Clinical features and treatment of bone marrow metastasis

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Abstract. Bone marrow metastasis (BMM) refers to the metastasis of malignant tumours originating from nonhematopoietic tissues to the bone marrow. The nonhematopoietic malignant tumour cells metastasize to the bone marrow via heterogeneous dissemination or direct invasion to form metastases and the bone marrow is infiltrated by tumour cells, resulting in the destruction of its structure and the development of haematopoietic disorders. In the present study, the clinical characteristics, prognosis and treatment of BMMs were investigated. The main clinical manifestations were moderate anaemia and thrombocytopenia. Out of 52 cases, a total of 18 patients were not treated and the remaining patients underwent chemotherapy, radiotherapy, surgery or autologous stem cell transplantation in the Affiliated Tumour Hospital of Tianjin Medical University from September 2010 to October 2021. The primary tumours of bone marrow metastatic cancer were usually neuroblastoma and tumours originating from the breast and stomach. When bone metastases occur, patients are not necessarily accompanied by BMMs. In the present study, bone metastases occurred mainly in patients with breast and prostate cancers. The median overall survival of patients treated with antitumor therapy was significantly higher than that of untreated patients (11.5 vs. 3.3 months P<0.01). For patients with BMM, it is of great importance to actively evaluate the patient's condition and select the appropriate treatment plan for improving their prognosis.

Introduction

In recent years, the incidence of tumours is increasing and significant progress has been made in the early diagnosis and comprehensive treatment of various tumours. However, the presence of distant metastases from tumours seriously affects the prognosis of the disease (1). Bone marrow metastasis (BMM) refers to the metastasis of malignant tumours originating from nonhematopoietic tissues to the bone marrow (2). The nonhematopoietic malignant tumour cells metastasize to the bone marrow via heterogeneous dissemination or direct invasion to form metastases. Subsequently, the bone marrow is infiltrated by cancer cells, resulting in the destruction of the bone marrow structure and the development of haematopoietic disorders (2). The clinical manifestations of BMMs are complex and diverse. Various cases are initially treated in the haematology department for haematological abnormalities, such as anaemia or thrombocytopenia (3). Neuroblastoma, Ewing's sarcoma and primitive neuroectodermal tumours are the most common BMMs noted in paediatric patients (4). BMMs from adult tumours are general in breast cancer, prostate cancer, gastrointestinal tumours, and lung cancer (5). Certain patients are at a stage where the primary lesion is unknown and a bone marrow biopsy may reveal BMMs, which may lead to a definitive diagnosis. The prognosis of metastatic bone marrow cancer is poor; rapid progression of disease seen in marrow infiltration of medulloblastoma results in a median interval of 12 months between the detection of bone marrow disease and mortality in adults (1); therefore, it is necessary to enhance the awareness of this disease by improving the early detection and diagnosis, as well as its treatment. This can, in turn, improve the patients' quality of life and disease prognosis, and prolong their survival. In the present study, the clinical features of 52 cases of BMM are summarized and reported.

Patients and methods

Patient selection. The patient data in the Affiliated Tumour Hospital of Tianjin Medical University were retrospectively reviewed. A total of 52 cases of patients with BMM were included with complete follow-up from September 2010 to October 2021. All patients were diagnosed based on bone marrow biopsy examination.

Data collection. Patient baseline and clinical data, including age, sex, laboratory tests (routine blood, liver and kidney function, lactate dehydrogenase, β2-microglobulin and bone marrow biopsy) and imaging examination [ultrasound (Philips EPIQ Elite; Philips Medical Systems B.V.) for superficial lymph nodes, computerized tomography (CT; Siemens 08098027; Siemens AG) or positron emission

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tomography (PET)-CT (GE Discovery PET/CT Elite; Cytiva) for chest, abdomen and pelvic] were collected. For bone marrow cytology, 6-7 bone marrow smears were performed from bone marrow aspiration under local anaesthesia and aseptically at the anterior or posterior superior iliac spine, with Wright's staining at 25˚C. Bone marrow smears were viewed in full with an Olympus BX53 light microscope (Olympus Corporation) at x100 magnification and then re-examined at x1,000 magnification to search for tumour cells. For bone marrow biopsy a Dako H&E staining instrument (CoverStainer; Dako; Agilent Technologies, Inc.). The operations were conducted at a humidity of 20-85% and a temperature 15-30˚C. Reagents included Dako hematoxylin and eosin staining solutions (Dako; Agilent Technologies, Inc.), 10% neutral formaldehyde, Besso dewaxing (clearing agent), Beso Sealant, Dako H&E special reagents (Dako Hematoxylin, Dako Eosin and Dako Bluing Buffer). The bone marrow specimens were fixed in 10% neutral formaldehyde for at ≥6 h and washed in water. They were then decalcified, dehydrated and paraffin-embedded. Thickness of sections was 3 µm. The staining procedure followed dewaxing and hydration of paraffin sections. Sections were stained in hematoxylin for 1-3 min, rinsed in water. and blued for 1-2 min, washed with water then stained with eosin for 1-3 min, washed with water then dehydrated with 95% ethanol for 2 min followed by anhydrous ethanol twice for 2 min and xylene twice for 2 min. Then the slides were sealed. The pathology was observed using an Olympus BX53 light microscope (Olympus Corporation) and the images captured at a x200 and x400x magnification. The present study was performed following The Declaration of Helsinki and applicable local regulatory requirements and laws including Tianjin Medical University Cancer Institute and Hospital for ethics approval and patient informed consent (approval no. bc2022043).

Patient treatment. A total of 16 patients were not treated and the remaining patients underwent the following treatment: i) Combined chemotherapy, where the chemotherapy regimen was based on the primary tumour and pathological type, and the range of the chemotherapy cycles was 2-6; ii) radiotherapy, where radiation was administered to a limited number of metastatic sites; iii) surgery, which was performed following 3-5 courses of chemotherapy for neuroblastoma; chemotherapy was continued following surgery for a total of ≤12 courses; iv) autologous haematopoietic stem cell transplantation (ASCT), which was performed for neuroblastoma with partial remission; an v) support for symptomatic treatment, which included red cell suspensions or platelet transfusion in patients with anaemia or thrombocytopenia.

Efficacy and adverse effects. Following 30 days after all types of treatment, PET-CT was utilized to evaluate the treatment efficacy. According to the World Health Organization standards (6), the acute and subacute adverse cancer drug reaction classification was also applied to evaluate the adverse effects.

Statistical analysis. All data were analysed using SPSS version 18.0 (SPSS, Inc.). The survival curves were constructed using the Kaplan-Meier method. Overall survival (OS) was defined as the interval from the diagnosis of BMM to death or the end of follow-up.

Table I. Distribution of primary tumour.

Primary cancer	Number (%)
Breast	15 (28.8)
Prostate	9 (17.3)
Neuroblastoma	7 (13.5)
Lung	6 (11.5)
Gastric	5 (9.6)
Colorectal	4 (7.7)
Others	6 (11.5)
Total	52

Results

Baseline characteristics. The present study recruited 30 male (58%) and 22 female (42%) patients. The age ranged from 4-85 yearswith the median being 54 years. Of these, six cases were ≤20 years old, four were 21-30 years old, six were 31-40 years old, eight were 41-50 years old, 11 were 51-60 years old, nine were 61-70 years old and eight were 71-80 years old. A total of 17 patients were >60 years of age. The primary cancer types included the following: Breast, prostate, lung, oesophageal, thyroid, endometrial and gastric cancers, malignant melanoma, neuroblastoma and embryonal rhabdomyosarcoma. The pathological types are shown in Table I. According to the TNM staging of the tumour, stage IV was defined as the presence of BMMs and all patients were classified as stage IV.

Clinical features of the patients. The main clinical manifestation was moderate anaemia in 35 patients, whereas six experienced severe anaemia. A total of 13 patients presented with scattered bleeding spots on the skin due to thrombocytopenia. Anaemia and bleeding symptoms were more severe as the disease progressed. Other symptoms included bone pain, emaciation, fatigue and the corresponding symptoms caused by the primary tumour. The majority of the patients were accompanied by other site metastasis (33 patients with lymph node metastases, 18 patients with bone metastases, 12 patients with liver metastases, four patients with pleural metastases, seven patients with peritoneal metastases and one patient with central metastases). The clinical features of the 52 patients with BMM are shown in Table II.

Clinical examination. Patients underwent the following clinical examinations: i) Complete blood count. A total of 42 patients presented with haemoglobin reduction and the minimum haemoglobin concentration was 45 g/l. A total of six patients presented with severe anaemia and accounted for 11.5% of the total sample size. The majority of them presented with normochromic anaemia. A total of 27 patients presented with thrombocytopenia. The minimum platelet count was $5x10^9$/l. The white blood cell count ranged from $1.27x10^9$/l

Table II. The clinical features of the 52 cases of bone marrow metastasis.

	Cancer type, N (%)						
Demographic and clinical features	Breast	Prostate	Neuroblastoma	Lung	Gastric	Colorectal	Others
Sex	-	-	-	-	-	-	-
Male	-	9 (17.3)	3 (5.8)	4 (7.7)	3 (5.8)	2 (3.8)	3 (5.8)
Female	15 (28.8)	-	4 (7.7)	2 (3.8)	2 (3.8)	2 (3.8)	3 (5.8)
Anemia	13 (25)	6 (11.5)	5 (9.6)	3 (5.8)	5 (9.6)	6 (11.5)	4 (7.7)
Bleeding	6 (11.5)	2 (3.8)	0	0	3 (5.8)	2 (3.8)	0
Emaciation	7 (13.5)	3 (5.8)	0	3 (5.8)	4 (7.7)	3 (5.8)	0
Fatigue	5 (9.6)	4 (7.7)	1 (1.9)	3 (5.8)	4 (7.7)	4 (7.7)	3 (5.8)
Lymph node metastasis	8 (15.4)	3 (5.8)	5 (9.6)	4 (7.7)	6 (11.5)	4 (7.7)	3 (5.8)
Visceral metastases	3 (5.8)	0	0	3 (5.8)	4 (7.7)	2 (3.8)	0
Soft tissue metastases	0	0	0	4 (7.7)	3 (5.8)	4 (7.7)	0
Bone metastases (bone pain)	7 (13.5)	5 (9.6)	0	1 (1.9)	3 (5.8)	2 (3.8)	0

to $12.74x10^9$/l. The white blood cell count was lower than normal in eight patients; ii) morphological characteristic of the bone marrow. Metastatic cancer cells were detected in bone marrow smears of all the examined patients. Scattered or clustered metastatic cancer cells were found in varying numbers on bone marrow smears, mostly at the head, tail or margins of the smears and in clusters of several or hundreds of metastatic cancer cells known as cancer nests (Fig. 1). Because lung cancer and breast cancer are more prevalent in male and female, respectively, these two representative tumours were chosen; prostate cancer, which is representative of male patients, was also selected; iii) bone marrow pathology. The cancerous tissues were in the form of nests or cords, 'squeezing out' hematopoietic tissue or space-occupying hyperplasia. There were hematopoietic cells, such as granulocytes, erythrocytes and megakaryocytes, around the cancer nest (Fig. 2). A post-treatment bone marrow biopsy is shown in Fig. 3, which indicates a normal bone marrow.

Patient treatment outcome. A total of 13 patients underwent chemotherapy treatment and the median course of chemotherapy was four (2-6). Following chemotherapy, the following clinical information was collected: Five patients achieved complete remission (CR), 11 patients presented with partial remission, 15 patients experienced stable disease (SD) and 21 patients developed progressive disease. The total effective rate was 30%. Anaemia symptoms were improved in 31 patients following chemotherapy, 15 of whom demonstrated normal haemoglobin levels. Thrombocytopenia was elevated in 25 patients compared with the pre-chemotherapy group and platelet levels were normal in 13 patients.

Survival outcome. A total of 52 patients were followed up until January 2022 and no patient was lost during the follow-up. The median follow-up period was 10 months (2-18 months). At the end of the follow-up period, six cases were diagnosed as CR, of whom four were neuroblastomas and the remaining were breast and prostate cancers. A total of six patients were in partial remission, of whom four were prostate and two breast cancer cases. A total of five patients achieved SD, of whom two and three patients presented prostate and breast cancer, respectively. A total of 35 patients did not survive due to disease progression, including 18 patients who were not treated. The median OS of patients treated with antitumor therapy was significantly higher than that of untreated patients (11.5 vs. 3.3 months $P<0.01$; Fig. 4).

Adverse effects related to treatment. During therapy, IV-grade myelosuppression occurred in 28 patients. Following treatment with recombinant human granulocyte colony-stimulating factor, the leucocyte levels returned to normal. Adverse reactions of the digestive system, such as nausea and vomiting, occurred in 36 patients. Serve pneumonia was observed in eight cases, which was alleviated after the combination of imipenem and fluconazole treatment.

Discussion

The clinical manifestations of BMM are complex and diverse due to the presence of different primary cancers; however, a series of symptoms are caused by cancer cell infiltration into the bone marrow, such as anaemia, thrombocytopenia, and fatigue (3). Haematological changes are often the earliest or main clinical manifestation of bone marrow metastatic carcinoma (3). Anaemia or thrombocytopenia result from a reduction in normal haematopoiesis and a decrease in haematopoietic cells due to the secretion of inhibitory cytokines by metastatic cancer cells or the inhibition of the release of haematopoietic stimulating factors by bone marrow stromal cells through cell-to-cell contact (7). When extramedullary tumour cells metastasize to the bone marrow, the normal haematopoietic system is inhibited and disrupted by the proliferation of cancer cells (8). In the present study, 41 patients presented with anaemia and 27 with thrombocytopenia. Therefore, anaemia or thrombocytopenia were the most common and dominant clinical manifestations of BMM.

When patients are found to present with unexplained blood abnormalities, the possibility of BMMs from malignant

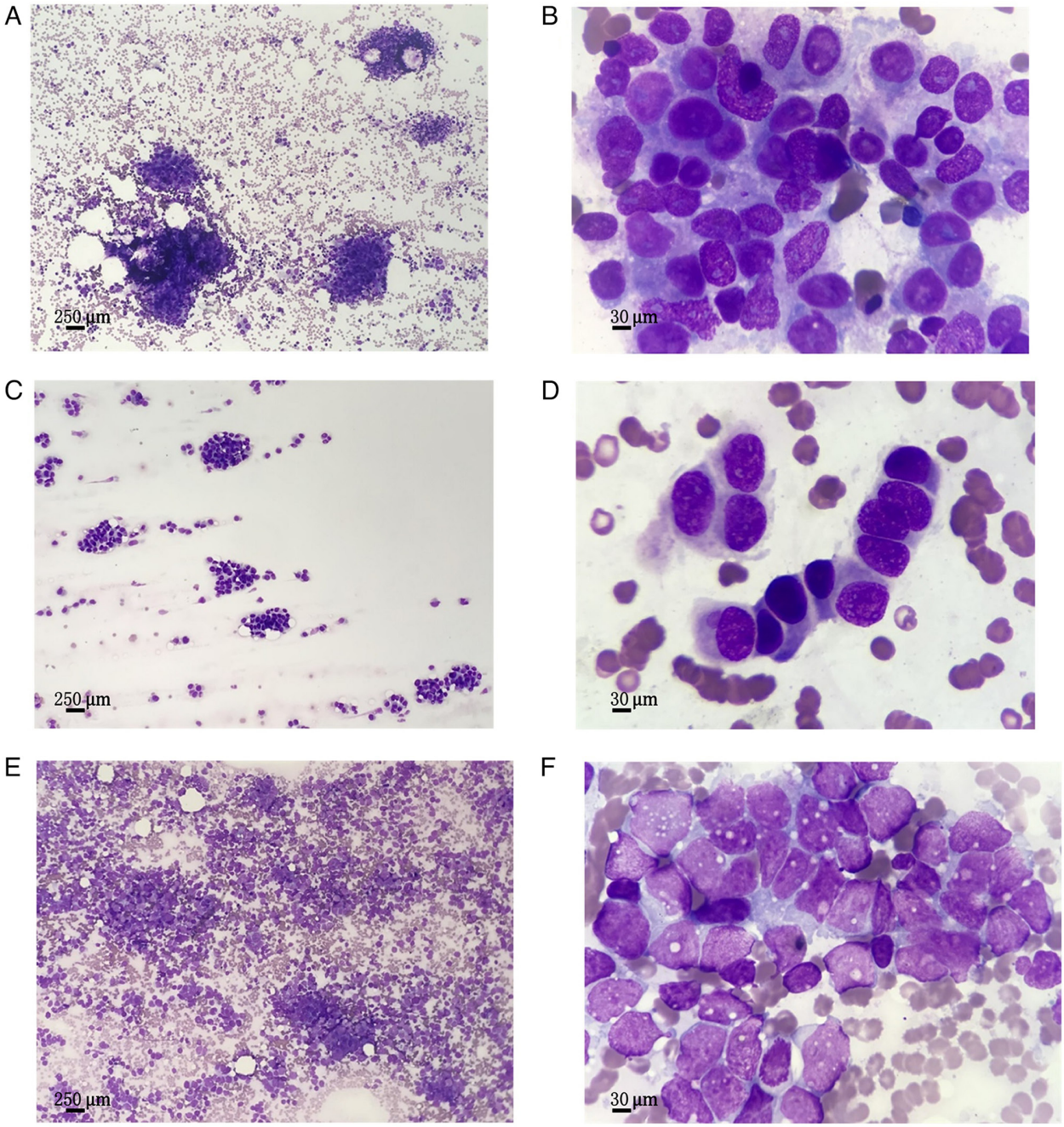

Figure 1. Morphological characteristic of bone marrow. Wright's staining of (A and B) prostate, (C and D) breast and (E and F) lung cancer. (A, C and E) magnification, x100. (B, D and F) Magnification, x1,000.

tumours must be considered. Of the 52 patients, seven were diagnosed with malignant tumours due to haematological abnormalities found at the time of examination; metastatic cancer cells were found through bone marrow aspiration and subsequently, the primary focus further confirmed the diagnosis of malignancy. An additional 45 patients for different primary malignancies with BMM presented due to haematological abnormalities. When an abnormal hemogram occurs in a patient with malignant tumours, the possibility of the patient experiencing BMMs must be considered to facilitate earlier detection and treatment. Bone marrow smear and bone marrow biopsy are the gold standard for the diagnosis of BMMs (9). However, it is not possible to identify tumour cells in a single bone marrow aspiration, since BMMs are multifocal and myelofibrosis occurs which increases the difficulty of obtaining the bone marrow (10). Multi-site bone marrow aspiration should be performed if necessary. In 52 patients, BMMs were confirmed through immunohistochemical analysis through bone marrow biopsy, which is important in the diagnosis of metastatic cancer of the bone marrow.

BMM occurs in breast, prostate, lung and gastric cancers, and in neuroblastoma; the incidence of BMM from breast cancer is significantly higher than that of other tumours (3). In the present study, a total of 15 patients exhibited breast cancer, accounting for 29%. Kopp *et al* (11) demonstrated that a high proportion of bone marrow metastases from breast cancer was

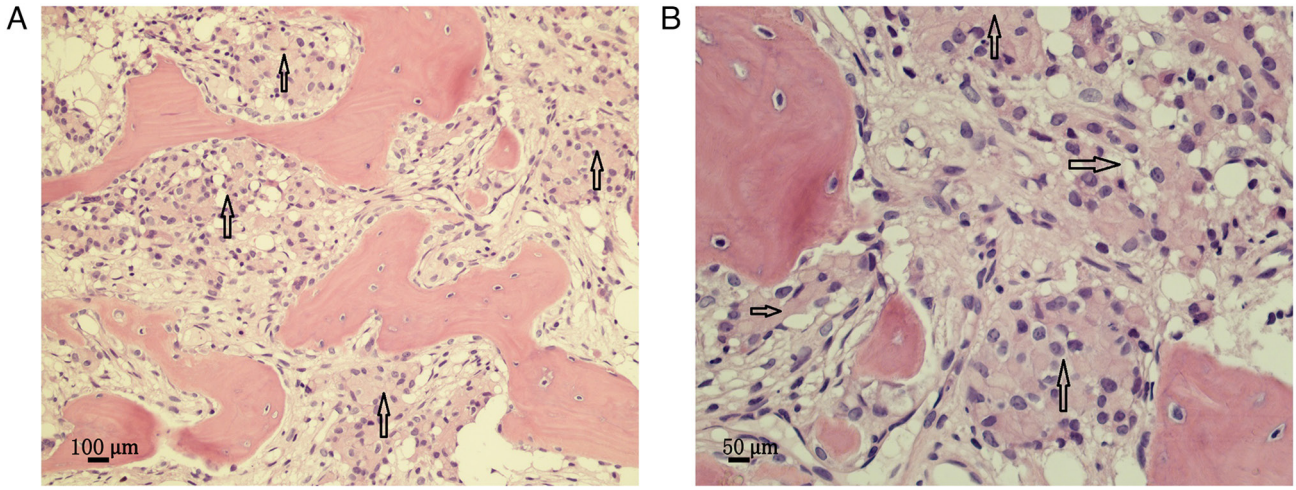

Figure 2. Bone marrow biopsy of patients with breast cancer. H&E staining at (A) x200 and (B) x400 magnification. Arrows show the location of the tumor.

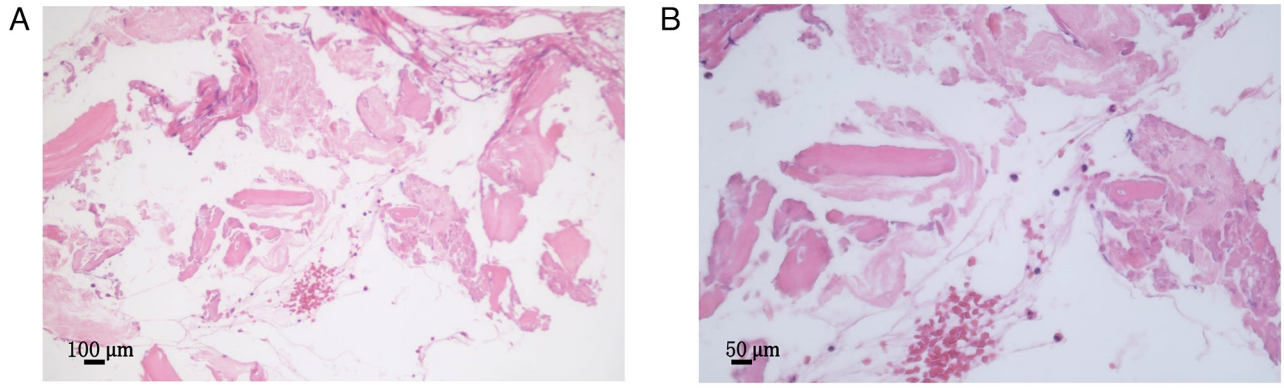

Figure 3. Bone marrow biopsy of patients with breast cancer following treatment. H&E staining at (A) x200 and (B) x400 magnification. After treatment, the metastatic lesions in the bone marrow disappeared.

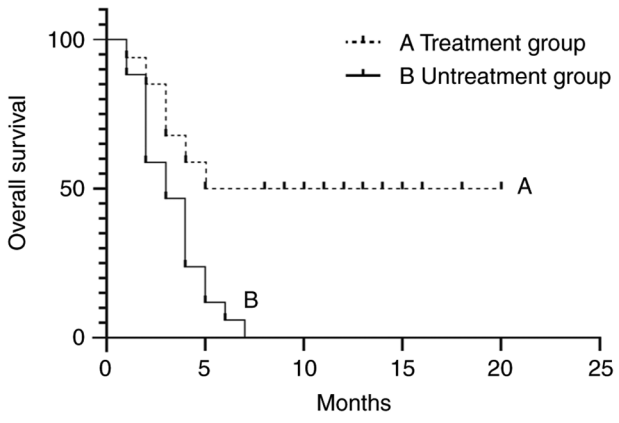

Figure 4. Effect of antitumor therapy on the survival of patients with bone marrow metastases.

associated with a predisposition to bone metastases from breast cancer. In the current study, 29 and 17% of patients presenting with breast or prostate cancer, respectively, developed bone metastases. When patients develop bone metastases, they may present with pathological fractures, hypercalcemia, bone pain and spinal cord compression. Bone metastasis is a complex multistep process in which disseminated tumour cells extravasate, enter the bone marrow compartment and occupy one of two specialized microenvironments or niches which consist of perivascular and endothelial cells of the sinusoids in the bone marrow and the endosteal niche. This step is followed by a period of dormancy in which the disseminated tumour cells adapt, survive and reside in the bone for a long period, possibly years or even decades (12,13). Therefore, when bone metastases occur, patients are not necessarily accompanied by BMMs. The third step is the reactivation of cancer cells that have acquired the ability to escape from dormancy, followed by their outgrowth to form micrometastasis, eventually leading to the development of overt bone metastasis (14). In the present study, bone metastases occurred mainly in patients with breast and prostate cancers. The mechanism of BMM development may be based on the ability of the tumour cells to overexpress chemokine receptor (CXCR) 4 and induce tumour cell invasion and homing to the bone marrow via the chemokine C-X-C motif ligand (CXCL)12/CXCR4 signalling pathway (15). Over the last few years, the potential pathogenetic role of bone marrow adipocytes (BMAds) and their molecular basis have been intensively investigated in marrow neoplastic diseases,

such as haematological malignancies and cancer metastasis. Therefore, it has been shown that BMAdscan modulate the migration and aggressiveness of neoplastic cells (16). Dello Spedale Venti *et al* (17) reported the possibility of BMAds being associated with tumour BMM.

Metastatic bone marrow cancer is a systemic, incurable disease with a poor prognosis which indicates that the patient is at an advanced stage. The median survival time of bone marrow metastatic carcinoma was 1.5-3 months (18). The reasons for the poor treatment outcomes were as follows: i) Patients who had received chemotherapy several times could have developed resistance to the tumour and patients with BMMs had poor bone marrow tolerance; therefore chemotherapeutic drugs which caused lower myelosuppression and required appropriate reductions in their dose were required to be selected as a treatment; ii) patients with poor body condition (with anaemia and thrombocytopenia) were prone to systemic infections, bleeding and other complications; iii) patients with an unknown primary focus could not be effectively treated with an antitumor therapy. It was previously proposed that metastatic cancer of the bone marrow could exhibit a poor prognosis and that the toxic side effects of antitumor therapy could reduce patient survival (19). A previous study indicated that the application of antitumor therapy could improve disease prognosis (20). The anaemia and thrombocytopenia of patients with BMMs could not be fundamentally altered by blood transfusion. A recent study showed that antitumor therapy could significantly improve symptoms, such as anaemia and control disease progression (21). In the present study, anaemia and thrombocytopenia were improved in 30 patients following antitumor treatment. There were only six patients who remained in CR at the end of follow-up, of whom four exhibited paediatric neuroblastoma following chemotherapy (or combined radiotherapy), surgery and autologous hematopoietic stem cell transplantation; the remaining two were cases of breast and prostate cancers, respectively. For paediatric neuroblastoma, ASCT could delay disease progression and prolong the child's survival time when surgery was unsatisfactory and the malignant cells could not be eliminated through radiotherapy and chemotherapy (22). The long-term survival rate for patients with paediatric neuroblastoma who developed BMMs was poor (23). According to research data from the last decade, the 3-year OR rate of the single ASCT group was 74.1% (24). Consequently, paediatric neuroblastoma with BMMs should be treated aggressively. Demir *et al* (25) reported that patients with breast cancer and BMM who accepted antitumor therapy survived longer than those who did not (17.3 vs. 0.93 months, respectively). Antiandrogen therapy was also shown to be effective in treating BMMs from prostate cancer (26). In the present study, by the end of the follow-up period, six patients were in partial remission, of whom four were cases with prostate cancer and two with breast cancer. The prognosis of breast and prostate cancers was slightly improved compared with that of other tumours. The median OS for untreated patients was only 3.3 months, while it was 11.5 months for treated patients. Antitumor therapy could improve OS in patients with BMM. For patients with BMM, it is important to actively evaluate the patient's condition and select the appropriate treatment plan for improving the disease prognosis.

In conclusion, although the prognosis for metastatic bone marrow cancer is poor, its treatment can improve patient survival. With the development of genetic testing technology, targeted drugs may offer novel opportunities for patients with metastatic bone marrow cancer in the future.

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Availability of data and materials

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HY performed the clinical trial study and drafted the manuscript. TY and WX performed the clinical data collection. ZC performed the statistical analysis. FH conceived the study and participated in its design, and helped to draft the manuscript. HY and FH confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The article was a retrospective study and had been approved by the Medical Ethics Committee of Tianjin Cancer Institute and Hospital (approval no. bc2022043).

Patient consent for publication

Written informed consent was obtained from the patients for publication of this case report and any accompanying images. A copy of the written consent is available from the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interests.

References

1. Clifton BA, Neill JS and Anderson MD: Treatment of Shh medulloblastoma with extraneural metastasis to the bone marrow. Current problems in cancer: Case Reports 4: 100104, 2021.
2. Shinden Y, Sugimachi K, Tanaka F, Fujiyoshi K, Kijima Y, Natsugoe S and Mimori K: Clinicopathological characteristics of disseminated carcinomatosis of the bone marrow in breast cancer patients. Mol Clin Oncol 8: 93-98, 2018.
3. La Gioia A, Fiorini F and La Gioia N: Bone marrow involvement by metastatic invasive lobular breast cancer. Int J Lab Hematol 44: 40-41, 2022.

4. Fan HJ, Huang C, Su Y, Wang XD, Zhou YC, Duan C, Zhao W, Zhao Q, Jin M and Ma XL: Clinical characteristics and prognosis of high-risk neuroblastoma with bone marrow metastasis in children. Zhonghua Er Ke Za Zhi 57: 863-869, 2019 (In Chinese).
5. Rani HS, Hui M, Manasa P, Uppin SG, Uppin MS, Paul TR and Sadashivudu G: Bone marrow metastasis of solid tumors: A study of 174 cases over 2 decades from a single institution in India. Indian J Hematol Blood Transfus 38: 8-14, 2022.
6. Edwards IR and Aronson JK: Adverse drug reactions: Definitions, diagnosis, and management. Lancet 356: 1225-1229, 2000.
7. Rana NA, Mahmood A, Robert HM, Zahir S, Asghar MB and Riaz S: Laboratory evaluation and pathological features of bone marrow metastasis in non-haematological malignancies. J Coll Physicians Surg Pak 32: 1367-1369, 2022.
8. Hofbauer LC, Bozec A, Rauner M, Jakob F, Perner S and Pantel K: Novel approaches to target the microenvironment of bone metastasis. Nat Rev Clin Oncol 18: 488-505, 2021.
9. Hong YM, Yoon KT, Cho M, Kang DH, Kim HW, Choi CW, Park SB, Heo J, Woo HY, Lim W and Islam SMB: Bone marrow metastasis presenting as bicytopenia originating from hepatocellular carcinoma. Clin Mol Hepatol 22: 267-271, 2016.
10. Shi XB, Deng WX and Jin FX: Bone marrow metastatic neuroendocrine carcinoma with unknown primary site: A case report and review of the literature. World J Clin Cases 10: 11074-11081, 2022.
11. Kopp HG, Krauss K, Fehm T, Staebler A, Zahm J, Vogel W, Kanz L and Mayer F: Symptomatic bone marrow involvement in breast cancer-clinical presentation, treatment, and prognosis: A single institution review of 22 cases. Anticancer Res 31: 4025-4030, 2011.
12. Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, Peto R, Pritchard KI, Bergh J, Dowsett M, *et al*: 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. N Engl J Med 377: 1836-1846, 2017.
13. Park SH, Keller ET and Shiozawa Y: Bone marrow microenvironment as a regulator and therapeutic target for prostate cancer bone metastasis. Calcif Tissue Int 102: 152-162, 2018.
14. Ripp J, Diab O, Woodroof J and Sun W: Colorectal adenocarcinoma presenting with isolated metastasis to the cortical bone and bone marrow: A case report and review of the literature. Clin Colorectal Cancer 20: e150-e154, 2021.
15. Jafari A, Fairfield H, Andersen TL and Reagan MR: Myeloma-bone marrow adipocyte axis in tumour survival and treatment response. Br J Cancer 125: 775-777, 2021.
16. Fairfield H, Dudakovic A, Khatib CM, Farrell M, Costa S, Falank C, Hinge M, Murphy CS, DeMambro V, Pettitt JA, *et al*: Myeloma-modified adipocytes exhibit metabolic dysfunction and a senescence-associated secretory phenotype. Cancer Res 81: 634-527, 2021.
17. Dello Spedale Venti M, Palmisano B, Donsanten S, Farinacci G, Adotti F, Coletta I, Serafini M, Corsi A and Riminucci M: Morphological and immunophenotypical changes of human bone marrow adipocytes in marrow metastasis and myelofibrosis. Front Endocrinol (Lausanne) 13: 882379, 2022.
18. DA Silva A, Levy C, Allouache D, Hrab I, Morel A, Faveyrial A, Gunzer K, Johnson A, Segura C, Licaj I, *et al*: Efficacy and safety of weekly paclitaxel in breast cancer with symptomatic bone marrow infiltration. Anticancer Res 40: 2955-2960, 2020.
19. Braun S, Vogl FD, Janni W, Marth C, Schlimok G and Pantel K: Evaluation of bone marrow in breast cancer patients: Prediction of clinical outcome and response to therapy. Breast 12: 397-404, 2003.
20. Buschhaus JM, Humphries BA, Eckley SS, Robison TH, Cutter AC, Rajendran S, Haley HR, Bevoor AS, Luker KE and Luker GD: Targeting disseminated estrogen-receptor-positive breast cancer cells in bone marrow. Oncogene 39: 5529-5662, 2020.
21. Arya L, Sundriyal D, Bhandari R, Srivastava R and Sehrawat A: Bone marrow metastases from solid organ cancer in adults. Indian J Surg Oncol 12: 545-548, 2021.
22. Mora J: Autologous stem-cell transplantation for high-risk neuroblastoma: Historical and critical review. Cancers (Basel) 14: 2572, 2022.
23. Moreno L, Guo D, Irwin MS, Berthold F, Hogarty M, Kamijo T, Morgenstern D, Pasqualini C, Ash S, Potschger U, *et al*: A nomogram of clinical and biologic factors to predict survival in children newly diagnosed with high-risk neuroblastoma: An international neuroblastoma risk group project. Pediatr Blood Cancer 68: e28794, 2021.
24. Park JR, Kreissman SG, London WB, Naranjo A, Cohn SL, Hogarty MD, Tenney SC, Haas-Kogan D, Shaw PJ, Kraveka JM, *et al*: Effect of tandem autologous stem cell transplant vs singletransplant on event-free survival in patients with high-risk neuroblastoma: A randomized clinical trial. JAMA 322: 746-755, 2019.
25. Demir L, Akyol M, Bener S, Payzin KB, Erten C, Somali I, Can A, Dirican A, Bayoglu V, Kucukzeybek Y, *et al*: Prognostic evaluation of breast cancer patients with evident bone marrow metastasis. Breast J 20: 279-287, 2014.
26. Hiroshige T and Eguchi Y: Prostate cancer with disseminated carcinomatosis of the bone marrow: Two case reports. Mol Clin Oncol 7: 233-236, 2017.