast cancer subtype that is difficult to detect at mammography screening, that defies current therapeutic regimens, and which has the worst patient outcome of all breast cancers. Our cell-culture study offers a possible explanation for this high fatality rate by providing evidence that this breast malignancy does not have its origin in the luminal cells of the breast lobules, but rather an origin in the pluripotent stem cells of the extralobular mesenchyme. This new evidence can account for the special features seen at clinical breast examination, imaging, large format histopathologic examination, and long-term patient outcome of this extensive, diffuse malignancy. It is past time for the medical community to acknowledge its failure to improve the poor outcome of these patients and begin a dedicated search for new therapeutic agents designed for efficacy against breast cancers originating from pluripotential hybrid stem cells in the mesenchyme.

List of abbreviations: CT, computer tomography; AI, artificial intelligence; ILC, invasive lobular carcinoma; BCMO, breast cancer of mesenchymal stem cell origin; H&E, haematoxylin-eosin staining; IHC, immunohistochemical biomarkers; MLO, medio-lateral projection; CC, craniocaudal projection; ER, estrogen receptor; PR, progesterone receptor; HER2; human epidermal growth factor receptor2

Volume 17 Issue 3 - 2026

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Received: May 21, 2026 | **Published:** June 09, 2026

Introduction

Breast malignancies, each with one of the following three imaging biomarkers: extensive architectural distortion, stellate tumour mass, and circular/spherical, often multifocal tumours, each with no associated calcifications, are all given the same histopathologic diagnostic term of "invasive lobular carcinoma" (ILC).[1–6] Since the mammographic appearance (imaging biomarker) of a breast tumour is a reflection of its underlying subgross histopathology, and also directly related to the patient's long-term outcome, we suggest using diagnostic terminology reflecting the site of origin of each individual tumour.[2]

The underlying histopathology of cases termed classic ILC and having the imaging biomarker of *extensive, non-calcified architectural distortion* is characterized by the excess amount of newly formed fibrous strands (accounting for the diffuse, firm thickening at physical breast examination) and by the malignant cells, appearing on the pathology slides as single rows or files, although in three dimensions the malignant cells and the fibrous tissue occur in alternate layers.[3] Our cell culture study has shown that these malignant cells have been transformed from the pluripotent hybrid stem cells of the mesenchyme.[7] This subgroup does not originate from the epithelial cells of the lobular acini as those are always normal in this malignancy, rendering the term invasive "lobular" carcinoma anatomically incorrect. The cell culture study has provided evidence that this highly fatal breast malignancy originates from the pluripotent hybrid stem cells of the extralobular mesenchyme. For this reason, we have proposed the term breast cancer of hybrid stem cell origin (BCMO).[2,3,7]

The underlying histopathology of cases having the imaging biomarker of *multilobulated spherical tumours* indicates an origin in the epithelial cells of the acini. For this subgroup, the histopathologic term "solid form of invasive lobular carcinoma" is correct.

The third imaging biomarker, a *stellate tumour mass* on the mammogram, most frequently measuring 1-19 mm in size, appears to originate from the pluripotent hybrid stem cells of the intralobular mesenchyme.[4,8] Each mammographically detectable tumour mass consists of an aggregate of multiple colonies of intralobular BCMO. The long-term survival of cases ≥20 mm in size is significantly better than survival of cases of extralobular BCMO.

The case presented in this article demonstrates the full malignant potential of the extralobular, diffusely infiltrating BCMO.

Case presentation

A 67-year-old woman was admitted to the hospital's emergency unit in poor general condition. Computed tomography (CT) of the abdomen revealed diffuse abdominal carcinosis, which also infiltrated the retroperitoneal adipose tissue and compressed the inferior vena cava and ureters, causing bilateral hydronephrosis. CT of the thorax detected diffuse densities in the left breast and left axilla, leading to the suspicion of a diffusely infiltrating breast cancer (Figure 1). Extensive sclerotic and lytic metastases were demonstrated in the pelvic bones and vertebral column (Figures 1,2). The patient was referred to the Department of Mammography for assessment of the finding. She had previously undergone bilateral breast reduction surgery, which left numerous scars, making interpretation of the mammograms challenging (Figure 3). Retrospective application of an AI algorithm indicated a pathologic lesion in the upper-outer quadrant of the left breast (Figure 3E). Multimodality imaging workup demonstrated extensive, multifocal malignancies in the upper-lateral half of the left breast and pathologic left axillary lymph nodes (Figure 4). Histologic examination of the 14G core biopsy specimen diagnosed invasive lobular carcinoma (Figure 4H,5) and malignant cells in the left pathologic axillary lymph nodes. A comprehensive search for the primary tumour found only the breast malignancy. The severely disseminated disease and the patient's poor general condition led to a consensus decision for conservative therapy.

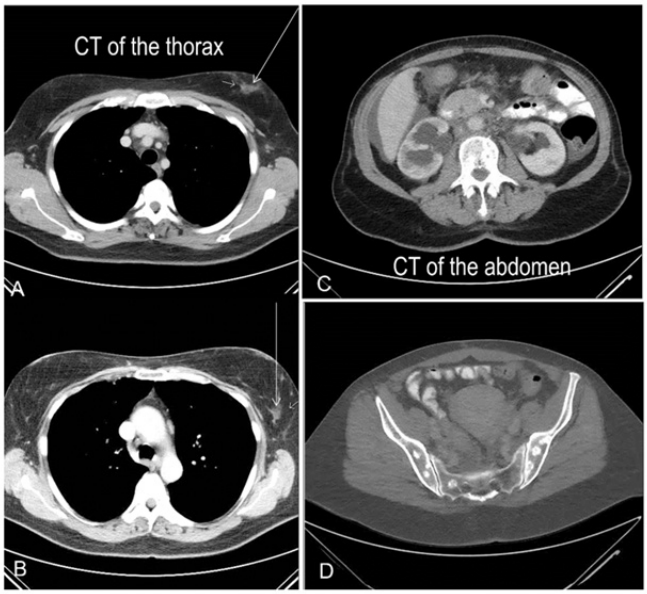


Figure 1 Thorax CT demonstrates a breast tumour (arrows). CT of the abdomen revealed diffuse abdominal carcinosis, which also infiltrated the retroperitoneal adipose tissue and compressed the inferior vena cava and ureters, causing bilateral hydronephrosis in addition to sclerotic and lytic metastases of the pelvic bones.

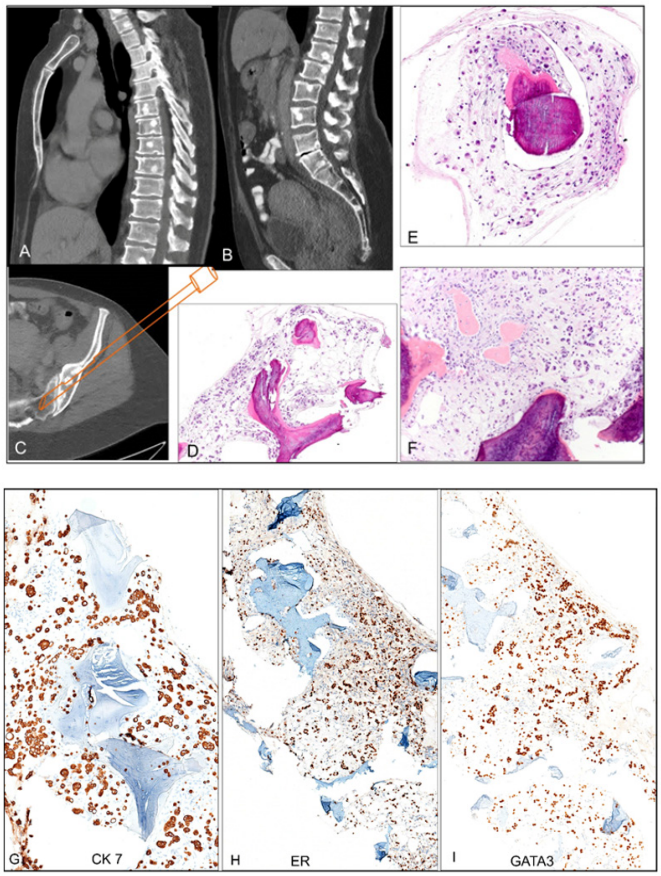
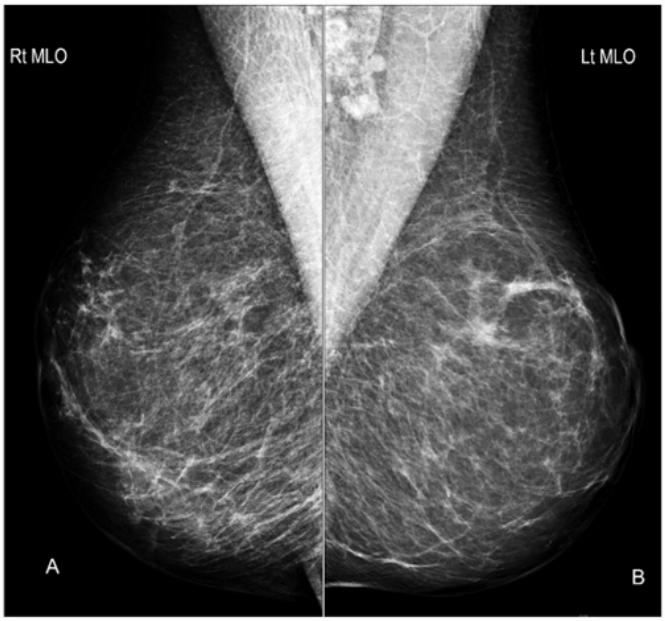


Figure 2 Extensive sclerotic and lytic metastases were demonstrated in the vertebral column and pelvic bones (A-C). Microscopic examination of the Iliac crest biopsy (C) samples, H&E staining (D-F), CK7 (G), ER (H) and GATA3 (I) staining show fragmented, spongiotic bone trabeculae containing invasive breast cancer cells in the bone marrow space, confirming adenocarcinoma metastases. The positive IHC biomarkers, CK 7, ER and GATA3, confirmed the breast cancer origin.



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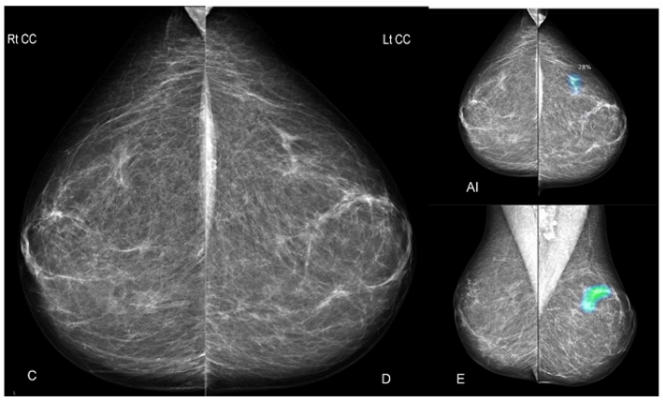


Figure 3 MLO and CC mammograms show no tumour mass or microcalcifications. The localized architectural distortion could be caused by scars from bilateral breast reduction surgery. AI algorithm indicates the presence of an abnormality in the upper-outer quadrant of the left breast.

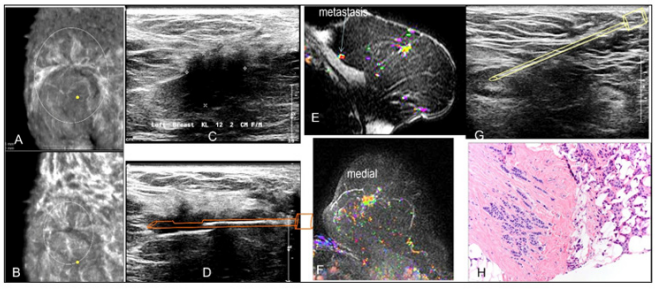


Figure 4 Multimodal imaging including automated breast ultrasound (A,B), hand-held ultrasound (C,D), and breast MRI (E,F) demonstrate an extensive, multifocal malignancy over a region measuring at least 51x62x36 mm. Several pathologic lymph nodes are seen in the left axilla. Fine needle aspiration biopsy of one pathologic axillary node (G) revealed malignant cells. Microscopic examination of the ultrasound guided 14G core biopsy specimen confirmed the diagnosis of classic invasive lobular carcinoma having the characteristic growth pattern of the cancers in single files (H) as the primary tumour.

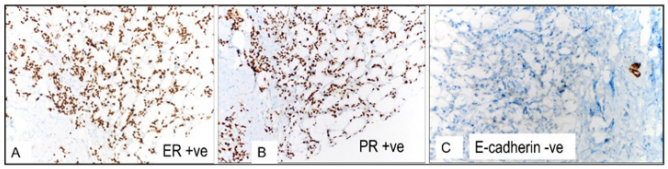


Figure 5 Immunohistochemical biomarkers of the primary breast tumour: ER and PR positive, E-cadherin negative.

Follow-up: Two years after diagnosis and initiation of treatment, the patient then developed a large perianal metastasis. Microscopic examination of the 14G core biopsy confirmed that this newly developed malignancy was the diffuse cancer of mesenchymal stem cell origin (BCMO) of the breast (aka classic invasive lobular carcinoma) (Figures 6,7).

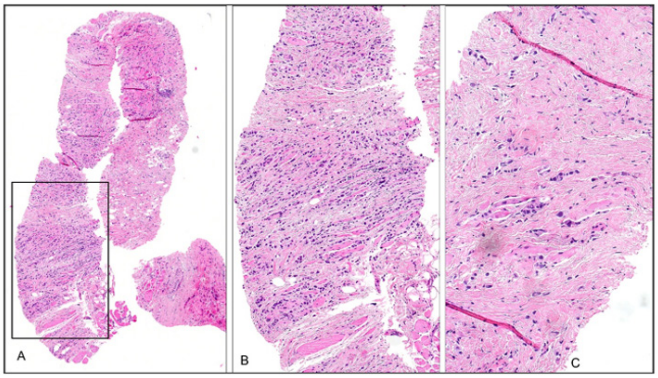


Figure 6 Low- and intermediate-power histopathology images (A-C) of the perianal cancer detected two years after the diagnosis of the primary breast cancer, showing a histopathology image identical to the classic invasive lobular carcinoma of the breast biopsy specimen.

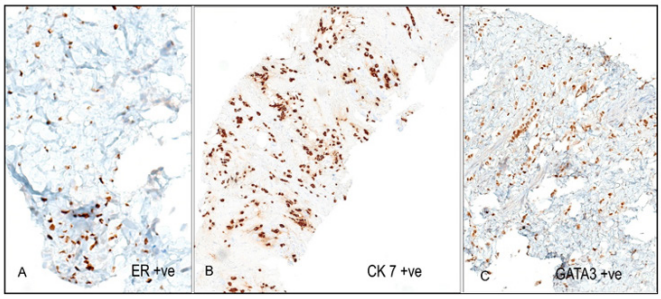
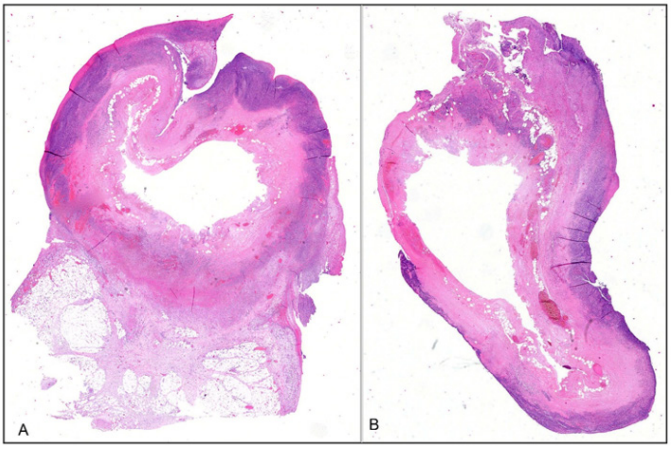


Figure 7 Immunohistochemical biomarkers of the core biopsy samples of the perianal tumour: positive staining for ER, CK 7 and GATA3 confirmed the breast cancer origin.

Further follow-up: An additional seventeen months later the patient was hospitalized for acute appendicitis. Histologic examination of the appendix revealed gangrenous inflammation and metastases of classic invasive lobular carcinoma in the appendix (Figures 8,9). The patient died from disseminating BCMO three years and ten months after diagnosis and initiation of treatment.



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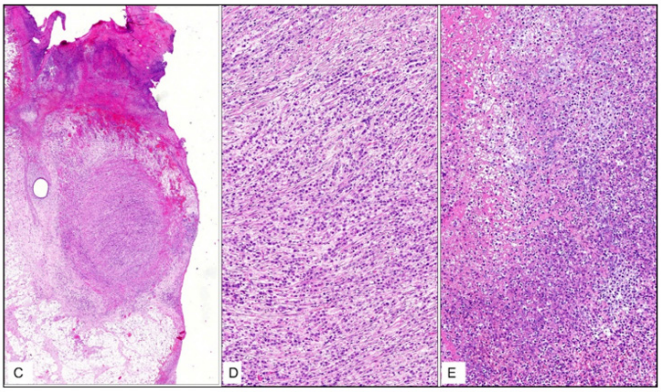

Figure 8 Low-power histopathology images (A-C) of several cross sections of the appendix. The cancer completely infiltrates the wall of the appendix. Intermediate-power (D,E) microscopic images of the diseased appendix. The histology report described acute gangrenous appendicitis, fibrinous periappendicitis and metastases from classic invasive lobular carcinoma with signet ring-like cells.

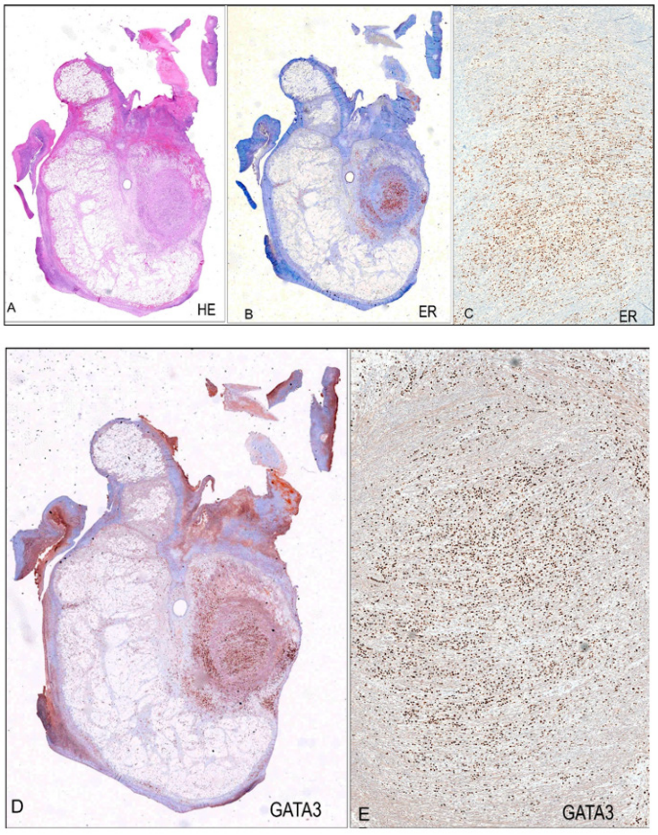

Figure 9 H&E staining of the appendix (A). The estrogen (B),C) and GATA3 (D,E) positivity confirm the breast tumour origin.

Outcome: Three years and ten months after diagnosis and initiation of treatment the patient died in disseminating BCMO. She had mesenteric, skeletal, perianal, and appendiceal metastases.

Discussion

Three of the breast malignancy subgroups gathered together under the common category of invasive lobular carcinoma, ILC, have distinctly separate imaging biomarkers which should alert physicians to potentially different sites of origin, despite their common terminology. Two of these having the imaging biomarkers of extensive architectural distortion and small stellate tumours, have a similar histopathological appearance at medium power and high power microscopy, but distinctly different subgross structure, corresponding to their imaging biomarkers. We have proposed that these two forms, not currently distinguished in the WHO Blue Book,[1] be named extralobular BCMO and intralobular BCMO.[3-8] The third subtype, termed ILC, solid type, appears to have an accurate nomenclature.

The tragic case reported here represents the classic ILC subtype, with the proposed term of extralobular BCMO, a subtype with a long-term fatality greater than that of any other breast cancer subtype and virtually unchanged over more than half a century.[3,5,7–9] The fact that there has been no improvement in outcome despite the considerable proliferation of new therapeutic agents should raise the alarm bell that the medical community has been barking up the wrong tree, since this disease subtype is apparently unaffected by all the new therapies. We continue to ask for a reconsideration of the terminology according to the site of origin of this devastating disease, so that therapeutic agents could be developed and selected for their effectiveness against a malignancy of mesenchymal pluripotential hybrid stem cell origin.[2–8]

Conclusion

The current WHO terminology, classic invasive lobular carcinoma, ILC, fails to account for the continuing lethality of this breast cancer subtype and deceives the breast cancer team members into believing that this disease with unusual attributes can be successfully treated with agents designed for breast cancers of truly lobular epithelial origin. The medical community needs to acknowledge its failure to improve the continuously poor outcome of these patients. This could facilitate a dedicated search for new therapeutic agents.

Acknowledgements

Special thanks to Ms. Helena Hermelin, the leader of the Research Laboratory at Falun Central Hospital, for scanning the histopathology glass slides and organizing the research archive. This work has been supported by funding from the American Cancer Society through a gift from the Longaberger Company's Horizon of Hope® campaign (Project NHPDCSGBR-GBRLONG).

Conflict of interest

The authors declare that they have no competing interests.

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