

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

Abstract

Background: The breast malignancy termed classic invasive lobular carcinoma has frequent and unusual sites of metastasis. We have published three recent articles concerning metastases of this diffusely infiltrating malignancy to unusual sites. This paper adds additional, unusual soft tissue metastases to our collection.

Case presentation: The two cases we describe here represent rare gastrointestinal metastases of diffuse invasive lobular carcinomas, where the metastatic sites were revealed by endoscopic examinations and the diagnosis was made by microscopic examination of the endoscopic biopsy specimen. In one of the cases, metastases were found in the duodenum; in the other, the cancer spread to the skeleton, and subsequently, focally to the ileocecal valve. The lack of imaging findings was once again a considerable challenge for the breast team.

Conclusion: The classic invasive lobular carcinoma has imaging, histopathologic and outcome features that are quite different from breast cancers of epithelial cell origin. We also call attention to the unusual sites of metastasis. We found that the proliferation index (Ki67) provided useful prognostic information, whereas other IHC biomarkers and tumour grade did not help in treatment planning.

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); LCIS, lobular carcinoma in situ; 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

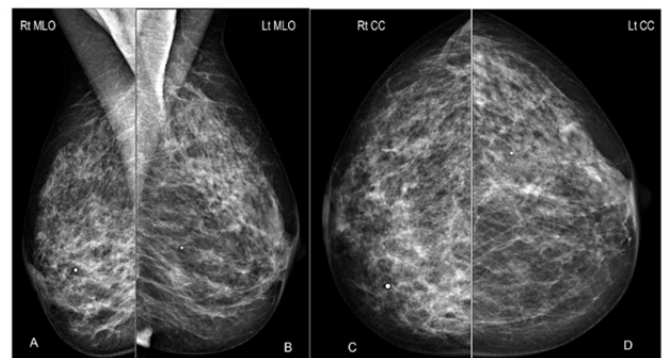
Classic invasive lobular carcinoma (ILC), for which our research group has proposed the term breast cancer of extralobular pluripotential mesenchymal stem cell origin (BCMO)^{1,2} does not present as a tumour mass or calcifications on the mammogram. Its imaging biomarker, non-calcified architectural distortion, may evade detection, so a substantial tumour burden may accumulate before diagnosis.³ The tumour dissemination pattern of ILC differs from the pattern of distant spread by other breast cancer subtypes. Rather than favouring lungs, liver and brain, ILC disseminates to the peritoneum, retroperitoneum, gastrointestinal tract and gynecological organs, more rarely involved by other breast cancer subtypes.⁴⁻⁶ We have described this unusual dissemination pattern in three earlier articles in this journal.⁷⁻⁹ The present report extends that series with two additional cases in which the presenting feature of metastasis was gastrointestinal involvement; duodenal in one, and ileocecal in the other following an unusually long disease-free interval after skeletal and nodal relapse. The primary tumour may escape detection by conventional imaging,

so the diagnosis will ultimately depend upon clinical suspicion and tissue sampling.

Case presentations

Case I

This 55-year-old woman felt a “thickening” in the medial portion of her right breast. Clinical breast examination confirmed the presence of a 10x5 cm firm, diffuse “thickening” in the central and medial portion of the right breast. Peau d’orange was observed overlying the lower portion of the breast, which had shrunk to a smaller size. Her most recent mammogram had been taken six years earlier, as she had declined to attend following her next three screening invitations (Figure 1–5).



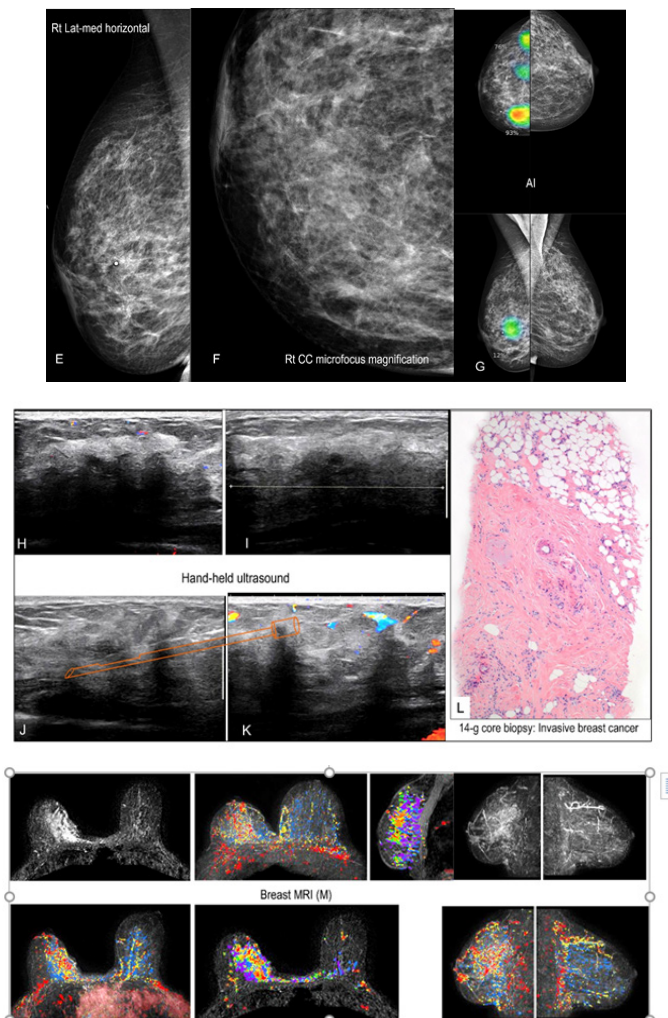


Figure 1 MLO (A,B), CC (C,D), latero-medial horizontal view (F) and microfocus magnification of the right CC projection (F) mammograms show increased density throughout the breast but no tumour mass or microcalcifications are detectable. AI marks individual foci on the right MLO and CC projections (G). Hand-held ultrasound (H-J) and Doppler (K) demonstrate the extensive and diffuse nature of this breast malignancy. Histologic examination of the ultrasound-guided I4G core biopsy specimen (L): Invasive breast cancer. Breast MRI (M) illustrates the true extent of the disease, occupying nearly the entire glandular tissue between the chest wall and the nipple and shows that the right breast is considerably shrunk.

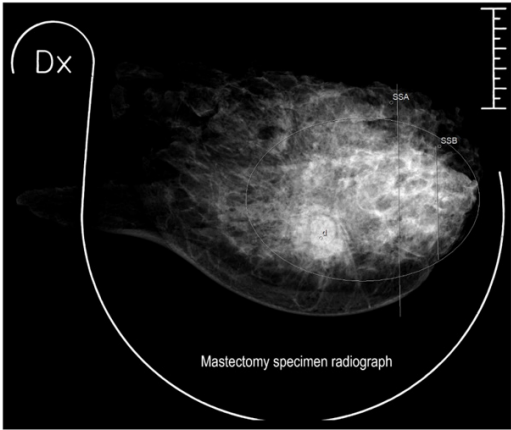


Figure 2 Mastectomy specimen radiograph.

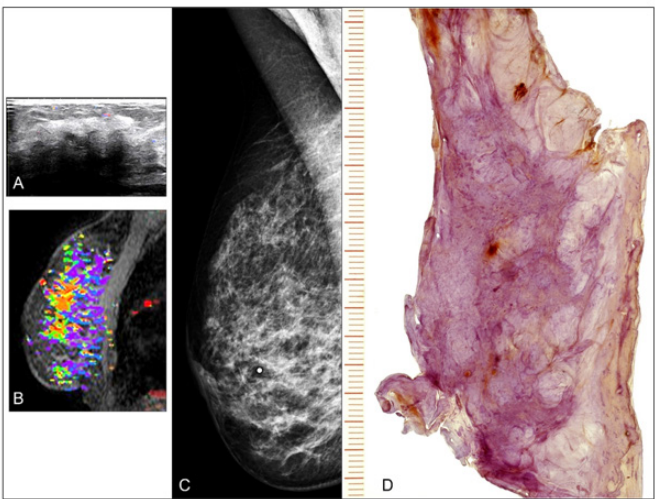
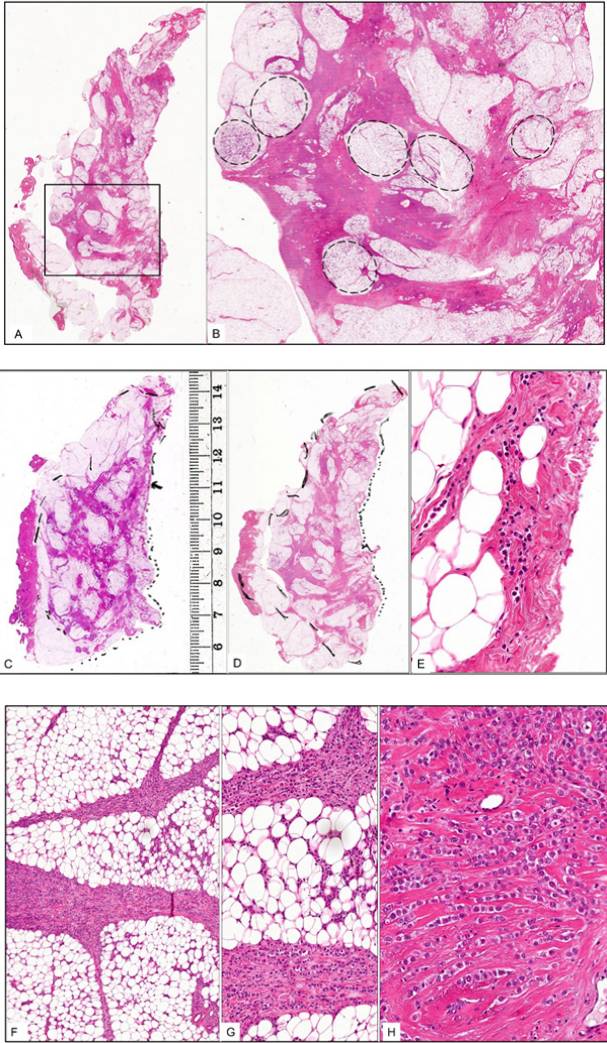


Figure 3 Correlation of the hand-held ultrasound (A), sagittal view of the right breast MRI (B) and the mammogram, MLO projection, (C) with the large format thick section, 3D histopathology image of the mastectomy specimen (D). The extensive purple region on the thick section histopathology image (D) represents breast cancer of mesenchymal stem cell origin (aka as ILC), best correlated with the MRI image (B).



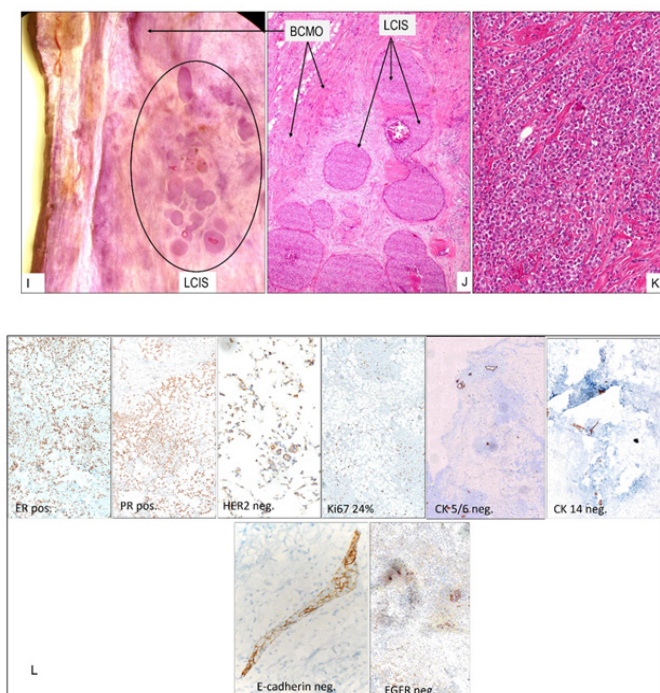


Figure 4 Large format thin section whole-mount histopathology images (A,C,D) demonstrate the >80 mm breast malignancy diffusely infiltrating the nipple and the entire fibroglandular tissue. The extensive involvement of the posterior surgical margin has been marked by the pathologist (C,D). While breast cancers of epithelial cell origin (stellate and circular tumour masses) have a convex contour, the excess amount of newly produced fibrous tissue in classic invasive lobular carcinoma (BCMO) has concave contours (B). Higher power histopathology images (H,K) show the characteristic histopathology features of this diffusely infiltrating malignancy: an excess amount of fibrous tissue, cancer cells lined up in rows (single files) and cancer cells occupying the interstitial space (F,G). LCIS foci can be associated with classic invasive lobular carcinoma (BCMO) (I,J) but this association does not necessarily indicate a causal relationship.¹⁰ Immunohistochemical biomarkers (L).

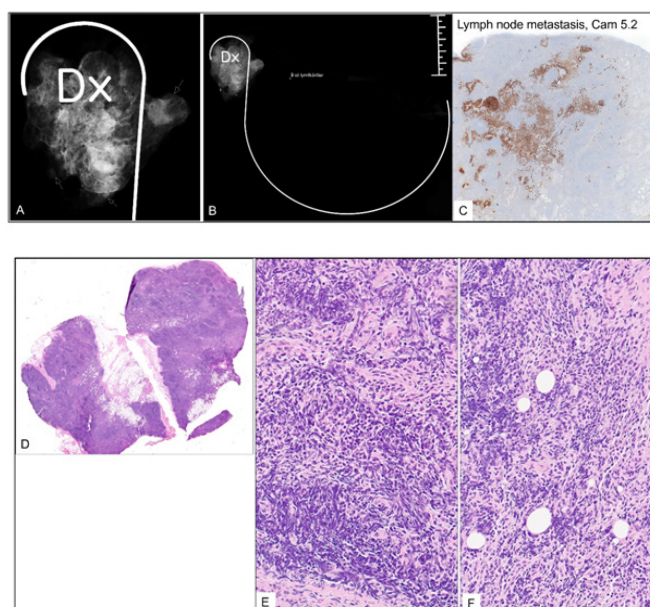


Figure 5 Axillary specimen radiographs (A,B) show pathologic lymph nodes. H&E staining (D-F) and immunohistochemical staining (C, G-J) demonstrate the metastases found in three out of seven surgically removed axillary lymph nodes.

Final histopathologic diagnosis: 85X38 mm moderately differentiated, classic invasive lobular carcinoma (BCMO) associated with LCIS. There was infiltration of the nipple, the entire fibroglandular tissue and the posterior surgical margins. Three axillary lymph nodes of the seven surgically removed nodes had metastases. IHC biomarkers: ER/PR positive, HER2, CK 5/6, CK 14, EGFR and E-cadherin negative. Ki67: 24%.

The histopathologic examination of the mastectomy specimen revealed cutaneous and subcutaneous spread of this invasive lobular carcinoma (BCMO) (Figure 6).

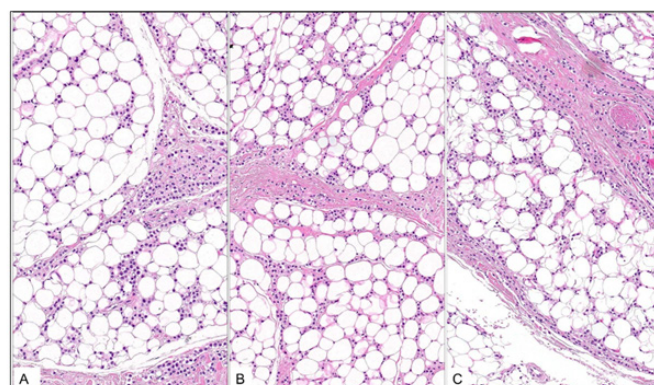


Figure 6 ILC (BCMO) spread to the interstitial space of the skin and subcutaneous tissue (A-C).

Follow-up: Eight months after diagnosis the patient developed metastases to the duodenum (Figure 7).

Case 2

This 56-year-old woman had attended six consecutive mammographic screening examinations and received a “well-letter” on each occasion (Figures 8–13). Five months after her latest screening mammograms, she was admitted to the hospital to determine the cause of her unbearable skeletal pain.

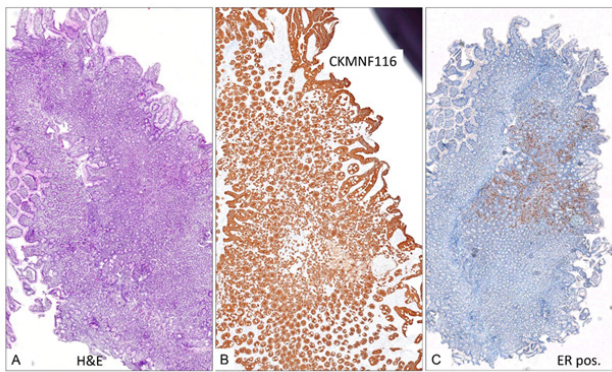


Figure 7 The invasive lobular carcinoma (BCMO) infiltrated the duodenal mucosa. H&E staining (A). CKMNF116 (B) and ER (C) staining positivity confirms a breast cancer origin.

Outcome: Nine months after diagnosis and initiation of treatment, the patient died from disseminated breast cancer of pluripotential mesenchymal stem cell origin (BCMO, aka ILC).

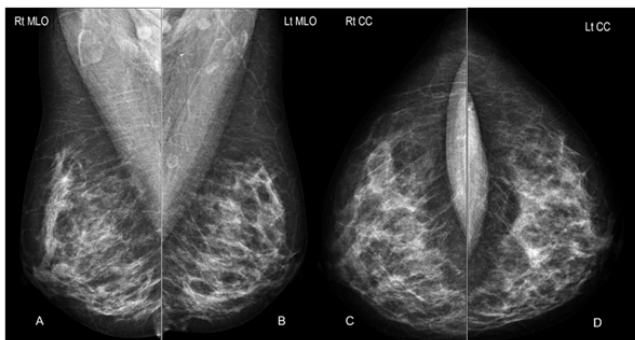


Figure 8 MLO (A,B) and CC (C,D) projections. Normal fibroglandular tissue bilaterally. Neither tumour mass, microcalcifications nor architectural distortion are seen.

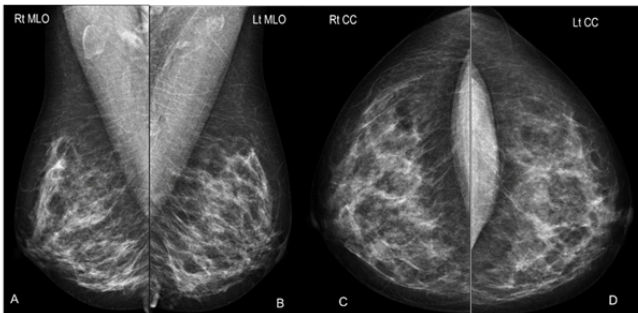


Figure 9 Eighteen months following her previous mammograms, MLO (A,B) and CC (C,D) projections. Involuting fibroglandular tissue bilaterally with no demonstrable mammographic abnormality.

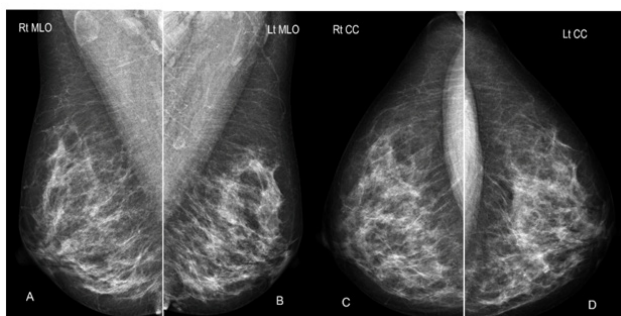


Figure 10 Eighteen months later: normal mammograms.

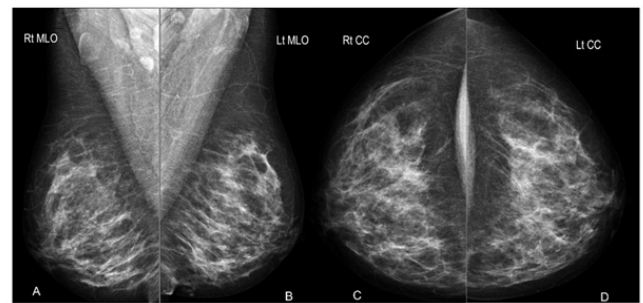


Figure 11 Nineteen months following the previous mammograms. She was still asymptomatic and her mammograms show no abnormality

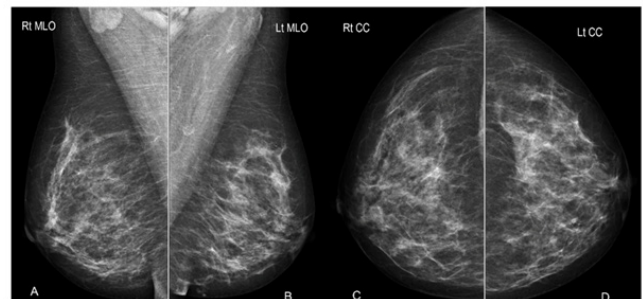


Figure 12 Next screening mammogram nineteen months later, still asymptomatic. The MLO (A,B) and CC (C,D) mammograms show normal, involuting fibroglandular tissue with no tumour mass, microcalcifications or architectural distortion.

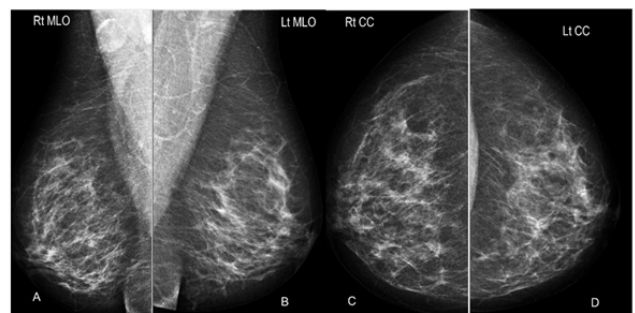


Figure 13 The mammograms twenty months following the previous screening mammogram did not show evidence of malignancy. The patient was suffering from severe skeletal pain.

At the age of 56 the patient complained about unbearable skeletal pain. She was admitted to the hospital for examination and treatment planning. Her mammograms showed no abnormality, clinical breast examination could not detect a palpable tumour in either breast; however, there was a palpable, pathologic lymph node in the right axilla. Hand-held ultrasound confirmed the presence of pathologic right axillary lymph node. Both FNAB and 14G core biopsy were performed (Figures 13,14).

Multimodality examination detected skeletal metastases in the pelvic and vertebral bones. Core biopsy of the metastasis in the pelvic crista was carried out (Figure 15).

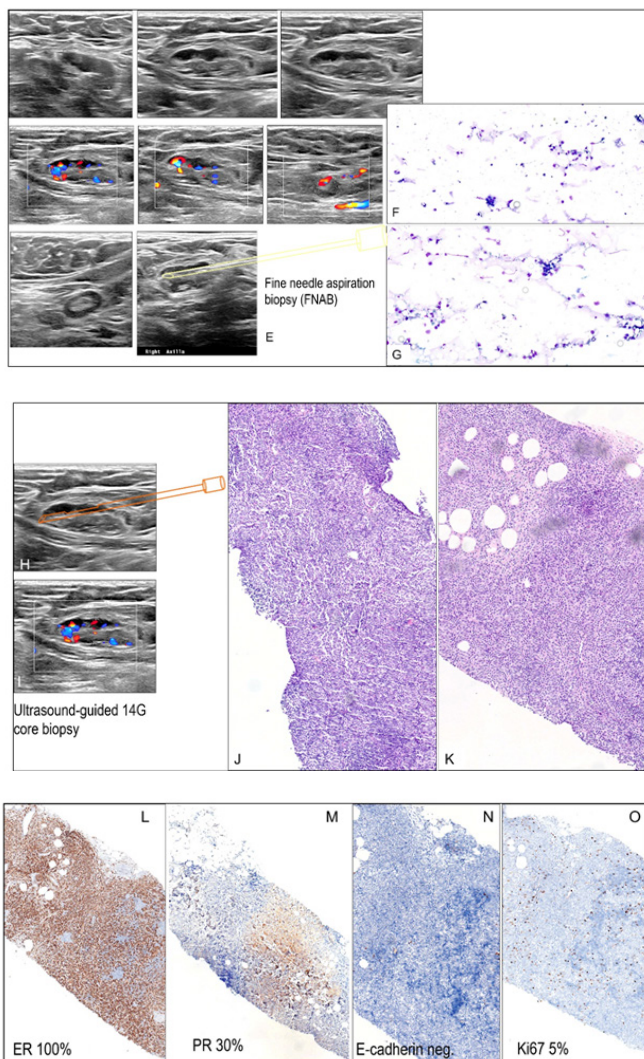


Figure 14 A series of hand-held ultrasound images (E), Doppler images included, showing pathologic axillary lymph nodes. Fine needle aspiration showed malignant cells (F,G). 14G core biopsy performed under ultrasound guidance (H,I). Histopathologic examination revealed metastases of ILC (J,K). The immunohistochemical biomarkers are shown on Figs. L-O.

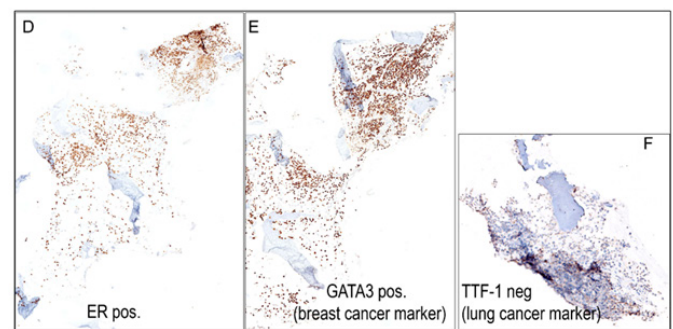
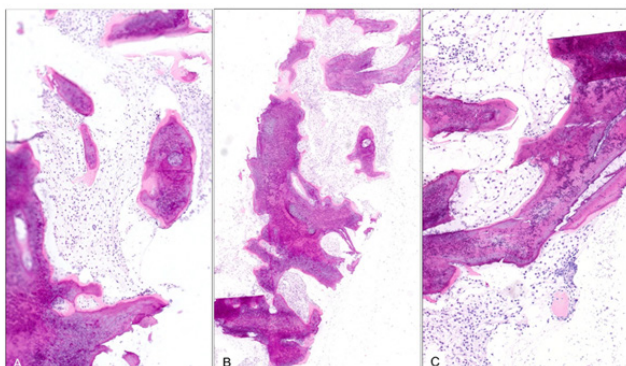


Figure 15 Histopathologic examination of the crista biopsy (A-C) showed ILC metastases. Immunohistochemical staining, ER (D) and GATA3 (E) positive confirmed that the metastases originated from the previously diagnosed ILC of the breast. The negative lung cancer marker, TTF-1 (F) suggests that the primary tumour is not in the lungs.

Follow-up: Five years and three months later the patient was examined for gastrointestinal symptoms. Colonoscopy detected a tumour in the ileocecal valve and histopathologic examination of the ileocecal valve specimen showed metastasis of the previously diagnosed breast cancer of mesenchymal stem cell origin (ILC) (Figure 16).

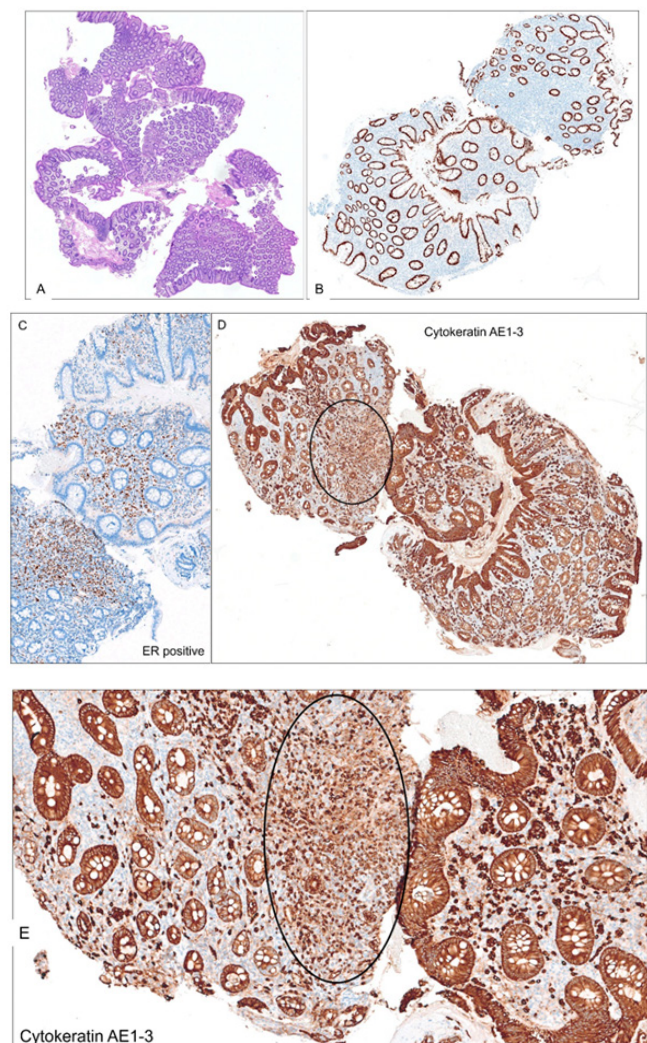


Figure 16 H&E staining (A) shows normal colon mucosa. CDX2 staining (B), a marker for intestinal tumour, is negative, excluding colon cancer. Malignant cells

infiltrate the lamina propria of the ileocecal valve. The immunohistochemical biomarkers ER (C) and cytokeratin AE1-3 (D,E) are positive, supporting the diagnosis of breast cancer metastases.

Follow-up: Five years and seven months after her diagnosis of skeletal and axillary lymph node metastases and four months after diagnosis of dissemination of her BCMO to the ileocecal valve, the patient was still alive.

Discussion

These two cases emphasize two important characteristics of ILC (BCMO), first, that it can be occult at imaging during every stage of its development. Second, when it becomes clinically apparent, its metastasis can be found in unusual distant sites.²⁻⁹

Case 1 illustrates a diffuse primary disease with an aggressive course: a malignancy >80 mm at the time of diagnosis that had already infiltrated the nipple and most of the fibroglandular tissue, extended to the posterior margin, spread to the skin, subcutaneous tissue, axillary nodes and duodenal mucosa within eight months, and was fatal within nine months despite ongoing treatment. Case 2 illustrates a more indolent disease: six consecutive normal screening mammograms, a primary breast lesion that was never radiologically visualized, and a first presentation as skeletal pain and axillary nodal disease followed by an ileocecal metastasis diagnosed more than five years later. The patient was alive at the latest follow-up. These two tumours were not biologically equivalent. Case 1 had a Ki67 proliferation index of 24%, about five times that of Case 2 (Ki67 5%). The difference between these two cases suggest that two tumours with the same histopathologic diagnosis and unusual metastatic pattern can carry different prognoses, where Ki67 captured the difference but histologic malignancy grade and stage at presentation did not. The detection problem was obvious already at the time of diagnosis in Case 1, when the AI-algorithm marked isolated spots while breast MRI showed a contiguous, diffuse malignancy from the chest wall to the nipple. This is consistent with our research group's unpublished observations that AI-assisted reading has restrictions in detecting the non-mass, diffusely infiltrating pattern characteristic of classic ILC, but is proficient at detecting mass-forming or calcified lesions. We consider it educational to compare these two cases having comprehensive imaging, histopathology and immunohistochemistry correlation with verified dissemination sites, and having the same ILC diagnosis but with divergent proliferation indexes and outcomes.

Conclusion

These two additional cases document the propensity of classic invasive lobular carcinoma to disseminate to unusual, often radiologically occult sites, in these cases to the duodenum and the ileocecal valve. Our classic invasive lobular carcinoma case series⁷⁻⁹ emphasizes the following points: 1) The history of a histopathologic diagnosis of ILC should put gastrointestinal metastases in the differential diagnosis with new abdominal or endoscopic findings, even after an interval of several disease-free years and even when

the original primary tumour was mammographically occult. 2) Differentiating a gastrointestinal metastasis of ILC from a primary gastrointestinal malignancy requires immunohistochemistry (ER, GATA3 and cytokeratin positivity with CDX2 negativity in our cases) because morphology and endoscopic appearance alone are not reliable. 3) The proliferation index alone (Ki67) provides useful information regarding treatment intensity in classic ILC.

Acknowledgments

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Conflict of interest

The authors declare that they have no competing interests.

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