

# Heterogeneity of extensive invasive lobular carcinoma. part I: combination of the classic diffuse and solid forms

## Abstract

**Background:** The imaging biomarkers of extensive breast malignancies termed invasive lobular carcinoma are non-calcified architectural distortion with or without associated spherical tumour masses. Microscopic examination of these extensive malignancies can reveal the following entities, either separately or in combination: the classic diffusely invasive form, the solid form, and the invasive form arising within multiple lobules.

**Case presentation:** This report describes a combination of the classic diffusely invasive and solid forms, corresponding to the imaging biomarkers of architectural distortion and multiple circular/oval tumour masses, respectively, in a 90-year-old patient. She died from disseminated breast cancer. Histopathologic examination showed the diffuse form in the distant metastases. There were also challenging calcifications on the mammograms.

**Conclusions:** The diffuse and solid forms of invasive lobular carcinoma occurred in combination in this case. The immunohistochemical biomarkers did not predict a fatal outcome. The diffuse form was the dominant malignancy in this case and is known to have the highest fatality rate of all breast cancers. Cell culture and imaging-histopathologic correlation provide evidence that the diffuse form has its origin in the mesenchymal stem cells and undergoes mesenchymal-epithelial transition, factors which can account for its consistently poor outcome over the past half century.

**Key words:** Invasive lobular carcinoma, imaging biomarkers, breast cancer of mesenchymal origin, mesenchymal-epithelial transition (MET)

Volume 17 Issue 1 - 2026

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**Received:** April 23, 2026 | **Published:** May 02, 2026

**Abbreviations:** MET, mesenchymal-epithelial transition; BCMO, breast cancer of mesenchymal origin; ILC, invasive lobular carcinoma

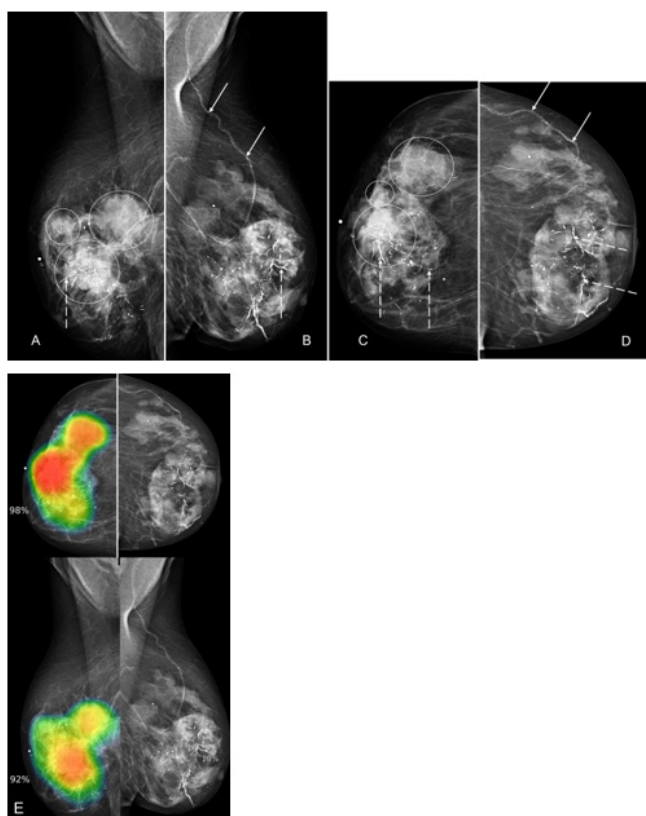
## Introduction

The breast cancer termed invasive lobular carcinoma has several different histopathological and imaging features.<sup>1,2</sup> Cell culture studies indicate that the breast malignancy termed diffuse invasive lobular carcinoma has its origin in the hybrid stem cells of the mesenchyme and not in the lobular epithelial cells.<sup>3</sup> We have suggested terminology reflecting the apparent site of tumour origin: breast cancer of mesenchymal origin (BCMO).<sup>2-5</sup> When the hybrid stem cells of the extralobular mesenchyme transform into epithelial-like cells through mesenchymal-epithelial transition, the resulting malignancy is extensive, clinically palpable as diffuse thickening and has architectural distortion as its characteristic imaging biomarker. This “classic” form has the highest fatality rate of all breast cancer subtypes, a rate which has not improved during the past half century despite the many developments in breast cancer care.<sup>2,4-6</sup> Creating a new terminology is justified by the continuing high fatality, its resistance to chemotherapy and radiation therapy, apparently due to its stem cell origin. When the hybrid stem cells of the intralobular

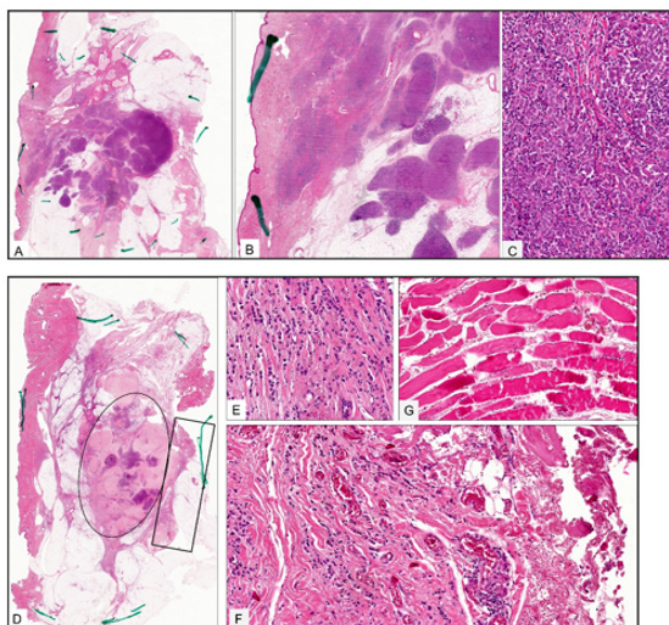
mesenchyme undergo similar transition, the disease is predominantly confined to the terminal ductal lobular units.<sup>4,5</sup> The solid invasive lobular carcinoma appears to originate from the lobular epithelial cells and has a strikingly different imaging biomarker, circular/oval-shaped lobulated tumour mass, and different histopathologic features. The diffuse form is characterized by the cancer cells arranged in single files, separated by an excess amount of newly formed fibrous strands, while the solid form is dominated by a large number of contiguous cells with no or minimal intervening connective tissue. These two malignancies, despite their many differences, are often diagnosed simultaneously in the same breast, as in the present case.

## Case presentation

A 90-year-old woman was referred for assessment of an extensive thickening occupying the entire central portion of the right breast. Clinical breast examination confirmed the finding and noted nipple-areola retraction as well as enlarged axillary lymph nodes. The mammographic (Figure 1) histopathologic (Figures 2,3) and immunohistochemical (Figure 4) findings illustrate the complex nature of this heterogeneous malignancy. The bilateral branching, high density calcifications are not related to the malignancy and are caused by occlusion and luminal calcifications.

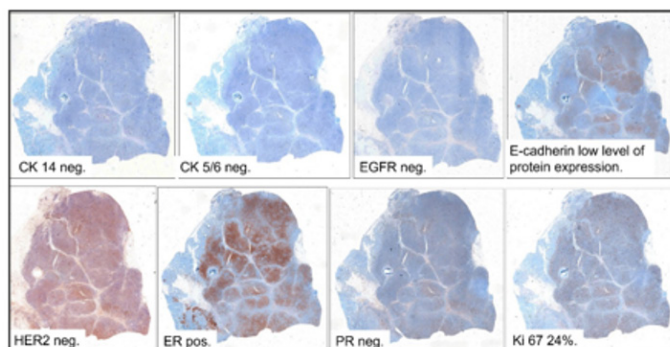


**Figure 1** Medio-lateral (A,B) and cranio-caudal projection (C,D) mammograms demonstrate the following pathologic findings: architectural distortion, multiple circular/oval, lobulated tumour masses (encircled on A,C), bilateral Mönckeberg's sclerosis type arterial calcifications (solid arrows), and the more interesting, challenging findings bilaterally, the extensive elongated, branching, high density calcifications (dashed arrows). Artificial intelligence image (E) indicates the diseased region in the right breast .

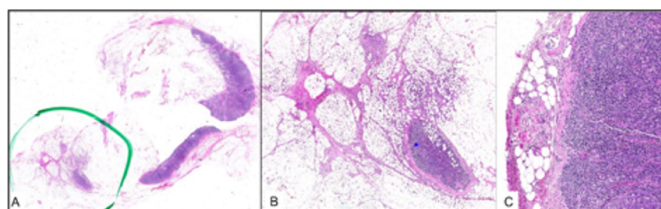


**Figure 2** Low- and intermediate histopathologic images of the multifocal solid invasive lobular carcinoma occupying the central portion of the right breast (A-C, and D encircled), corresponding to the multifocal circular/oval

tumour masses seen on the mammograms (Figure 1 A,C). The tissue within the rectangle (D) is shown at higher power (E-G). The diffuse carcinoma originating in the mesenchymal stem cells of the extralobular mesenchyme (aka ILC) (E) was the dominant histopathologic finding, also infiltrating the pectoral major muscle (F,G).



**Figure 3** Immunohistochemical staining of the solid component interpreted as written on the individual images. The combination of CK 14, CK 5/6 and EGFR negativity indicates a non-basal type tumour. The ER positivity rules out triple negative tumour type.

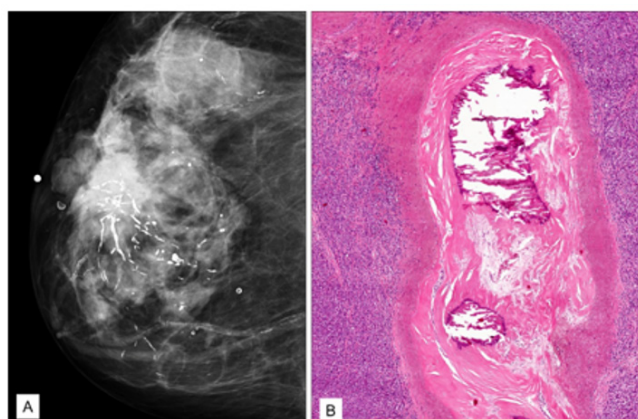


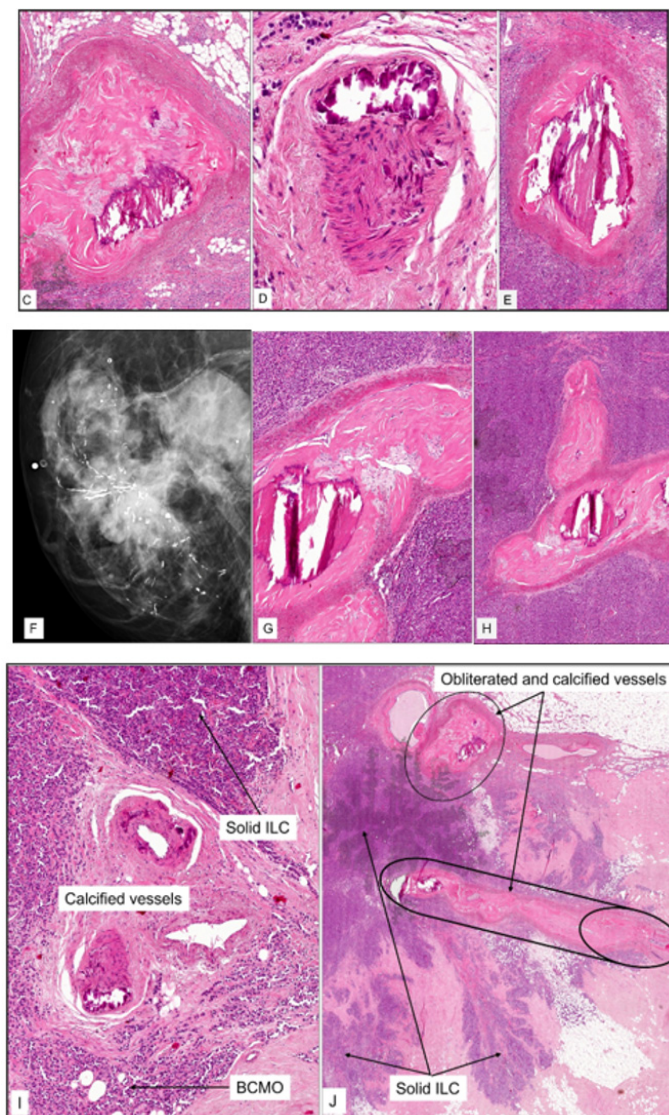
**Figure 4** Low-power histopathology images of the metastatic axillary lymph nodes.

### Histopathologic diagnosis

70x45 mm region with predominantly classic diffusely invasive breast malignancy of mesenchymal origin (BCMO) associated with a poorly differentiated solid form of invasive lobular carcinoma foci. Extensive lymph vessel invasion, with three of the six surgically removed axillary lymph nodes having metastases, the largest focus measuring 6 mm. The skin, areola and the posterior margin were infiltrated by carcinoma. Immunohistochemical biomarkers determined from the solid component: ER positive, PR and HER2 were negative, CK 5/6, CK 14 and EGFR negative. E-cadherin: low level of protein expression.

The bilateral branching, high density intraluminal calcifications on the mammograms were within the hyalinised material occluding the arteries (Figure 5).





**Figure 5** Mammographic-large format thin section histopathologic correlation of the bilateral branching calcifications. The tube-like structures in longitudinal section (B,G,H,I) and in cross section (C-E,I,J) are partially or completely occluded arteries. These are surrounded by the solid form of invasive lobular carcinoma (B,C,E,GH,,I,J) and also by the diffuse BCMO (I).

### Follow-up

The patient developed skin metastases on her back five years and four months after diagnosis and initiation of treatment (Figures 6,7).

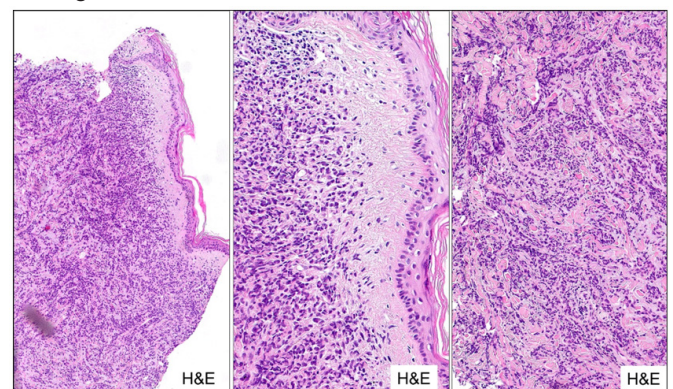
### Outcome

The patient died from disseminating breast cancer of mesenchymal origin (aka invasive lobular carcinoma) seven years after diagnosis and initiation of treatment. The immunohistochemical biomarkers did not predict the fatal outcome, while the imaging biomarkers, the non-calcified architectural distortion and large, multiple spherical tumour masses clearly predicted the fatal course of the disease.

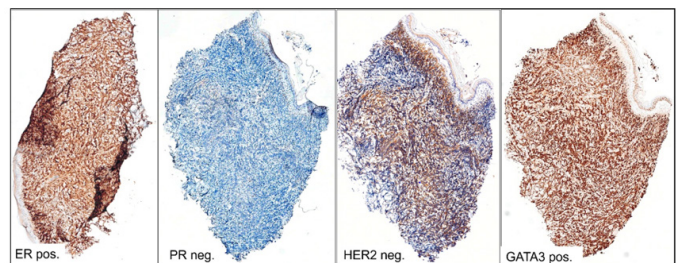
### Discussion

The term “classic invasive lobular carcinoma” does not reflect the true site of origin of this diffusely invasive breast malignancy, since

the epithelial cells in the major ducts as well as in the terminal ducts and lobular acini are still normal, although they may be surrounded by malignant cells. Mammographic detection of the diffusely invasive BCMO is always difficult before it becomes palpable due to its lack of a central tumour mass and calcifications. The excess amount of newly formed fibrous strands forms a mammographic image resembling a complex spider’s web. While the immunohistochemical biomarkers have a reliable prognostic value in breast cancers originating in the luminal epithelial cells (acinar adenocarcinoma of the breast), they have a documented misleading impact in clinical practice due to the considerable discrepancy between the predicted and observed patient outcome.<sup>7</sup> The resistance to therapeutic methods, the high fatality rate despite the favourable immunohistochemical biomarkers, and the E-cadherin negativity can all be attributed to a mesenchymal stem cell origin.



**Figure 6** Low- and intermediate power histopathology images of the skin metastases on the patient’s back caused by the diffusely invasive breast cancer of mesenchymal origin.



**Figure 7** Immunohistochemical biomarkers of the distant metastases correspond to the IHC staining results of the primary breast cancer. GATA3 staining positivity together with ER positivity confirm the breast cancer origin.

The tumour burden increases considerably when it is combined with the multifocal solid invasive lobular carcinoma (ILC). Detection of the solid ILC is facilitated by its convex contour and frequent multifocal nature.

### Conclusion

Precision medicine should require a revision of the current diagnostic criteria for a group of diseases having the same terminology (invasive lobular carcinoma) but vastly different clinical, imaging and histopathologic features. The long-term outcome of BCMO, termed as the classic diffusely invasive ILC, has not improved during the past several decades despite alleged improvements in therapeutic regimens. Acknowledging the mesenchymal stem cell origin of this misunderstood disease could lead to the development of novel therapeutic regimens providing better cost/benefit and harm/benefit ratios and a significantly improved long-term patient outcome.

## Acknowledgement

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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