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Bone Marrow Biopsy Reveals Occult Invasive Lobular Carcinoma Without Hypermetabolic Breast Lesion on FDG PET/CT

Abstract

Bone marrow metastasis (BMM) from breast cancer is exceedingly rare and more often associated with invasive lobular carcinoma (ILC) than with invasive ductal carcinoma. ILC is characterized by a diffuse infiltrative growth pattern that often escapes detection on mammography, leading to delayed diagnosis and advanced disease. It also demonstrates low FDG avidity, with hypermetabolic activity typically limited to metastatic sites. We describe a 64-year-old woman who presented with chest pain, cytopenias, renal impairment, and hypercalcemia. Imaging revealed diffuse bony lucencies on FDG PET/CT without hypermetabolic activity in the breasts, raising concern for hematologic malignancy. Bone marrow biopsy, however, confirmed metastatic ILC (ER-positive, PR-negative, HER2-negative, GATA3-positive). Subsequent breast imaging identified a large right breast mass with axillary involvement. She was initiated on endocrine therapy with letrozole and ribociclib, along with monthly zoledronic acid, resulting in partial improvement of cytopenias, normalization of calcium levels, and effective symptom control. This case highlights the stealth nature of ILC, the limitations of conventional imaging, and the indispensable role of bone marrow biopsy with immunohistochemistry in the evaluation of unexplained cytopenias.

Although BMM portends a poor prognosis, advances in endocrine and targeted therapy offer improved outcomes and underscore the importance of reporting such cases to guide clinical practice.

Introduction

Bone marrow metastasis (BMM) from breast cancer is exceedingly rare, occurring in only ~0.17% of cases, and is more commonly associated with ILC than Invasive ductal carcinoma (1–3). Invasive lobular carcinoma (ILC) accounts for approximately 5–15% of all breast cancers and is characterized by an infiltrative growth pattern that makes it difficult to detect through routine screening and physical examination (4,5). ILC often fails to form well-defined masses and is less conspicuous on mammography, which has a reported sensitivity of only 57–79% for ILC, with up to one-third of cases not visualized (6). This diagnostic challenge contributes to delayed presentation, and patients often present with more advanced disease.

BMM indicates advanced disease and portends a poor prognosis (2,3).

Here, we present a rare case of metastatic invasive lobular carcinoma (ILC) with no hypermetabolic breast lesion on FDG PET/CT, diagnosed solely through bone marrow biopsy in a patient with unexplained cytopenias and no prior breast cancer screening. This case highlights the importance of including solid-organ malignancies in the differential diagnosis of hematologic abnormalities and underscores the need for further published case reports to guide clinicians in similar scenarios.

Case Presentation

A 64-year-old woman with a history of smoking (one pack/day in her 20s, quit 5 years before consultation) presented to the ER with acute chest pain, shortness of breath, nausea, and vomiting. A CT angiogram of the chest was obtained because of elevated D-dimer, which revealed no pulmonary embolism but showed a patchy consolidative lesion in the

16 60 left upper lobe and a 5 mm ground-glass nodule in the right lower lobe.
61 Follow-up imaging was recommended to monitor the progression of the
62 nodule.

63 A repeat chest CT in three months demonstrated interval enlargement of
64 the left upper lobe lesion with an 11 × 11 mm solid component,
65 suspicious for primary bronchogenic malignancy. This prompted an
66 FDG PET/CT scan, which was performed the following month. It
67 revealed no hypermetabolic uptake in the lung lesion but demonstrated
68 new diffuse bony lucencies (Figure 1A-C), most prominent in the spine
69 and pelvis, raising concern for hematologic malignancy; notably, there
70 was no evidence of hypermetabolic activity at the breasts.

71 Laboratory evaluation demonstrated progressive anemia,
2 72 thrombocytopenia, and renal impairment (hemoglobin 7.3 g/dL, platelets
73 102–144 × 10³/μL, creatinine 1.3 mg/dL, eGFR 43–54 mL/min/1.73 m²),
74 with Hypercalcemia (corrected calcium 12.4 mg/dL) also noted. She
75 reported fatigue, right hip pain, and intermittent night sweats over six
76 months, but denied weight loss or palpable lymphadenopathy. She
77 required red blood cell transfusions due to anemia and analgesics for
78 bone pain.

79 We suspected multiple myeloma given her unexplained cytopenias, renal
2 80 impairment, and bone lesions. A bone marrow biopsy of the right iliac
81 crest was performed. Histopathology revealed a markedly hypercellular
82 marrow infiltrated by metastatic carcinoma consistent with lobular
83 carcinoma of breast origin. Immunohistochemistry showed ER positivity
84 (50%), PR negativity, HER2 negativity, and GATA3 positivity. There
85 was no evidence of multiple myeloma or lymphoproliferative disorder.
86 On further questioning, the patient reported a slowly enlarging right
87 breast mass present for several years but never previously reported or
88 evaluated. She had not undergone mammography in more than 10 years.

2 89 Family history was notable for a sister with breast cancer. Diagnostic

mammography and ultrasound confirmed a 5–6 cm irregular right breast mass with dermal involvement (Figure 2), nipple retraction, and two enlarged right axillary lymph nodes. She had skin thickening and bumpiness over the concerning region of the breast upon physical examination. Her tumor markers were elevated as well (CA 15-3: 83.8 U/mL; CA 27-29: 143 U/mL)

A whole-body bone scan confirmed multifocal osseous involvement without evidence of pathologic fracture.

The patient was counseled on hormone receptor–positive metastatic breast cancer, treatment pathways, and prognosis. We recommended endocrine therapy with a CDK4/6 inhibitor. She was initiated on letrozole in combination with ribociclib 600 mg daily (3 weeks on/1 week off) per the MONALEESA trial protocol. Interval CT imaging and serial tumor markers were scheduled for response monitoring.

She was also referred to palliative care for supportive management. Her cytopenias showed partial improvement following the initiation of therapy, with the most recent laboratory values showing hemoglobin 8.6 g/dL, platelets $163 \times 10^3/\mu\text{L}$, and calcium 9.6 mg/dL. She continues on monthly intravenous zoledronic acid for bone metastases and additional pain management with oxycodone 10 mg every 6–8 hours and topical lidocaine patches as needed.

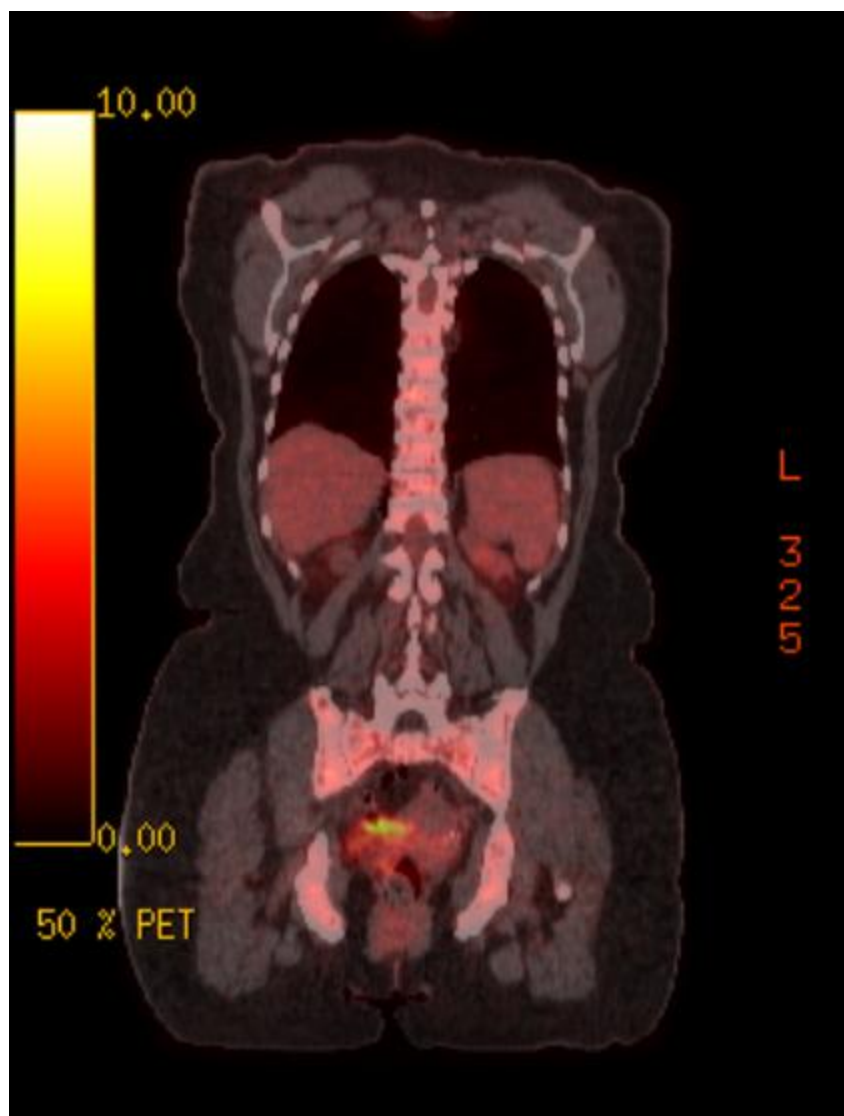
The patient is tolerating letrozole and ribociclib well. Despite extensive marrow infiltration, she remains functionally independent with adequate pain control, and her cytopenias are gradually improving with therapy.

Figure 1A-C. PET/CT images demonstrating diffuse, heterogeneous FDG uptake throughout the bones, with a focal increase in the posterior right iliac. On CT, focal lucencies throughout the skeleton, predominantly in the spine and pelvis. No discrete hypermetabolic lesion

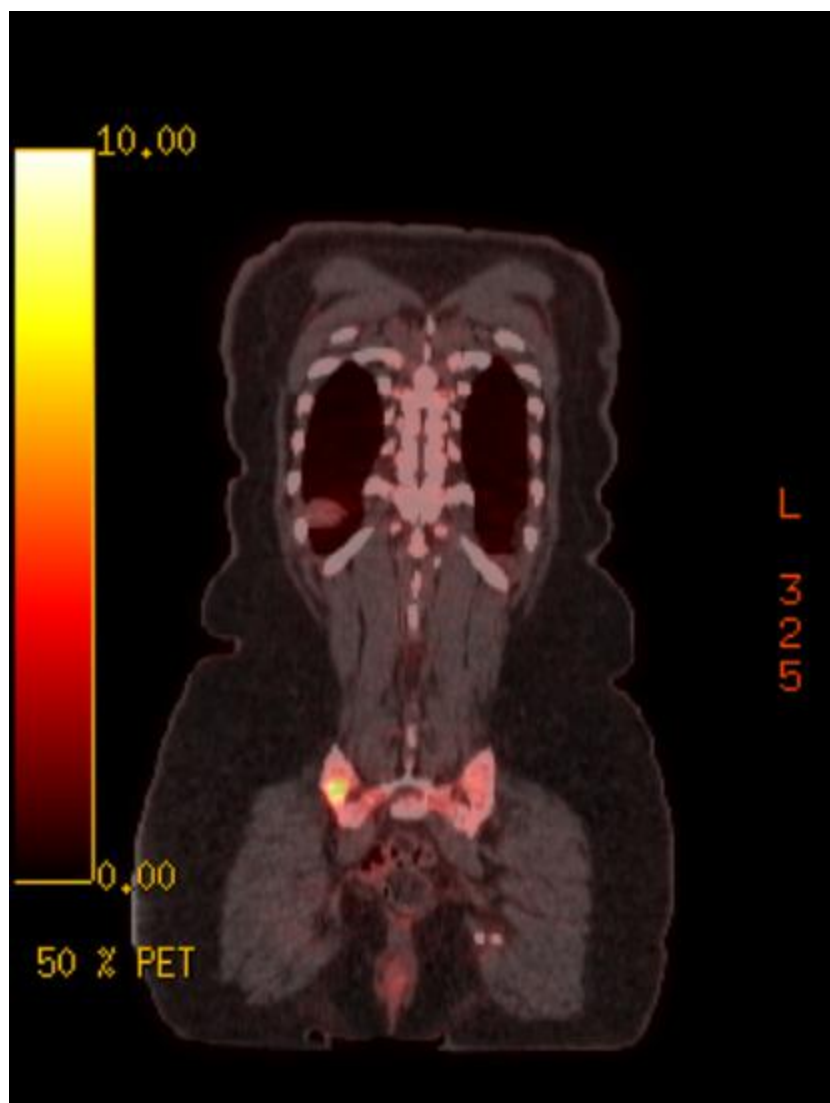
119 is identified in either breast, highlighting the absence of a primary
120 hypermetabolic focus.

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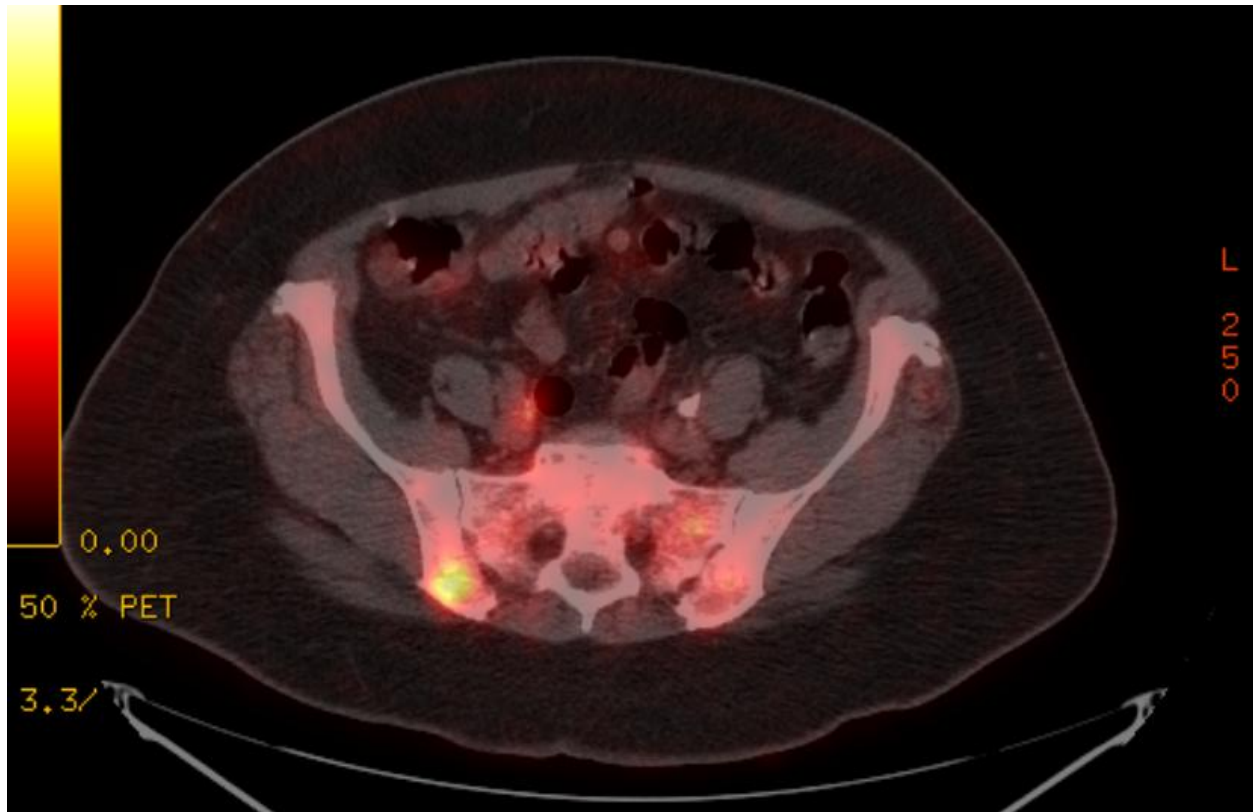
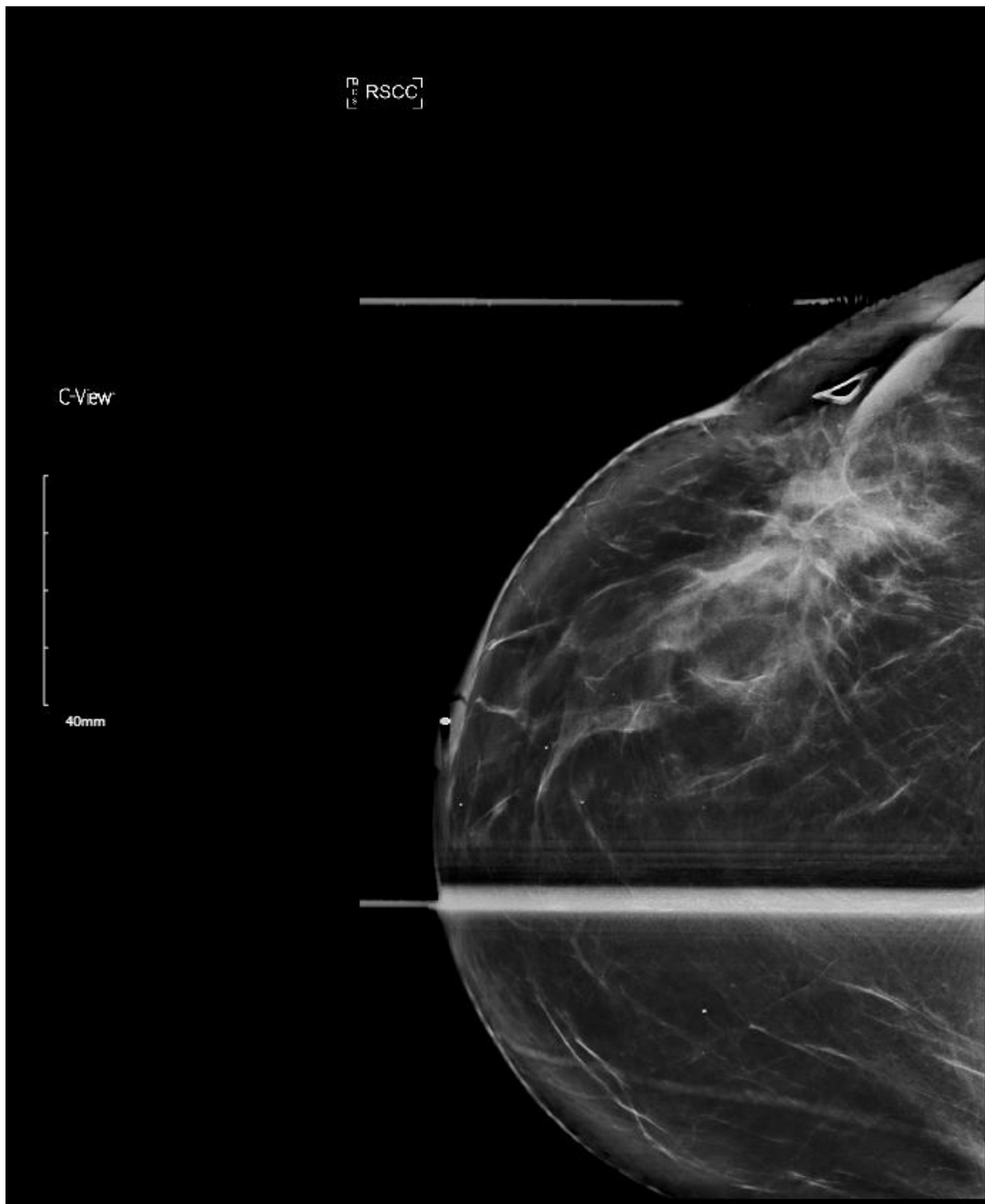


Figure 2. Diagnostic mammography of the right breast. Craniocaudal view showing 59 mm focal asymmetry with associated distortion and ill-defined regions of increased density consistent with infiltrating lobular carcinoma.



130

131 **Discussion**

132 Bone marrow metastasis (BMM) as the first manifestation of breast
133 cancer is rare, particularly in patients without a prior diagnosis (1).

134 Invasive lobular carcinoma (ILC) is notorious for its “stealth” behavior,
135 often evading early detection. Unlike invasive ductal carcinoma, ILC
136 grows in a diffuse, single-file pattern with low cellular density and
137 minimal desmoplastic reaction, making it less likely to form palpable
138 masses or detectable lesions on standard imaging (5). Furthermore,
139 lobular tumors rarely produce calcifications, a feature that typically
140 facilitates mammographic detection. As a result, mammography
141 frequently underestimates tumor size; spiculated masses are more
142 common, while well-circumscribed lesions occur in <1% of cases (5,6).
143 Advanced modalities such as breast MRI, digital breast tomosynthesis,
144 and contrast-enhanced mammography have improved sensitivity, but
145 limitations remain due to costs and high false positive rate (6).

22 146 Imaging plays an evolving role in evaluating metastatic ILC. ¹⁸F-FDG
8 147 PET/CT, while widely used in staging breast cancer, has lower
148 sensitivity for ILC because of its reduced cellular density, low GLUT-1
149 expression, and lower proliferation index (Ki-67) (7,8). In contrast, ¹⁸F-
150 FES PET/CT, which targets estrogen receptor expression, has shown
151 superior sensitivity in detecting ILC lesions, particularly in bone.
152 Combined use of FDG and FES tracers may also provide prognostic
153 information, with high FDG uptake correlating with worse outcomes
154 (7,9,10).

155 In our patient, ¹⁸F-FDG PET/CT revealed paradoxical findings: no
156 hypermetabolic activity in the breast, yet diffuse uptake in the bone
157 marrow. This phenomenon may be explained by the biology of ILC and
158 its bone marrow niche (11). While the primary breast lesion remained
159 metabolically inactive due to low glycolytic activity, the diffuse
160 metastatic deposits in bone marrow likely exhibited increased FDG
161 uptake because of higher tumor cell concentration and the marrow’s
162 supportive microenvironment, which is rich in growth factors and
163 nutrients that promote tumor proliferation (11–13). These findings, along

with the development of progressive cytopenias (anemia, thrombocytopenia), hypercalcemia, and bone pain, painted a clear clinical picture of hematologic disorder. The differential diagnosis, appropriately, included hematologic malignancies like multiple myeloma.

Given the overlapping clinical and radiologic picture, bone marrow biopsy remains an indispensable diagnostic tool. It is inexpensive, definitive, and considered the “gold standard” for confirming marrow metastases in unsuspected cases (6). In our patient, biopsy excluded hematologic disease and revealed carcinoma with classic lobular morphology. Metastatic ILC can have a similar single-file appearance on histology, which can make it difficult to differentiate from other metastases or from a primary tumor of the organ in question.

Immunohistochemistry is necessary to confirm the diagnosis (6,14). In our case, Immunohistochemistry confirmed the diagnosis, which showed GATA3 positivity, ER 50%, PR negativity, and HER2 negativity, consistent with the molecular fingerprint of ILC (3,6,15). The loss of E-cadherin, a hallmark of ILC, facilitates the diffuse infiltration seen both in the breast and in metastatic sites such as bone marrow (14,15).

BMM carries significant clinical consequences. In this case, marrow replacement led to progressive cytopenias (anemia, thrombocytopenia), transfusion dependence, bone pain, and hypercalcemia (3,16).

Hypercalcemia likely reflected cytokine-driven osteoclast activation and tumor-mediated bone resorption (17,18). Literature suggests that BMM from breast cancer, often from ILC, portends a poor prognosis, with survival ranging from 6.4 to 19 months (3,15). Although early screening might have identified the breast lesion in our patient, the insidious growth pattern of ILC means that even routine mammography may not have prevented progression.

The patient's tumor profile (HR+/HER2-) guided therapy toward modern standards of care (5,15). She was initiated on letrozole (aromatase inhibitor) with ribociclib (CDK4/6 inhibitor), in line with the MONALEESA-2 trial, which demonstrated superior progression-free survival (~24 months) compared to endocrine therapy (12.3 months) alone (19,20). This regimen is biologically rational, as the cyclin D-CDK4/6 pathway is a downstream effector of estrogen receptor signaling (20). Encouragingly, our patient showed partial improvement in cytopenias and normalization of calcium levels after treatment initiation.

Bone-directed therapy is a crucial adjunct. Monthly zoledronic acid was added to inhibit osteoclast-mediated bone resorption, thereby alleviating hypercalcemia, reducing bone pain, and preventing skeletal-related events (SREs) such as fractures (20). Denosumab, a RANK-ligand antibody, can be used as an alternative to zoledronic acid and may better delay skeletal-related events in BMM (18). Despite advances, BMM in ILC remains an adverse prognostic marker. However, the introduction of CDK4/6 inhibitors and targeted endocrine therapy has meaningfully improved outcomes, offering patients prolonged disease control and improved quality of life compared with historical expectations (3,18-20).

Conclusion

This case exemplifies the diagnostic complexity and aggressive course of invasive lobular carcinoma, which presented with bone marrow metastasis (BMM) and hematologic decline in the absence of a known primary in our case. The absence of a hypermetabolic breast lesion on FDG PET/CT, coupled with cytopenias and bone pain, initially mimicked a hematologic malignancy, underscoring the importance of maintaining a broad differential diagnosis. In such cases, Bone marrow biopsy along with IHC staining is proven to establish the correct diagnosis and direct treatment. Despite the poor prognosis associated

with BMM, our patient demonstrated encouraging early clinical improvement with combination endocrine therapy and a CDK4/6 inhibitor, alongside bisphosphonate therapy for bone protection. This case reinforces the need for heightened awareness of the “stealth” nature of ILC, the limitations of conventional imaging, and the critical role of bone marrow biopsy in unexplained cytopenias. Broader reporting of such cases will aid clinicians in recognizing similar presentations and avoiding diagnostic delays.

Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

1. Kenzhegulov YN, Zhamoldin DK, Aleinikov VG, Kerimbayev TT, Zhetpisbaev B, Akshulakov S. Extensive thoracic vertebral and chest wall metastases as the initial presentation of breast cancer: a case report and literature review. *Front Oncol.* 2025 July 17;15:1632700.
2. Nakagawa T, Hayashi K, Ogawa A, Oda G, Onishi I, Yamamoto M, et al. Bone Marrow Carcinomatosis in a Stage IV Breast Cancer Patient Treated by Letrozole as First-Line Endocrine Therapy. *Case Rep Oncol.* 2022 Apr 22;15(1):436–41.
3. F B. Breast carcinoma initially diagnosed by Bone Marrow Metastasis; case report and literature review. *Obstet Gynecol Int J.* 2022 Dec 5;13(6):374–6.

- 254 4. Yang C, Lei C, Zhang Y, Zhang J, Ji F, Pan W, et al. Comparison of Overall Survival
255 Between Invasive Lobular Breast Carcinoma and Invasive Ductal Breast Carcinoma: A
256 Propensity Score Matching Study Based on SEER Database. *Front Oncol.* 2020 Dec
257 22;10:590643.
- 258 5. Costantini M, Montella RA, Fadda MP, Tondolo V, Franceschini G, Bove S, et al. Diagnostic
259 Challenge of Invasive Lobular Carcinoma of the Breast: What Is the News? *Breast Magnetic*
260 *Resonance Imaging and Emerging Role of Contrast-Enhanced Spectral Mammography.* *J*
261 *Pers Med.* 2022 May 25;12(6):867.
- 262 6. Johnson K, Sarma D, Hwang ES. Lobular breast cancer series: imaging. *Breast Cancer Res*
263 *BCR.* 2015 July 11;17(1):94.
- 264 7. Liu C, Ma G, Xu X, Song S, Yang Z. Can 18F-FES PET Improve the Evaluation of 18F-FDG
265 PET in Patients With Metastatic Invasive Lobular Carcinoma? *Clin Nucl Med.* 2024
266 Apr;49(4):301–7.
- 267 8. Fujii T, Yajima R, Kurozumi S, Higuchi T, Obayashi S, Tokiniwa H, et al. Clinical Significance
268 of 18F-FDG-PET in Invasive Lobular Carcinoma. *Anticancer Res.* 2016 Oct;36(10):5481–5.
- 269 9. Ulaner GA, Jhaveri K, Chandarlapaty S, Hatzoglou V, Riedl CC, Lewis JS, et al. Head-to-
270 Head Evaluation of 18F-FES and 18F-FDG PET/CT in Metastatic Invasive Lobular Breast
271 Cancer. *J Nucl Med Off Publ Soc Nucl Med.* 2021 Mar;62(3):326–31.
- 272 10. Manohar PM, Peterson LM, Jenkins IC, Wu QV, Kurland BF, Novakova-Jiresova A, et al.
273 [18 F]-Fluoroestradiol PET (FES-PET) and [18 F] Flurodeoxyglucose PET (FDG-PET)
274 Imaging May Aid in Managing Therapy in Patients with Metastatic Lobular Breast Cancer.
275 *Mol Imaging Biol.* 2025 June;27(3):410–20.
- 276 11. He H, Gonzalez A, Robinson E, Yang WT. Distant Metastatic Disease Manifestations in
277 Infiltrating Lobular Carcinoma of the Breast. *Am J Roentgenol.* 2014 May;202(5):1140–8.
- 278 12. Inukai J, Ohnishi A, Tagawa S, Hayashi K, Sakamoto N, Nakamura T, et al. Diseases
279 showing diffuse bone uptake on FDG-PET. *J Nucl Med.* 2019 May 1;60(supplement 1):1155.
- 280 13. Gunalp B, Oner AO, Ince S, Alagoz E, Ayan A, Arslan N. Evaluation of radiographic and
281 metabolic changes in bone metastases in response to systemic therapy with (18)FDG-
282 PET/CT. *Radiol Oncol.* 2015 June;49(2):115–20.
- 283 14. Wong YM, Jagmohan P, Goh YG, Putti TC, Ow SGW, Thian YL, et al. Infiltrative pattern
284 of metastatic invasive lobular breast carcinoma in the abdomen: a pictorial review. *Insights*
285 *Imaging.* 2021 Dec;12(1):181.
- 286 15. Klumpp LC, Shah R, Syed N, Fonseca G, Jordan J. Invasive Lobular Breast Carcinoma
287 Can Be a Challenging Diagnosis Without the Use of Tumor Markers. *Cureus [Internet].* 2020
288 May 31 [cited 2025 Sept 1]; Available from: [https://www.cureus.com/articles/32860-invasive-](https://www.cureus.com/articles/32860-invasive-lobular-breast-carcinoma-can-be-a-challenging-diagnosis-without-the-use-of-tumor-markers)
289 [lobular-breast-carcinoma-can-be-a-challenging-diagnosis-without-the-use-of-tumor-markers](https://www.cureus.com/articles/32860-invasive-lobular-breast-carcinoma-can-be-a-challenging-diagnosis-without-the-use-of-tumor-markers)
- 290 16. Yang R, Jia L, Lu G, Lv Z, Cui J. Symptomatic bone marrow metastases in breast
291 cancer: A retrospective cohort study. *Front Oncol.* 2022 Dec 19;12:1042773.

- 292 17. Jayarangaiah A, Kemp AK, Theetha Kariyanna P. Bone Metastasis. In: StatPearls
293 [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Sept 1]. Available
294 from: <http://www.ncbi.nlm.nih.gov/books/NBK507911/>
- 295 18. Steger GG, Bartsch R. Denosumab for the treatment of bone metastases in breast
296 cancer: evidence and opinion. *Ther Adv Med Oncol*. 2011 Sept;3(5):233–43.
- 297 19. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al.
298 Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole
299 versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast
300 cancer. *Ann Oncol Off J Eur Soc Med Oncol*. 2018 July 1;29(7):1541–7.
- 301 20. Pangarsa EA, Astuti PD, Rizky D, Tandarto K, Setiawan B, Winarno AA, et al. First-line
302 endocrine therapy combined with CDK 4/6 inhibitor in disseminated carcinomatosis of bone
303 marrow (DCBM) luminal breast cancer: a case report. *J Med Case Reports*. 2024 Dec
304 5;18(1):591.

305

306

307