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Extramedullary Involvement of the Breast by Systemic Multiple Myeloma as the Initial Presentation of Plasma Cell Myeloma: A Rare Case

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ABSTRACT

Background: Extramedullary involvement by systemic multiple myeloma is a rare manifestation of plasma cell myeloma, most commonly arising in the upper aerodigestive tract. Breast involvement is exceptionally uncommon and can mimic primary or recurrent breast carcinoma, creating diagnostic challenges.

Case presentation: A 64-year-old woman with a history of invasive ductal carcinoma presented with a new breast lesion on screening mammography. Imaging demonstrated a small, circumscribed nodule, and core biopsy revealed monoclonal plasma cell infiltration. Magnetic resonance imaging (MRI) showed multiple breast lesions, while bone marrow biopsy confirmed more than 90% plasma cell involvement with high-risk cytogenetics, including 1q21 amplification. These findings established a diagnosis of extramedullary involvement of the breast by systemic multiple myeloma (MM). The patient was treated with daratumumab-based systemic therapy, achieving remission with eventual minimal residual disease negativity on follow-up testing. She remains without clinical or radiographic evidence of breast disease.

Conclusion: Breast involvement by systemic MM is a rare manifestation of plasma cell myeloma and should be considered in the differential diagnosis of new breast lesions. Early biopsy and comprehensive pathologic evaluation are essential to avoid misdiagnosis and guide appropriate systemic therapy.

INTRODUCTION

Multiple myeloma (MM) is a malignant proliferation of clonal plasma cells primarily involving the bone marrow.¹ A small subset (approximately 3% to 5%) initially manifests as extramedullary involvement by systemic multiple myeloma, most commonly in the upper aerodigestive tract.² Breast involvement is exceptionally rare and represents a small fraction of both extramedullary involvement by systemic multiple myeloma and breast neoplasms.³

Breast plasmacytomas may mimic benign or malignant breast lesions, including recurrent or primary breast carcinoma, making radiologic interpretation particularly difficult. Imaging findings are often nonspecific, making histopathologic confirmation essential to avoid misdiagnosis and unnecessary surgical intervention.⁴

Extramedullary disease is associated with aggres-

sive tumor biology and frequently correlates with high-risk cytogenetic abnormalities, including chromosome 1q21 amplification.⁵

We report a case of extramedullary involvement of the breast by systemic MM as the initial presentation of MM in a patient with prior breast carcinoma, highlighting key diagnostic challenges and the role of cytogenetic and minimal residual disease (MRD)-guided management.

CASE PRESENTATION

A 64-year-old woman with a history of right breast invasive ductal carcinoma diagnosed 6 years earlier and treated with lumpectomy, sentinel lymph node biopsy, radiation therapy, and adjuvant endocrine therapy presented for routine screening mammography. Screening mammography demonstrated a 0.5-cm partially ob-



Figure 1. Screening Mammography

Routine screening mammography revealed a partially obscured 0.5-cm mass in the 6-o'clock position of the right breast.

scured mass in the 6-o'clock position of the right breast and was assigned a Breast Imaging Reporting and Data System (BI-RADS) 0 (Incomplete: Need Additional Imaging Evaluation) assessment (Figure 1).

Subsequent diagnostic mammography demonstrated a persistent circumscribed low-density nodule at the 6-o'clock position and a questionable area of increased density adjacent to the prior lumpectomy site. Targeted ultrasound showed no sonographic correlate to the area of increased density but identified a 0.9-cm well-circumscribed echogenic mass at the 6-o'clock position corresponding to the mammographic finding (Figure 2).

Based on the combined diagnostic mammographic and sonographic findings, the examination was again assigned a BI-RADS 0 (Incomplete: Need Additional Imaging Evaluation) assessment, with breast magnetic resonance imaging (MRI) recommended for further characterization. Given the persistent imaging abnormality and the patient's history of breast cancer, ultrasound-guided core needle biopsies were performed before MRI. Core needle biopsy of the 6-o'clock lesion demonstrated a dense monoclonal plasma cell infiltrate consistent with a plasma cell neoplasm (Figure 3).

Plasma cells were positive for CD138 and showed



Figure 2. Targeted Ultrasound of the Right Breast
Targeted ultrasound of the right breast demonstrated a well-circumscribed hyperechoic mass measuring 0.86 × 0.61 cm at the 6-o'clock position, with features that may overlap with both benign and malignant lesions.

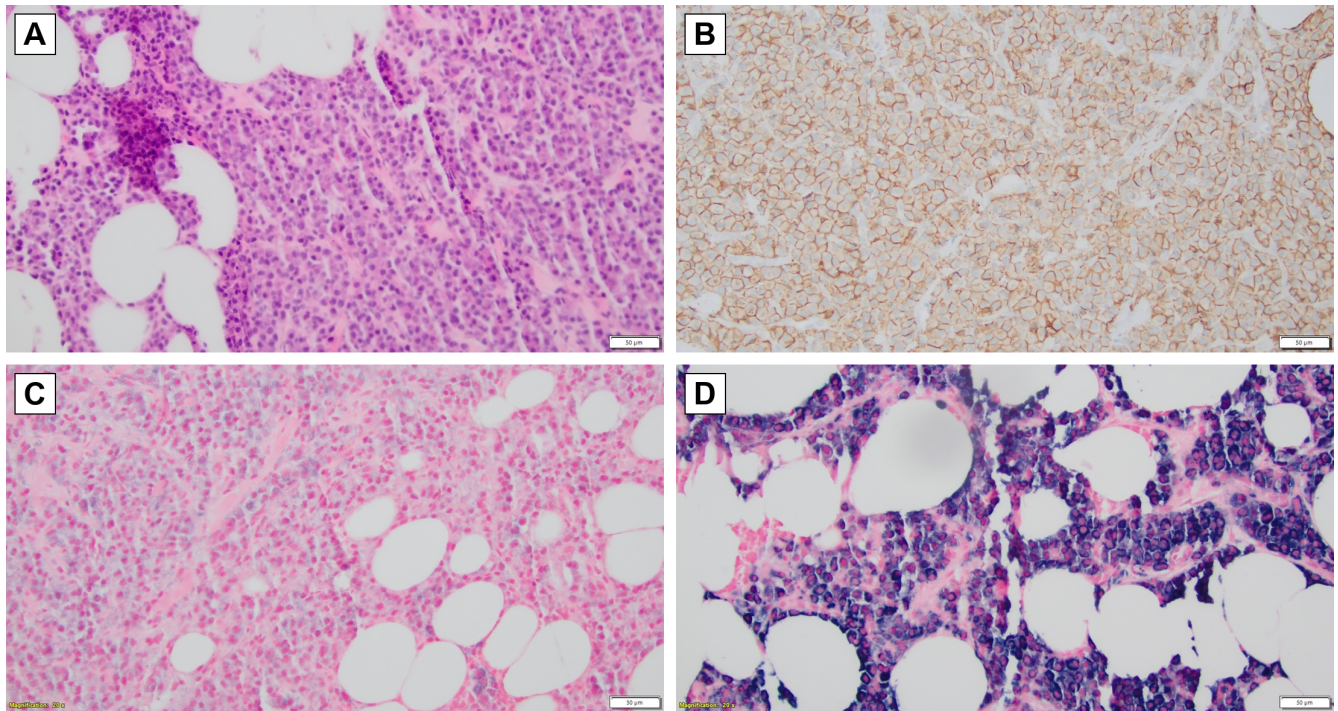


Figure 3. Right Breast Core Biopsy

Hematoxylin and eosin (H&E)-stained section demonstrates mammary tissue infiltrated by sheets of plasma cells. A, H&E, 20 $\times$; B, CD138, 20 $\times$; C, lambda in situ hybridization, 20 $\times$; D, kappa in situ hybridization, 20 $\times$.

kappa restriction by in situ hybridization, while they were negative for cytokeratin AE1/AE3. Immunostains showed plasma cells that were positive for cyclin D1 and CD117, while they were negative for CD20 and CD56. Ki-67 was not performed as part of the original diagnostic evaluation. The diagnosis was supported by morphology, light-chain restriction, immunophenotype, and subsequent bone marrow evaluation.

Breast MRI demonstrated multiple well-circumscribed enhancing masses throughout the four quadrants of the right breast measuring up to 6 mm without contralateral disease or axillary lymphadenopathy. There was no abnormal non-mass enhancement in either breast. No evidence of recurrent breast malignancy was noted. This MRI examination was assigned BI-RADS 6 because the plasma cell neoplasm had already been confirmed by core needle biopsy (Figure 4). Whole-body fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) demonstrated no additional FDG-avid extramedullary lesions or focal osseous abnormalities. Although PET/CT did not demonstrate overt systemic disease, subsequent bone marrow biopsy revealed diffuse plasma cell infiltration involving more than 90% of the marrow. This finding highlights that diffuse marrow involvement may not always be detected by PET/CT, emphasizing the complementary role of bone marrow examination in the staging of multiple myeloma.⁶

The patient was initiated on induction therapy with daratumumab, lenalidomide, bortezomib, and dexamethasone (D-RVD) in February 2025. After 6 cycles, bortezomib was discontinued in June 2025 because of treatment-related peripheral neuropathy,

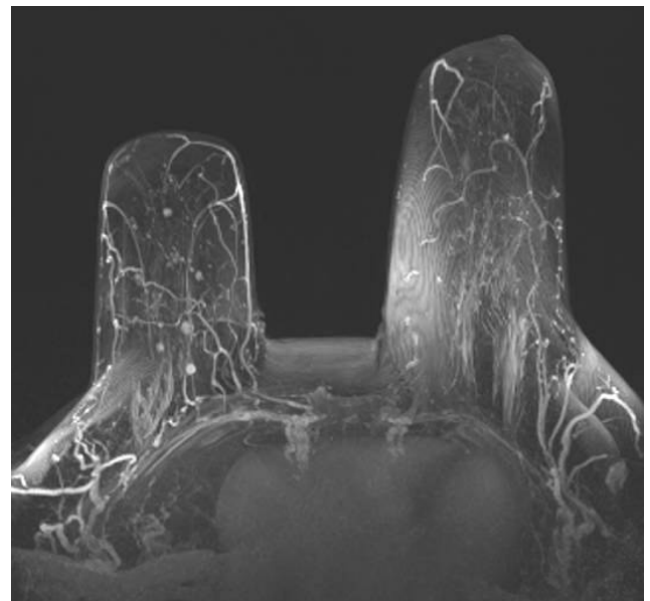


Figure 4. Breast Magnetic Resonance Imaging Findings

Breast magnetic resonance imaging (MRI) demonstrated multiple enhancing, circumscribed subcentimeter masses throughout the right breast without contralateral involvement or axillary lymphadenopathy. Bone marrow biopsy showed more than 90% plasma cell involvement, with fluorescence in situ hybridization (FISH) revealing high-risk cytogenetic abnormalities, including 1q21 amplification, trisomy 5, and gain of chromosome 9. These findings established extramedullary breast involvement by systemic multiple myeloma and helped avoid unnecessary surgery for presumed recurrent breast carcinoma.

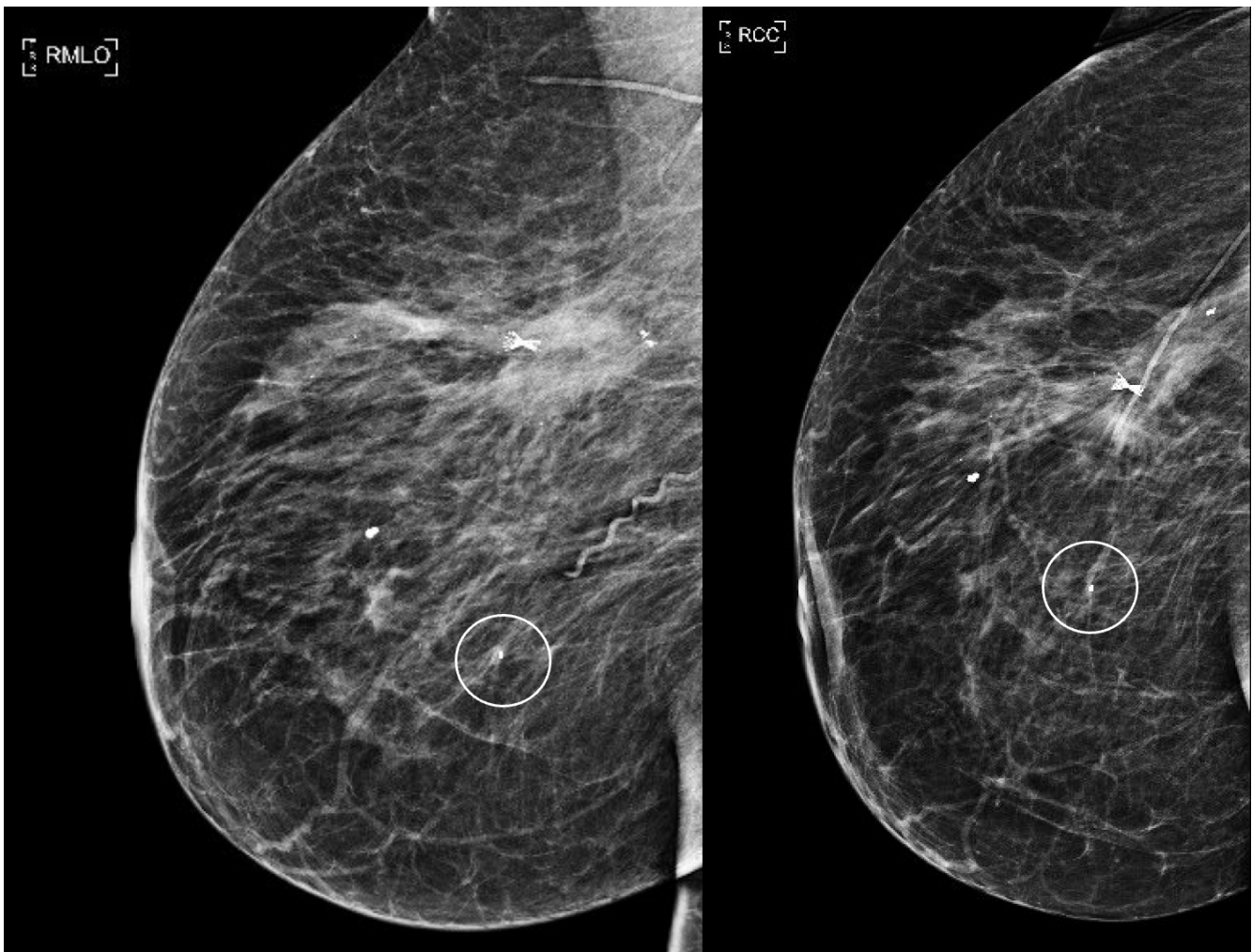


Figure 5. Follow-up Mammography

Follow-up mammography demonstrated no residual or recurrent mass at the previously biopsied site in the right breast, with no new suspicious findings, consistent with treatment response.

and lenalidomide was temporarily held in August 2025 for stem cell collection. A repeat bone marrow biopsy performed in September 2025 demonstrated no morphologic or immunophenotypic evidence of residual plasma cell neoplasm and was MRD-negative on ClonoSEQ next-generation sequencing. She subsequently began maintenance therapy with daratumumab and lenalidomide in October 2025. At her most recent follow-up in March 2026, approximately 13 months after initiation of induction therapy and 5 months after starting maintenance therapy, she remained in clinical remission, with MRD undetectable by ClonoSEQ. Follow-up mammography and targeted ultrasound demonstrated only stable post-lumpectomy scarring, with complete resolution of the previously identified plasma cell lesion and no new suspicious imaging findings (Figures 5 and 6).

She continues maintenance therapy, with a repeat bone marrow biopsy planned for July 2027 to assess for sustained MRD-negative remission and determine whether a treatment holiday may be appropriate.

DISCUSSION

A review of published reports over the past decade demonstrates that breast plasma cell neoplasms



Figure 6. Follow-up Ultrasound

Follow-up ultrasound of the right breast demonstrated no residual mass at the 6-o'clock position, further supporting complete radiographic response to systemic therapy.



span a broad clinical spectrum, including solitary extramedullary plasmacytoma, secondary breast involvement by relapsed or established multiple myeloma, bilateral disease, implant-associated disease, and breast involvement as the initial manifestation of systemic MM (Table 1).

Distinguishing between these entities is clinically important because management and prognosis differ substantially.^{25,26} Breast involvement by plasma cell neoplasms accounts for less than 1% of breast tumors and approximately 0.2% of all breast malignancies.^{16,27} While extramedullary involvement by systemic multiple myeloma comprises approximately 4% of plasma cell neoplasms, breast involvement remains uncommon and only rarely represents the initial manifestation of MM.²¹ Due to nonspecific imaging features, these lesions may

mimic benign breast masses, metastatic disease, or primary breast carcinoma, especially in patients with a prior history of breast cancer.⁴ Solitary plasmacytomas generally demonstrate excellent local control following radiation or surgical excision; however, long-term surveillance remains essential because of the risk of progression to systemic MM.²¹

According to the current World Health Organization (WHO) Classification of Haematolymphoid Tumours and the International Consensus Classification (ICC), plasma cell neoplasms comprise solitary plasmacytoma of bone (SPB), extramedullary plasmacytoma (EMP), and plasma cell myeloma (MM). Plasma cell myeloma may demonstrate extramedullary involvement during the course of the disease. Solitary extramedullary plasmacytoma is defined by the absence of systemic bone marrow involvement or other

Table 1. Published cases of breast plasma cell neoplasms reported since 2016

Study	Patient	Clinical presentation	Diagnosis/category	Treatment	Key teaching point
Park, 2016 ⁷	35F	Bilateral breast lesions preceding systemic disease	Breast plasmacytoma preceding MM	Systemic myeloma therapy	Breast involvement can rarely be an early manifestation before MM is fully established.
da Cunha Fischer et al., 2016 ⁸	52F	Bilateral breast masses	Bilateral breast plasmacytoma	Systemic therapy	Demonstrates bilateral breast involvement by plasma cell neoplasm.
Urano et al., 2019 ⁹	85F	Relapsed MM presenting as breast lesion	Relapsed MM with breast extramedullary disease	Systemic therapy	Imaging findings may resemble primary breast malignancy.
Beydoun et al., 2019 ¹⁰	Female	Breast implant-associated lesion	Breast implant-associated plasmacytoma	Local/systemic management	Rare implant-associated plasma cell neoplasm; important non-ALCL implant differential.
Vong et al., 2020 ¹¹	74F	Breast mass in patient with MM	Extramedullary breast involvement by MM	Systemic therapy	Highlights need for biopsy and systemic evaluation.
Eden et al., 2020 ¹²	73F	Bilateral breast lesions	Secondary extramedullary MM involving both breasts	Systemic therapy	Bilateral disease can occur without axillary nodal involvement.
Mehta et al., 2021 ¹³	50F	Solitary breast mass	Solitary extramedullary plasmacytoma	Local therapy	Solitary breast EMP (extramedullary plasmacytoma) requires exclusion of systemic MM.
Tawel et al., 2022 ¹⁴	55F	Painless unilateral breast mass	Extramedullary breast lesion of MM	Systemic therapy	Reinforces histopathologic and imaging correlation.
Mo et al., 2022 ¹⁵	59F	Multiple bilateral breast nodules in known MM	Bilateral breast involvement by MM	Systemic/palliative care	Multifocal bilateral breast MM has nonspecific imaging and poor prognosis.
McCormack et al., 2023 ¹⁶	79F	Incidental unilateral breast mass	Solitary extramedullary plasmacytoma	Excision/radiotherapy	Isolated breast EMP (extramedullary disease) can occur without systemic MM.
Shiva et al., 2024 ¹⁷	55F	Solitary breast lesion	Solitary plasmacytoma of the breast	Local therapy	Adds to rare primary/solitary breast plasmacytoma literature.



Table 1 (continued)

Study	Patient	Clinical presentation	Diagnosis/category	Treatment	Key teaching point
Madan et al., 2024 ¹⁸	60F	Enlarging right breast mass	Isolated breast plasmacytoma	Surgical excision + radiotherapy	Workup excluded MM; no recurrence at 2 years.
Alsaleh et al., 2024 ¹⁹	54F	Bilateral breast involvement after prior EMP/MM evolution	Breast involvement in MM	Systemic therapy	Shows late progression with bilateral breast disease.
Venkataraman et al., 2025 ²⁰	32F	Large left breast mass as initial presentation	Extramedullary breast involvement by newly diagnosed MM	RVD, ASCT, consolidative RT, maintenance	Breast EMD may be the initial manifestation of MM.
Silva et al., 2025 ²¹	36F	Rapidly enlarging breast mass	Breast involvement as initial MM manifestation	Systemic therapy	Mimicked primary breast cancer; biopsy established plasma cell neoplasm.
Liu et al., 2025 ²²	Middle-aged F	Breast mass found during MM follow-up	MM with mammary extramedullary disease	Chemotherapy	Emphasizes differential diagnosis from breast cancer.
Messina et al., 2025 ²³	83F	Multiple bilateral breast lesions in relapsed/refractory MM	Breast localization/metastasis of MM	Fifth-line chemotherapy	Initially misdiagnosed as primary breast carcinoma; aggressive course.
Engele et al., 2026 ²⁴	73M	Bilateral breast masses in relapsed MM	Bilateral breast plasmacytomas in male patient	Systemic therapy	Exceptionally rare male bilateral breast involvement.
Present case	64F	Screening-detected breast lesion in patient with prior breast cancer	Extramedullary involvement of breast by systemic MM	D-RVD induction → daratumumab/lenalidomide maintenance	Initial breast presentation of systemic MM with MRD-negative response.

Abbreviations: ALCL, anaplastic large cell lymphoma; ASCT, autologous stem cell transplantation; D-RVD, daratumumab, lenalidomide, bortezomib, and dexamethasone; EMD, extramedullary disease; EMP, extramedullary plasmacytoma; F, female; M, male; MM, multiple myeloma; RVD, lenalidomide, bortezomib, and dexamethasone; RT, radiotherapy.

myeloma-defining events, whereas extramedullary involvement by systemic MM represents dissemination of an established plasma cell myeloma outside the bone marrow. In our patient, extensive bone marrow involvement (>90% plasma cells) together with high-risk cytogenetic abnormalities established the diagnosis of extramedullary involvement by systemic multiple myeloma, rather than a solitary extramedullary plasmacytoma.^{25,26}

Radiologically, breast plasmacytomas lack pathognomonic features and commonly appear as circumscribed or microlobulated masses on mammography and ultrasound.²¹ Histopathologic evaluation supplemented by immunohistochemistry is essential. Demonstration of plasma cell markers such as CD138/CD38 and light-chain restriction confirms monoclonality and helps distinguish plasma cell neoplasms from primary breast carcinoma or metastatic disease.²⁸ However, histologic and immunophenotypic findings alone cannot reliably distinguish a solitary extramedullary plasmacytoma from extramedullary involvement by systemic multiple myeloma. Comprehensive systemic evaluation—including bone marrow examination, laboratory studies, and whole-body imaging—is required to establish the correct diagnosis and guide management.

The histopathologic differential diagnosis of

plasma cell-rich lesions involving the breast includes plasmablastic lymphoma (PBL), lymphoplasmacytic lymphoma (LPL), extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) with plasmacytic differentiation, reactive plasma cell infiltrates, and recurrent breast carcinoma with plasmacytoid morphology. Accurate diagnosis requires integration of morphologic findings, immunophenotypic studies, and systemic clinical evaluation. Although plasmablastic lymphoma (PBL) may share expression of plasma cell markers such as CD138 and frequently lacks CD20 expression, it typically demonstrates a markedly elevated proliferative index (Ki-67), frequent MYC rearrangements, and Epstein-Barr virus-encoded RNA (EBER) positivity by in situ hybridization, particularly in immunocompromised patients. In contrast, our lesion demonstrated a mature plasma cell immunophenotype characterized by diffuse CD138 positivity, kappa light-chain restriction, cyclin D1 positivity, CD117 expression, absence of CD20 expression, and lack of morphologic features of plasmablastic differentiation. Lymphoplasmacytic lymphoma (LPL) and marginal zone lymphoma (MALT) with plasmacytic differentiation were considered unlikely because these entities typically retain expression of mature B-cell markers, including CD20 and PAX5, and demonstrate



an accompanying neoplastic lymphoid population, features that were absent in our case. Likewise, reactive plasma cell infiltrates are polyclonal, whereas the demonstration of kappa light-chain restriction confirmed a monoclonal plasma cell proliferation. Recurrent breast carcinoma was excluded by the absence of cytokeratin AE1/AE3 expression together with diffuse plasma cell marker expression. Finally, systemic evaluation demonstrating greater than 90% bone marrow plasma cell involvement and high-risk cytogenetic abnormalities established the diagnosis of extramedullary involvement by systemic multiple myeloma.

Cyclin D1 expression is identified in a subset of plasma cell neoplasms and most commonly reflects dysregulation of the CCND1 gene secondary to the t(11;14)(q13;q32)/IGH::CCND1 translocation, a recurrent primary cytogenetic abnormality in multiple myeloma. However, cyclin D1 immunoreactivity is not entirely specific for t(11;14), and immunohistochemical expression should not be considered a surrogate for cytogenetic confirmation. In our case, testing for t(11;14) was not available; therefore, cyclin D1 expression was interpreted as supportive immunophenotypic evidence rather than definitive evidence of CCND1 rearrangement.^{29,30}

Extramedullary spread in MM is associated with aggressive tumor biology and altered adhesion signaling. Loss of CD56 and CXCR4 expression reduces bone marrow homing, while increased CD44 expression facilitates migration and soft tissue colonization. These molecular alterations contribute to treatment resistance and poorer prognosis in extramedullary disease.³¹

Prognosis in extramedullary MM is strongly influenced by cytogenetic abnormalities, particularly chromosome 1q21 gain/amplification, which is associated with advanced disease and inferior survival.³² Our patient's cytogenetic profile, including 1q21 amplification, trisomy 5, and chromosome 9 gain, supported classification as high-risk disease and justified intensified systemic treatment. This case adds to the limited literature describing breast involvement in patients with high-risk cytogenetic abnormalities, including 1q21 amplification. Although an association has been described between 1q21 amplification and aggressive extramedullary disease, a specific relationship with breast involvement has not been established.

Once extramedullary disease occurs in association with systemic MM, treatment should follow systemic myeloma protocols. Combination regimens incorporating immunomodulatory agents, proteasome inhibitors, and monoclonal antibodies have improved response rates, although extramedullary disease remains associated with inferior outcomes.³¹ MRD assessment using next-generation sequencing provides important prognostic information, as persistent MRD predicts relapse despite radiographic remission.³³ In high-risk extramedullary disease, persistent MRD may support consideration of consolidation strategies such as ASCT or cellular therapy.

This case emphasizes the need for a broad differ-

ential diagnosis and integration of pathologic, cytogenetic, and molecular findings to guide management.

Unlike primary breast carcinoma, breast involvement by systemic multiple myeloma is not treated with surgical excision, as it represents a manifestation of disseminated hematologic malignancy rather than localized breast disease. Consequently, the role of surgery is limited to obtaining tissue for diagnosis, while definitive treatment consists of systemic antimyeloma therapy tailored to disease stage and cytogenetic risk. Local therapies, including surgery or radiation, may be considered for solitary plasmacytoma or for selected palliative indications such as pain control, impending pathologic fracture, or symptomatic local mass effect; however, they do not provide disease control in patients with systemic multiple myeloma. In the present case, recognition of the lesion as extramedullary involvement by systemic multiple myeloma avoided unnecessary surgical excision and appropriately redirected management toward systemic induction therapy with daratumumab, lenalidomide, bortezomib, and dexamethasone.³⁴

In summary, extramedullary involvement of the breast by systemic MM is a rare but clinically significant manifestation. Diagnosis requires a high index of suspicion and histopathologic confirmation, followed by comprehensive systemic evaluation. The presence of high-risk cytogenetics and extramedullary disease should prompt intensified systemic treatment and MRD-guided surveillance strategies.

CONCLUSION

Extramedullary involvement of the breast by systemic MM is a rare but important diagnostic consideration in patients presenting with new breast lesions, particularly those with a history of breast cancer. Because imaging findings are often nonspecific, early biopsy is essential to establish the diagnosis and avoid unnecessary surgical intervention. The presence of extramedullary disease and high-risk cytogenetics, such as 1q21 amplification, warrants aggressive systemic therapy and close MRD-guided surveillance. This case highlights the importance of maintaining a broad differential diagnosis and integrating pathologic, cytogenetic, and molecular data to guide management.

ETHICAL CONSIDERATIONS

Written informed consent for publication was obtained from the patient. Institutional review board approval was not required for single-patient case reports under our institutional policy.

DATA AVAILABILITY

All data relevant to this case are included within the manuscript. Additional information may be provided on reasonable request.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest related to this publication.



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AI DISCLOSURE

No artificial intelligence (AI) tools were used in the preparation of this manuscript.

AUTHOR CONTRIBUTIONS

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