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Original Article

Bone Marrow Metastasis of Non-hematolymphoid Malignancies: A 10-Year Retrospective Experience from a Single Academic Institution

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Abstract

Background and objectives: Bone marrow metastasis (BMM) from non-hematolymphoid malignancies with resultant cytopenia(s) can mimic primary hematolymphoid disorders. This study aimed to investigate the clinical and pathological characteristics of BMM from non-hematopoietic tumors. ***Methods:*** We conducted a retrospective cohort study of patients diagnosed with BMM by non-hematolymphoid malignancies at our institution over the past 10 years. Demographic and clinical characteristics, histopathological findings of bone marrow, types of metastatic tumors, and prognosis were analyzed. ***Results:*** A total of 54 cases were included. The four most common malignancies with BMM, regardless of gender, were prostatic adenocarcinoma (29.6%), breast carcinoma (25.9%), colorectal adenocarcinoma (5.5%), and lung carcinoma (5.5%). The main clinical and laboratory manifestations were anemia (90.7%), reticulocytosis (80.5%), thrombocytopenia (73.9%), bone pain (55.5%), disseminated intravascular coagulation (39.6%), leukoerythroblastosis (35.3%), and leukopenia (24%). The vast majority (96.3%) of metastatic tumors were identified by morphology alone; however, in approximately 2.7% of cases, immunohistochemistry was required due to subtle morphologic features. In 29.6% (16/54) of patients, BMM was identified prior to or concurrently with other metastatic sites. The median time interval between the initial diagnosis of non-hematolymphoid malignancies and BMM was 29 months. Although patients who received anti-tumor treatment after BMM diagnosis showed significantly improved prognosis ($P < 0.01$), no significant differences were observed between those treated with immunotherapy versus chemotherapy and/or radiotherapy ($P = 0.145$). ***Conclusions:*** Prostate and breast carcinomas are the most common malignancies associated with BMM, with anemia, reticulocytosis, and thrombocytopenia being the most frequent clinical manifestations. While our data demonstrate that anti-neoplastic treatments, regardless of regimen, significantly improve overall survival after BMM, no significant survival differences were observed when prostate and breast carcinomas were compared with other types of BMM.

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Introduction

The global incidence of cancer continues to rise despite advancements in early detection and treatment.[1] While survival rates have improved, distant metastases,[2] including bone marrow (BM) metastasis (BMM), remain major contributors to poor prognosis.[2] The BM, a specialized blood-rich organ confined within the bone cavity, provides a unique microenvironment for hematopoiesis; however, metastatic tumor cells can infiltrate this niche, disrupting normal blood cell production.[3]

BMM from non-hematopoietic malignancies is relatively rare but can cause significant hematologic abnormalities such as anemia, thrombocytopenia,[4,5] leukoerythroblastosis, and even disseminated intravascular coagulation in certain circumstances.[6] Patients with BMM may face significant constraints in chemotherapy dosage due to the BM's compromised functional reserve, potentially limiting the efficacy of standard treatments.[7] Differentiating BMM-related cytopenias from those induced by treatment can also pose a diagnostic challenge, requiring a high index of suspicion in patients with known solid tumors.[8]

BM biopsy, aided by cytomorphology and immunohistochemistry, remains the gold standard for diagnosing BMM.[9] Previous studies have shown that breast, prostate, lung, and gastrointestinal (GI) tumors are among the most common malignancies metastasizing to the BM in adults.[2,10–12] Tumor cells often exploit signaling pathways to establish themselves within the BM, where they can remain dormant for extended periods before eventually reactivating and proliferating.[13] This interaction, coupled with influences from BM adipocytes and other stromal components, creates a niche that facilitates tumor cell survival and, in some cases, resistance to therapy.[14]

Keywords: Bone marrow; Metastasis; Non-hematolymphoid malignancies; Cytopenias; Anemia; Reticulocytosis; Thrombocytopenia.

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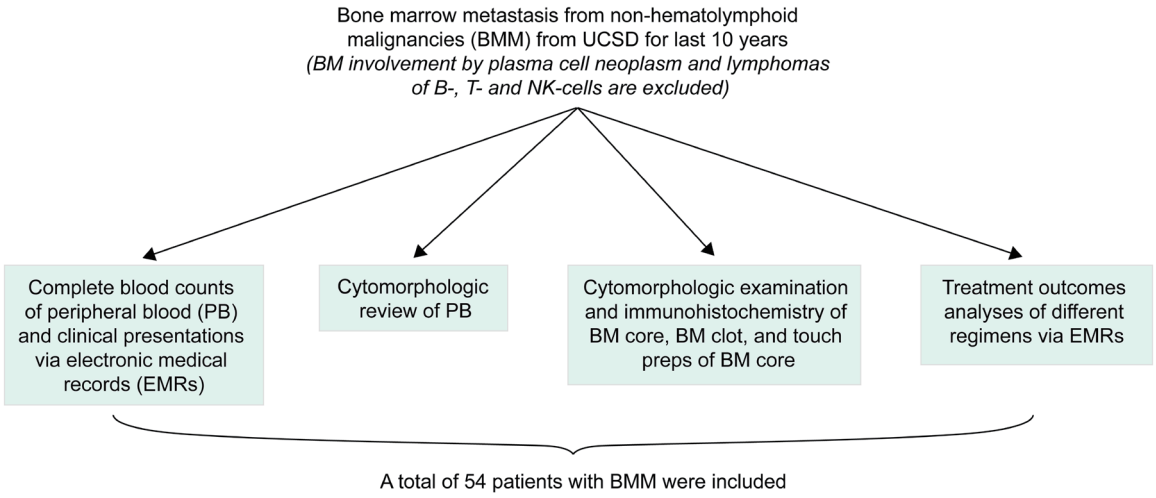

Fig. 1. A diagram of the study design. BM, bone marrow; NK, natural killer; UCSD, University of California San Diego.

The prognosis for patients with BMM is generally poor,[15] with survival durations typically measured in months or less.[16] However, targeted therapies, particularly immunotherapy, offer some hope for improving outcomes.[17]

This study presents a 10-year retrospective analysis of 54 BMM cases at our institution, highlighting the most common types of malignancies, laboratory findings, and clinical presentations to aid in early and accurate diagnosis. We also demonstrate that treatment, even at the advanced stage of BMM, was associated with increased median overall survival (OS).

Materials and methods

Case selection

The overall methodology of this study is summarized in Figure 1. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2024) and was approved by the Institutional Review Board of the University of California San Diego (No. 808383). Given the retrospective nature of the study, the requirement for informed consent was waived. By searching the Department of Pathology database at the University of California San Diego between January 2013 and May 2023, a total of 54 patients were identified with BMM from non-hematolymphoid malignancies. BM involvement by plasma cell neoplasms and lymphomas of B-, T-, and natural killer-cell origin was excluded.

All relevant data, including demographic information, clinical presentation, hematological indices, and pathological findings, were collected by reviewing the patients' electronic medical records. Data on treatment regimens, including chemotherapy, radiotherapy, combined chemotherapy and radiotherapy, immunotherapy, and supportive care, were also gathered from electronic medical records to assess therapeutic outcomes.

BM processing and associated studies

BM biopsies were obtained from the posterior or anterior iliac crest under local anesthesia. BM core biopsies and clots were fixed in 10% neutral formalin, decalcified (core biopsies only) with Immunocal for approximately 30 m, and processed for paraffin embedding, sectioning, and staining with hematoxylin and eosin (H&E) according to standard protocols. Corresponding peripheral blood (PB) smears, BM touch preparations, and BM aspirate smears were stained with Wright-Giemsa. The percentage of reticulocytes in PB was retrieved from the Sysmex XN-9100 (Sysmex America, Inc., Lincolnshire, IL 60069, USA). Sysmex employs a combination of fluorescence (a fluorescent dye that specifically stains reticulocytes based on RNA content, enabling the identification of immature red blood cells) and impedance measurement to count and size cells, thus differentiating reticulocytes from mature red blood cells. BM touch preparations and smears were evaluated by light microscopy to identify tumor cell infiltration and associated hematological abnormalities. Routine H&E-stained sections from core and clot samples were the primary specimens for identifying metastatic tumor cells within the BM. In cases with subtle morphological features, immunohistochemistry was employed to confirm the final diagnosis. The presence of myelofibrosis and other secondary BM changes due to tumor infiltration was also recorded.

Statistical analyses

Statistical analyses were conducted using SPSS Statistics 29.0.0 (IBM SPSS, Inc.), and survival analyses (OS) were generated using the Kaplan-Meier method. OS was calculated from the date of BMM diagnosis to the date of death or last follow-up. Statistical significance was set at $P < 0.05$, and results were used to evaluate the prognostic impact of treatment after BMM diagnosis. Progression-free survival was defined as the length of time during and after treatment that a patient lives with the disease without worsening.

Results

Incidence and type of BMM

This study included a total of 54 patients diagnosed with BMM originating from non-hematolymphoid malignancies, with an equal distribution of 27 males and 27 females. The median age at BMM diagnosis was 64 years (range, 37–84 years). The most prevalent primary tumors associated with BMM were prostatic adenocarcinoma (29.6%), invasive carcinoma of the breast (25.9%), colorectal adenocarcinoma (5.5%), and lung adenocarcinoma (5.5%) (Table 1). Less common non-hematolymphoid malignancies with BMM are listed in Table 2, including angiosarcoma, Merkel cell carcinoma, and clear cell renal cell carcinoma (one case each in both males

Table 1. Summary of bone marrow metastasis by non-hematolymphoid malignancies

	Site and type of non-hematolymphoid malignancies, N (%)							
	Breast	**Prostate**	**Colo-rectal**	**Lung**	**Thyroid**	**Unknown primary**	**Other (see Table 2)**	**Total**
Sex								
Male	–	16 (29.6)	3 (5.5)	1 (1.8)	0	0	6 (11.1)	
Female	14 (25.9)		0	2 (3.7)	2 (3.7)	3 (5.5)	7 (12.9)	
Clinical features								
Anemia	13 (24)	13 (24)	3 (5.5)	3 (5.5)	2 (3.7)	3 (5.5)	12 (22.2)	49 (90.4)
Thrombocytopenia	8 (14.8)	13 (24)	2 (3.7)	2 (3.7)	2 (3.7)	2 (3.7)	11 (20.3)	40 (73.9)
Bone pain	3 (5.5)	14 (25.9)	2 (3.7)	1 (1.8)	1 (1.8)	–	9 (16.6)	30 (55.3)
Leukopenia	5 (9.2)	5 (9.2)	–	–	1 (1.8)	–	2 (3.7)	13 (23.9)
Abnormal imaging	3 (5.5)	2 (3.7)	1 (1.8)	1 (1.8)	–	–	–	7 (12.8)
Other metastases								
Bone Mets	14 (25.9)	15 (27.7)	1 (1.8)	2 (3.7)	2 (3.7)	2 (3.7)	7 (12.9)	33 (79.4)
Lymph node Mets	10 (18.5)	8 (14.8)	1 (1.8)	3 (5.5)	1 (1.8)	1 (1.8)	7 (12.9)	31 (57.1)
Visceral organ Mets	6 (11.1)	5 (9.2)	1 (1.8)	–	2 (3.7)	–	5 (9.2)	19 (35)

N, number of positive cases; %, positive cases/total cases.

and females). Additionally, one case each of gastric signet-ring adenocarcinoma, malignant melanoma, and mixed germ cell tumor with BMM occurred in males, whereas one case each of uterine carcinosarcoma (malignant mixed Mullerian tumor), endometrioid adenocarcinoma, ovarian carcinoma (unspecified type), and undifferentiated malignant spindle cell neoplasm occurred in females. All patients were classified as stage IV based on the presence of BMM, indicating advanced disease. Beyond BMM, metastases were also present in other organs: bone (79.4%), lymph nodes (57.2%), and visceral organs (44.2%) (Table 1).

Clinical manifestations of BMM

The clinical presentations of patients with BMM varied but were predominantly characterized by hematologic abnormalities, including anemia (90.4%), thrombocytopenia (73.9%), and leukopenia (23.9%). Anemia was frequently moderate, with a mean hemoglobin level of 8.8 g/dL (95% confidence interval, 8.30–9.31), and tended to worsen as the disease advanced. Reticulocytosis (>2.5% reticulocytes) was observed in PB in 80.5% of patients. The mean platelet count was 90.46 × 10^9/L (95% confidence interval, 65.25–115.67), and thrombocytopenia manifested clinically with petechial bleeding in some cases. Consequently, 84.9% of patients required transfusion of red blood cells and/or platelets due to anemia or thrombocytopenia. White blood cell counts ranged from 1.2 to 96.4 × 10^9/L, and leukoerythroblastosis was identified in 35.3%. Among patients with BMM, 18.5% had single-lineage cytopenia, 50% had bi-lineage cytopenia, and 22.2% had trilineage cytopenia (pancytopenia). Furthermore, 39.6% of patients developed disseminated intravascular coagulation within six months after BM biopsy. In addition to hematological abnormalities, bone pain was present in 55.5% of patients. Other reported symptoms included fatigue, weight loss, and generalized weakness, likely reflecting both disease burden and multi-organ metastases. In terms of metastatic timing, 29.6% (16/54) of patients had BMM prior to or concurrent with other metastatic sites. Notably, three patients were diagnosed with BMM before the primary malignancy was identified (prostatic adenocarcinoma, adenocarcinoma of likely GI origin, and neuroendocrine carcinoma of GI origin).

Pathologic features of BMM

Histopathological analysis revealed that metastatic tumor cells within the BM were predominantly arranged in scattered clusters or sheets, often forming cohesive "nests" that disrupted normal BM architecture. Routine H&E staining was

Table 2. Other non-hematopoietic malignancies identified with bone marrow metastasis

Male	**Female**
Angiosarcoma	Angiosarcoma
Clear cell renal cell carcinoma	Carcinosarcoma (malignant mixed Mullerian tumor) of the uterus
Gastric signet ring adenocarcinoma	Clear cell renal cell carcinoma
Malignant melanoma	Endometrioid adenocarcinoma
Merkel cell carcinoma	Merkel cell carcinoma
Mixed germ cell tumor	Ovarian cancer (unknown type)
	Undifferentiated malignant spindle cell neoplasm

N = 1 for each cancer listed.

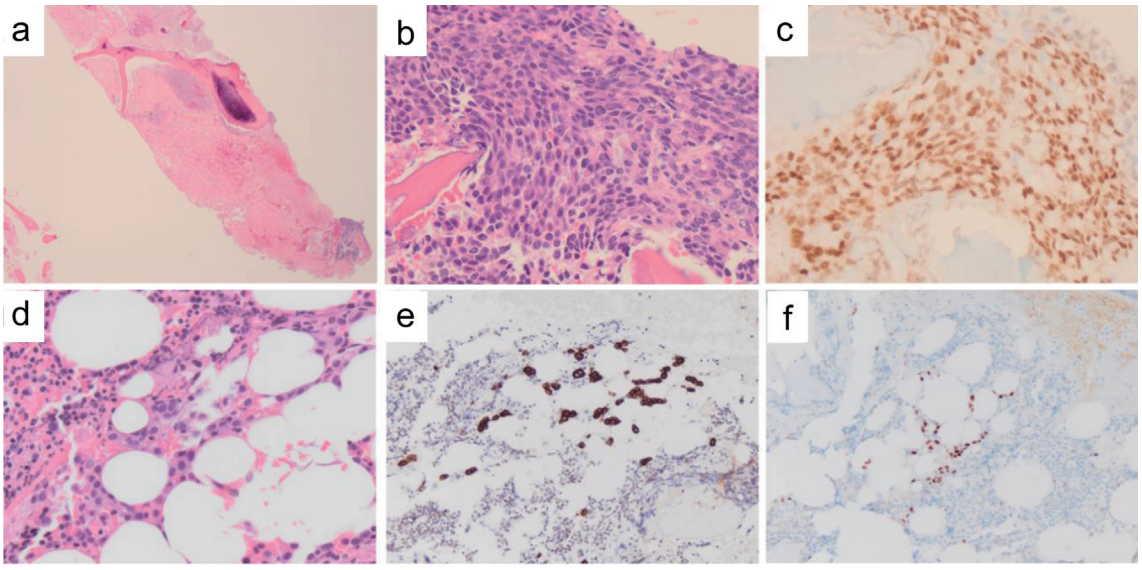

Fig. 2. Representative microphotographs of a conspicuous (a–c), and a subtle (d–f) case of bone marrow metastasis. (a) Low (20×) and (b) high (400×) power images of carcinoma involving nearly the entire bone marrow. (c) The carcinoma cells are positive for CDX2 (400×), consistent with colon carcinoma. (d) High-power (400×) image of bone marrow with very rare medium-sized atypical cells. (e, f) The atypical cells are positive for AE1/AE3 (e, 200×) and ER (f, 200×), consistent with breast carcinoma. CDX2, caudal type homeobox 2; ER, estrogen receptor.

sufficient to identify BMM in 96.3% of cases (Fig. 2a–c), where the morphological features of metastatic cells clearly demonstrated their non-hematopoietic origin. In the remaining 3.7% of cases (n = 2) (Fig. 2d), immunohistochemical staining was required to confirm the diagnosis. One case, with extremely rare atypical cells, required pancytokeratin to confirm epithelial nature and estrogen receptor to confirm the cell of origin (Fig. 2e and f). Another case, with extensive necrosis and rare viable tumor cells, showed strong AE1/AE3, pancytokeratin, and CDX2 positivity, confirming a metastatic carcinoma of likely GI origin (data not shown). Secondary BM changes, notably myelofibrosis, were also observed in 29.6% of patients.

Treatment outcomes

Of the 54 patients, 16 did not receive specific anti-tumor therapy, either due to clinical ineligibility or patient preference. The remaining 38 patients received targeted treatments, including chemotherapy, radiotherapy, immunotherapy, or other supportive interventions, tailored to the primary malignancy. Survival outcomes demonstrated a significant benefit for those receiving active treatment: the median OS for treated patients was 11.5 months, compared with 3.3 months in the untreated cohort ($P < 0.01$) (Fig. 3). Kaplan-Meier survival analysis further confirmed these findings, showing improved OS in patients who underwent therapy for BMM, emphasizing the impact of timely and appropriate treatment even at advanced stages. Comparison of immunotherapy (n = 9) versus chemotherapy and/or radiotherapy (n = 29) revealed median OS of five months and 10.6 months, respectively, with no statistically significant difference ($P = 0.145$). Furthermore, no significant differences in OS were observed between patients with prostatic adenocarcinoma or breast carcinoma compared with the overall OS of all BMM patients (Fig. 4).

Discussion

In the present study, we found that prostate and breast carcinomas were the most common non-hematological malig-

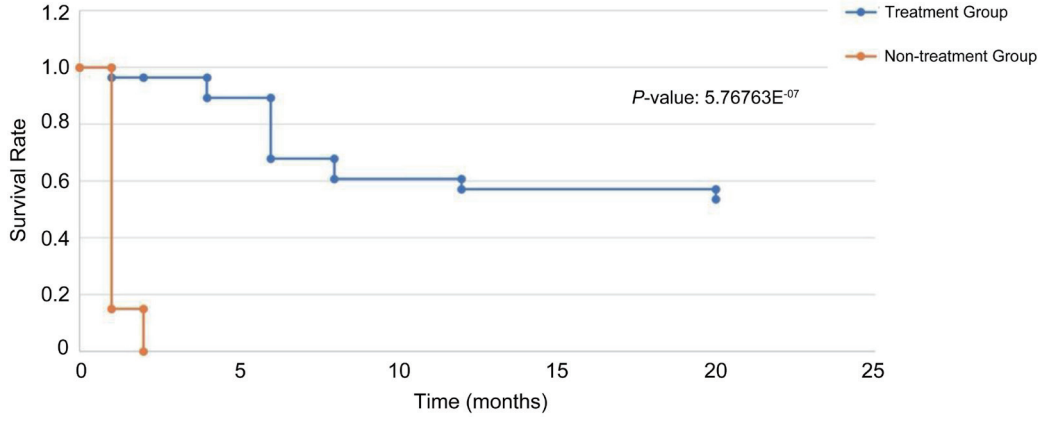

Fig. 3. Kaplan–Meier analysis of overall survival based on treatment status after bone marrow metastasis.

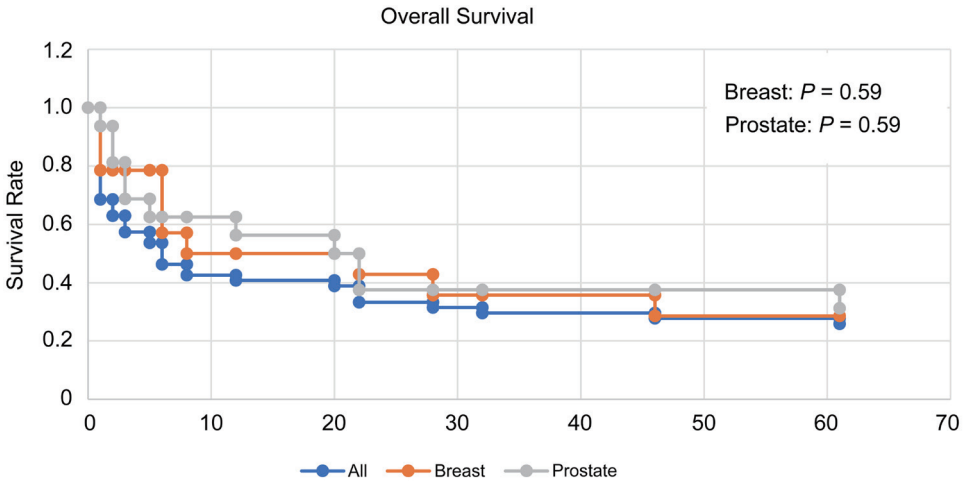

Fig. 4. Overall survival (OS) of breast and prostate cancers with bone marrow metastasis (BMM).

nancies associated with BMM, consistent with the known tendency of these cancers to involve the bone and BM.[4] One limitation of our study is that we could not include pediatric patients, as our institution does not serve a pediatric population. In children, neuroblastoma is the most common non-hematological malignancy with BMM.[18] While exploring the mechanisms underlying why certain non-hematolymphoid malignancies tend to metastasize to the BM is beyond the scope of this study, previous research has addressed this phenomenon. For example, Yang *et al*.[19] demonstrated that this tropism may be related to specific molecular mechanisms, including the expression of chemokine receptors such as C-X-C chemokine receptor type 4 on tumor cells, which facilitate homing to and invasion of the BM through interactions with CXCL12 in the BM microenvironment. Additionally, studies suggest that BM adipocytes may support the proliferation and survival of metastatic cells within the BM, potentially promoting tumor aggressiveness and resistance to therapy.[20,21] Insights into the molecular underpinnings of BMM could lead to future therapeutic strategies targeting these interactions to inhibit BM invasion by metastatic cells.

BM biopsy remains the gold standard for diagnosing BMM, as tumor cells can often be identified by their distinct cytomorphology on H&E-stained sections. In our study, H&E staining alone was sufficient for diagnosis in the vast majority of cases (96.3%); however, immunohistochemical analysis was essential in a small fraction of cases with subtle or ambiguous morphological features. This highlights the importance of a comprehensive diagnostic approach that combines routine cytohistomorphological examination with immunohistochemistry to ensure timely and accurate identification of metastatic cells in the BM. It is worth noting that all BM biopsies in our study were performed unilaterally from the posterior or anterior iliac crest. As a result, cases of BMM could have been missed due to false-negative findings. Bilateral biopsies, aided by imaging studies, would likely reduce the false-negative rate.[22]

The diverse clinical manifestations of BMM largely arise from impaired hematopoiesis due to tumor cell infiltration into the BM. In our study, the most prevalent symptoms were anemia and thrombocytopenia, reflecting disruption of the BM microenvironment by metastatic tumor cells. These hematologic abnormalities are often the earliest indicators of BM involvement, underscoring the importance of considering BMM in patients with unexplained cytopenias, especially in those with a known primary malignancy. However, anemia and/or thrombocytopenia may also result from other disorders, including but not limited to hereditary conditions (e.g., thalassemia, Fanconi anemia),[23] acquired disorders such as aplastic anemia,[24] primary myeloid and lymphoid neoplasms (acute or chronic forms),[25] autoimmune diseases,[26,27] infections (e.g., parvovirus B19,[28] HIV[29]), medications, and nutritional deficiencies (e.g., iron, vitamin B12, folic acid). The pathophysiology of BMM-related cytopenia(s) is complex. Tumor cells within the BM microenvironment may suppress normal hematopoiesis by secreting inhibitory cytokines and disrupting hematopoietic growth factors through direct cell-to-cell interactions. These mechanisms, compounded by the space-occupying effect of tumor cell nests within the BM,[30,31] lead to reduced production of red cells, platelets, and leukocytes. The high rates of anemia and thrombocytopenia observed in our cohort are consistent with previous studies, emphasizing that these symptoms are hallmarks of BMM and warrant prompt investigation, particularly in patients with a history of non-hematological malignancy.

The prognosis for patients with BMM is generally poor, as reflected in the significantly shorter median OS of untreated patients compared with those who received treatment in our cohort. This finding underscores the potential impact of timely therapy, even in cases of advanced disease. Our findings align with prior studies demonstrating that patients receiving chemotherapy, radiotherapy, or other targeted therapies have better outcomes than untreated patients. Notably, immunotherapy did not provide an OS benefit compared with chemotherapy and/or radiotherapy, likely due to two factors: first, the small sample size and heterogeneity of immunotherapy regimens, and second, the possibility that many patients receiving immunotherapy were diagnosed with BMM at a more advanced stage. Buschhaus *et al*.[32] reported that managing BMM is particularly challenging due to the aggressive nature of marrow infiltration and the advanced stage of disease at presentation. Nonetheless, despite the toxic side effects of cytotoxic therapies, including severe myelosuppression, the benefits in controlling symptoms such as anemia and thrombocytopenia, and in extending survival, remain substantial.[32] Although we did not assess treatment-related adverse effects, our findings suggest that active treatment can positively affect both survival and symptom control in patients with BMM.[33]

The presence of BMM often coincides with other metastatic

sites, primarily in the bone and lymph nodes, as observed in our cohort. This supports the hypothesis that BMM may precede or accompany bone metastases in many patients.[7] The process of tumor cell dissemination to the BM involves multiple stages, beginning with extravasation into the marrow and, in some cases, a prolonged dormancy period. Over time, dormant tumor cells may reactivate, leading to overt metastasis and clinical symptoms.[34] Understanding this complex metastatic cascade could facilitate the development of therapies designed to disrupt dormancy or prevent reactivation, thereby potentially prolonging survival and improving quality of life.[31,35,36]

Conclusions

BMM represents a critical and challenging aspect of cancer progression, often signaling advanced disease with poor prognosis. Our study reinforces the importance of early recognition of BMM in patients with unexplained hematologic abnormalities and known primary malignancies, as timely diagnosis and treatment can significantly improve survival outcomes. Further research into the molecular mechanisms governing BMM, including the role of BM adipocytes and chemokine signaling, may yield novel therapeutic strategies to target these pathways.

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Conflict of interest

HYW is the Editor-in-Chief of the *Journal of Clinical and Translational Pathology*. The authors have no other conflicts of interest to declare.

Author contributions

Data collection, data analysis, drafting of the manuscript (FS, XC), original research plan conception, writing the final version of the manuscript (HYW), and reviewing and editing of all versions of the manuscripts (RLW, MDD). All authors approved the final draft.

Ethical statement

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2024) and was approved by the Institutional Review Board of the University of California San Diego (No. 808383). Given the retrospective nature of the study, the requirement for informed consent was waived.

Data sharing statement

Data are not publicly available due to privacy concerns and ethical restrictions. However, de-identified data may be available from the corresponding author upon reasonable request and with appropriate institutional approvals.

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