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RESEARCH ARTICLE

BONE MARROW BIOPSY REVEALS OCCULT INVASIVE LOBULAR CARCINOMA WITHOUT HYPERMETABOLIC BREAST LESION ON FDG PET/CT

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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 onmammograph y, 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 hypercalce mia. 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). Subsequ ent 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

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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:-

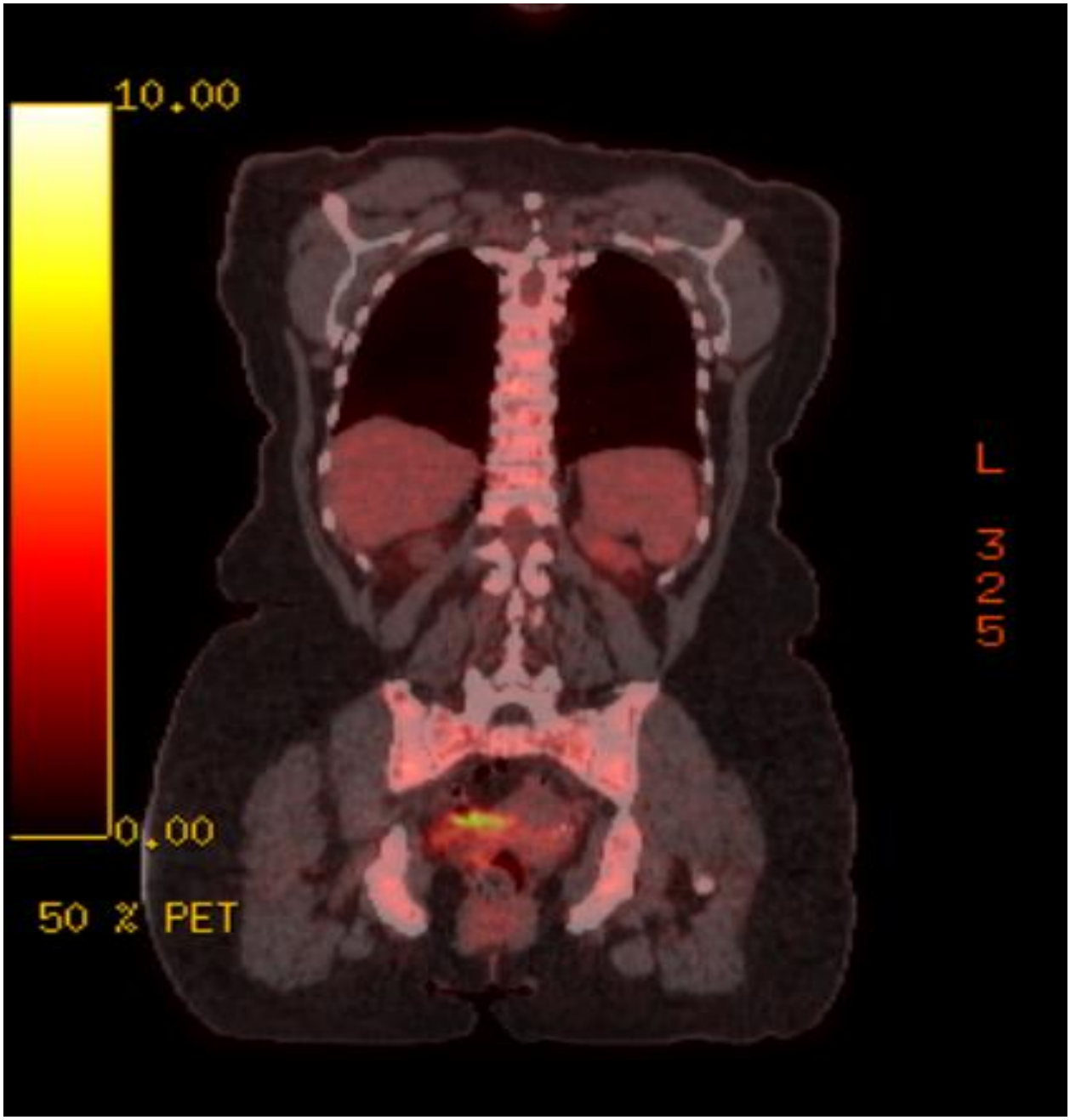
A 64-year-old woman with a history of smoking (one pack/day in her 20s, quit 5 years before consultation) presented to the ER with acute chest pain, shortness of breath, nausea, and vomiting. A CT angiogram of the chest was obtained because of elevated D-dimer, which revealed no pulmonary embolism but showed a patchy consolidative lesion in the left upper lobe and a 5 mm ground-glass nodule in the right lower lobe. Follow-up imaging was recommended to monitor the progression of the nodule.A repeat chest CT in three months demonstrated interval enlargement of the left upper lobe lesion with an 11 × 11 mm solid component, suspicious for primary bronchogenic malignancy.

This prompted an FDG PET/CT scan, which was performed the following month. It revealed no hypermetabolic uptake in the lung lesion but demonstrated new diffuse bony lucencies (Figure 1A-C), most prominent in the spine and pelvis, raising concern for hematologic malignancy; notably, there was no evidence of hypermetabolic activity at the breasts.Laboratory evaluation demonstrated progressive anemia, thrombocytopenia, and renal impairment (hemoglobin 7.3 g/dL, platelets 102–144 × 10^3/μL, creatinine 1.3 mg/dL, eGFR 43–54 mL/min/1.73 m^2), with Hypercalcemia (corrected calcium 12.4 mg/dL) also noted.

She reported fatigue, right hip pain, and intermittent night sweats over six months, but denied weight loss or palpable lymphadenopathy. She required red blood cell transfusions due to anemia and analgesics for bone pain.We suspected multiple myeloma given her unexplained cytopenias, renal impairment, and bone lesions. A bone marrow biopsy of the right iliac crest was performed. Histopathology revealed a markedly hypercellular marrow infiltrated by metastatic carcinoma consistent with lobular carcinoma of breast origin. Immunohistochemistry showed ER positivity (50%), PR negativity, HER2 negativity, and GATA3 positivity. There was no evidence of multiple myeloma or lymphoproliferative disorder.On further questioning, the patient reported a slowly enlarging right breast mass present for several years but never previously reported or evaluated. She had not undergone mammography in more than 10 years. 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 × 10^3/μL, 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 is identified in either breast, highlighting the absence of a primary hypermetabolic focus.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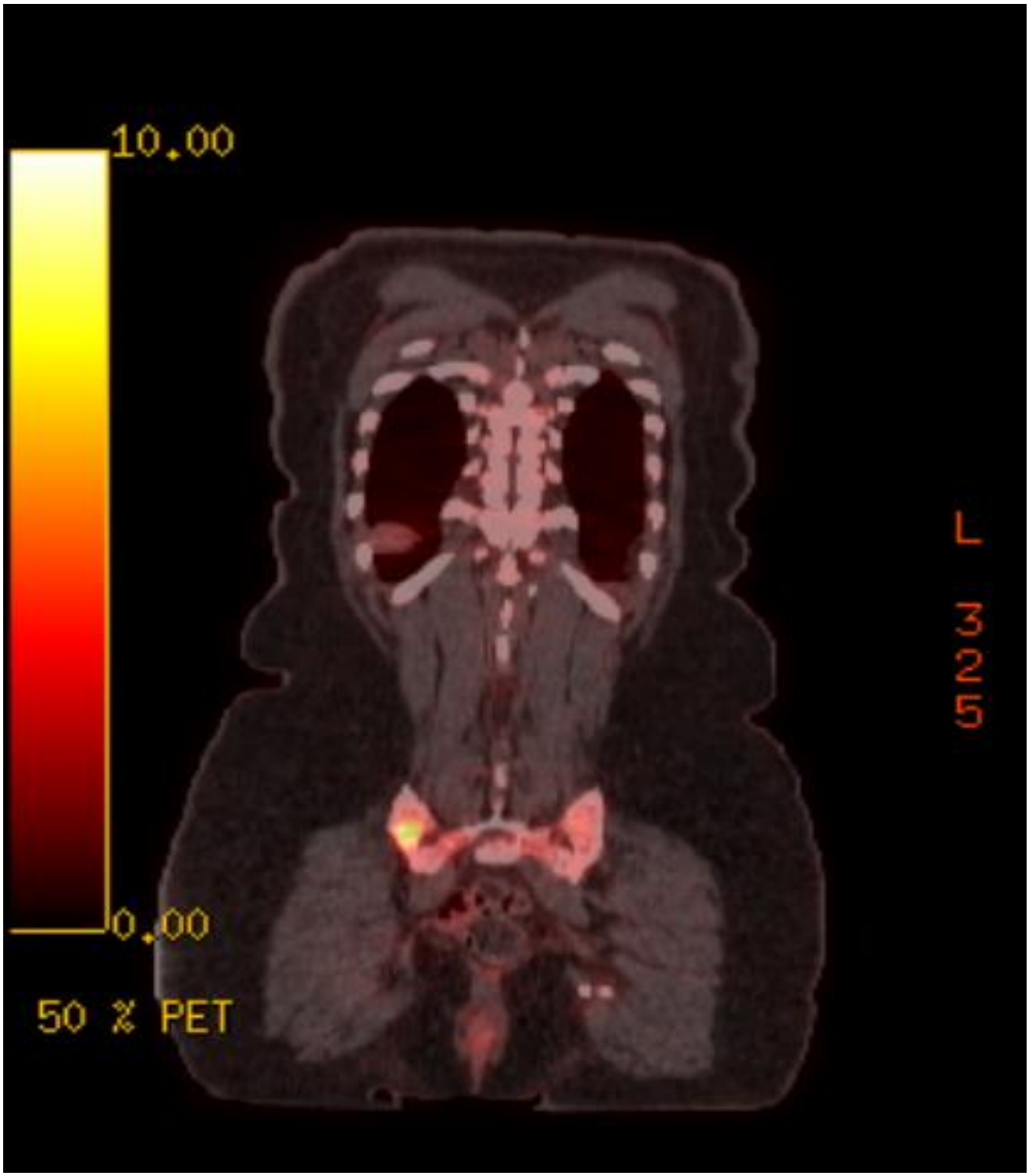
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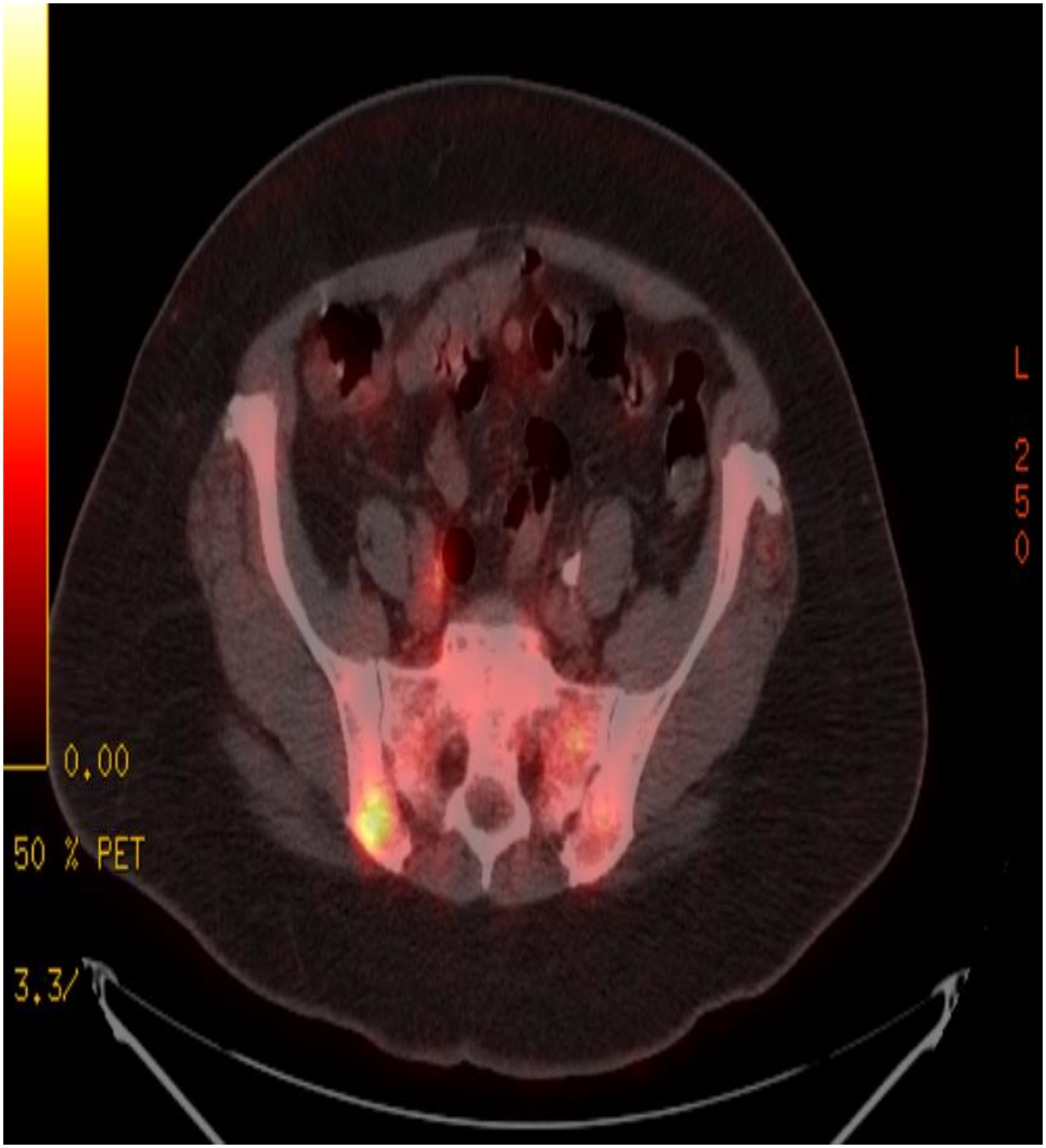
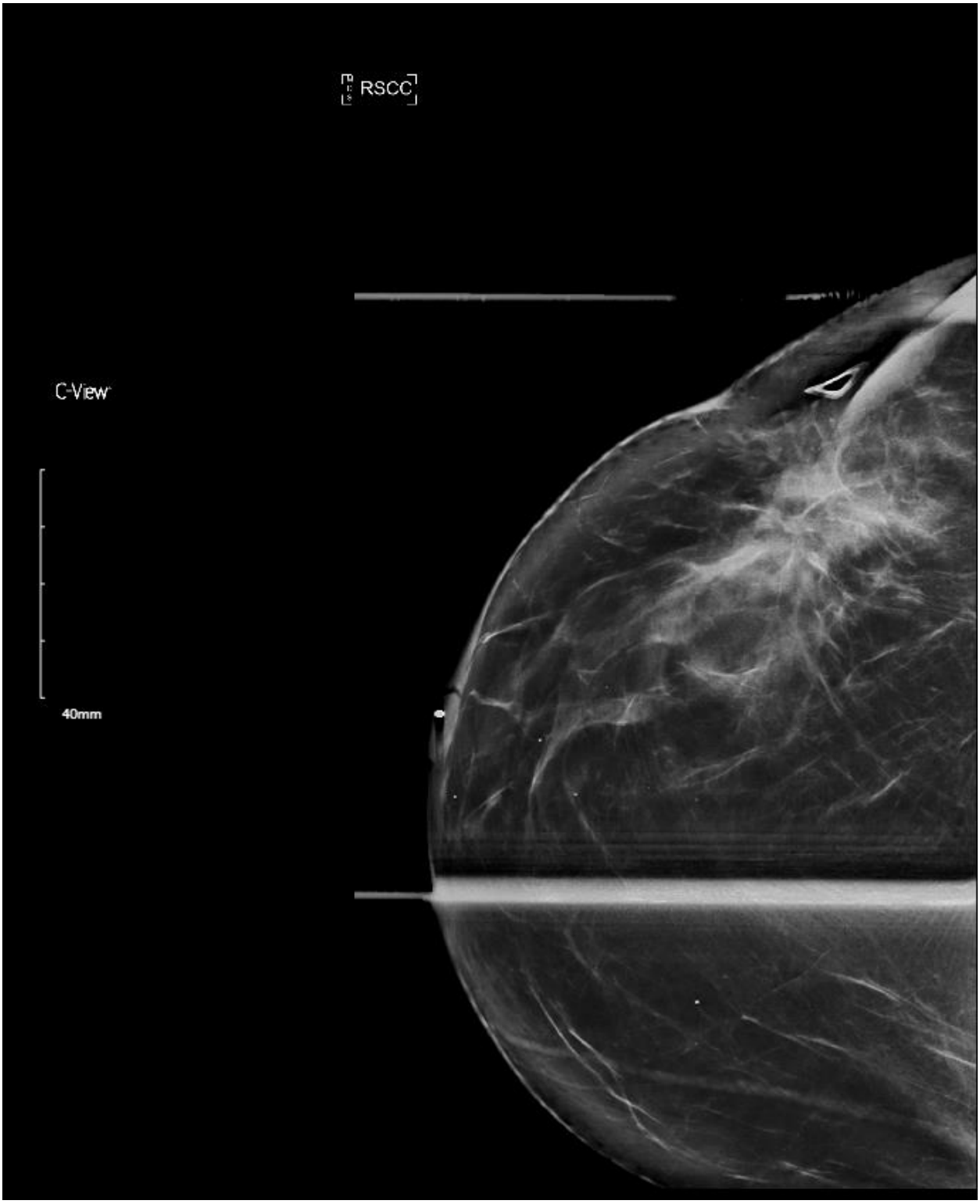


Figure 2. Diagnostic mammography of the right breast. Craniocaudal view showing 59 mm focal asymmetry with associated distortion and ill-defined regions of increased density consistent with infiltrating lobular carcinoma.



Discussion:-

Bone marrow metastasis (BMM) as the first manifestation of breast cancer is rare, particularly in patients without a prior diagnosis (1). Invasive lobular carcinoma (ILC) is notorious for its "stealth" behavior, often evading early detection. Unlike invasive ductal carcinoma, ILC grows in a diffuse, single-file pattern with low cellular density and minimal desmoplastic reaction, making it less likely to form palpable masses or detectable lesions on standard

imaging (5). Furthermore, lobular tumors rarely produce calcifications, a feature that typically facilitates mammographic detection. As a result, mammography frequently underestimates tumor size; spiculated masses are more common, while well-circumscribed lesions occur in <1% of cases (5,6). Advanced modalities such as breast MRI, digital breast tomosynthesis, and contrast-enhanced mammography have improved sensitivity, but limitations remain due to costs and high false positive rate (6).

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

In our patient, ^18F-FDG PET/CT revealed paradoxical findings: no hypermetabolic activity in the breast, yet diffuse uptake in the bone marrow. This phenomenon may be explained by the biology of ILC and its bone marrow niche(11). While the primary breast lesion remained metabolically inactive due to low glycolytic activity, the diffuse metastatic deposits in bone marrow likely exhibited increased FDG uptake because of higher tumor cell concentration and the marrow's supportive microenvironment, which is rich in growth factors and 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:
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Abbreviations:
ILC – Invasive lobular carcinoma
BMM – Bone marrow metastasis
IDC – Invasive ductal carcinoma
FDG PET/CT - Fluorodeoxyglucose positron emission tomography/computed tomography
IHC – Immunohistochemistry
HR – Hormone receptor
HER2 – Human epidermal growth factor receptor 2
SREs – Skeletal-related events
CDK4/6 inhibitors – Cyclin-dependent kinase 4/6 inhibitors

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