Case Report

Disseminated carcinomatosis of the bone marrow caused by prostate cancer diagnosed with only bone marrow biopsy

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Abbreviations & Acronyms
DCBM = disseminated carcinomatosis of the bone marrow
HE = hematoxylin-eosin
MRI = magnetic resonance imaging
PSA = prostate specific antigen

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Introduction: Disseminated carcinomatosis of the bone marrow caused by prostate cancer is a rare condition with poor prognosis. Diagnosis has mostly been by primary prostate biopsy.

Case presentation: A 60-year-old man had malaise, low platelet count (9000/μL), and high prostate-specific antigen (1382 ng/mL). Bone marrow biopsy showed strongly positive immunostaining NKX3.1, leading to diagnosis of prostate cancer bone marrow metastasis, cT3aN1M1b. Definitive diagnosis by prostate biopsy was difficult because of the sparsity of atypical glands. He had progression to castration-resistant prostate cancer after 3 months of hormonal therapy, and received 27 courses of docetaxel and six courses of cabazitaxel as chemotherapy, but finally died of respiratory failure 33 months after the start of treatment.

Conclusion: Aggressive biopsy of the metastatic sites should be considered if a prostate biopsy at the primary site cannot be diagnosed definitively.

Key words: bone marrow metastasis, disseminated carcinomatosis of the bone marrow, metastasis-to-metastasis, prostate cancer, thrombocytopenia.

Keynote message

Even in metastatic prostate cancer with disseminated carcinomatosis of the bone marrow, there may be low tumor volume at the primary site. Aggressive biopsy of metastatic sites as well as the primary site should be considered.

Introduction

DCBM is a rare condition, mostly caused by gastric cancer, and much less commonly by prostate cancer. Most advanced metastatic prostate cancers are definitively diagnosed by prostate biopsy. We report a case of metastatic prostate cancer with DCBM that had low tumor volume at the primary site.

Case presentation

A 60-year-old man with no previous medical or family history had malaise from the previous 2 months, low platelet count (9000/μL), and high prostate-specific antigen (PSA, 1382 ng/mL), so he was referred for hematological and urological examination. Digital rectal examination revealed a hard nodular palpable mass in the right lobe. Blood tests showed blasts, high levels of lactate dehydrogenase 509 IU/L, and alkaline phosphatase 1687 IU/L, but not disseminated intravascular coagulation. For differential diagnosis of the low platelet count, bone marrow puncture was performed by the hematologist who examined the patient before the urologist, it revealed a cluster of atypical cells suspicious for adenocarcinoma (Fig. 1a). Bone marrow biopsy also showed infiltration of atypical cells with glandular structures between the trabecular bone (Fig. 1b), and immunostaining of NKX3.1 was strongly positive (Fig. 1c), leading to the diagnosis of DCBM, a bone marrow metastasis of prostate cancer. MRI and bone scintigraphy showed a nodular lesion in the right peripheral zone and multiple

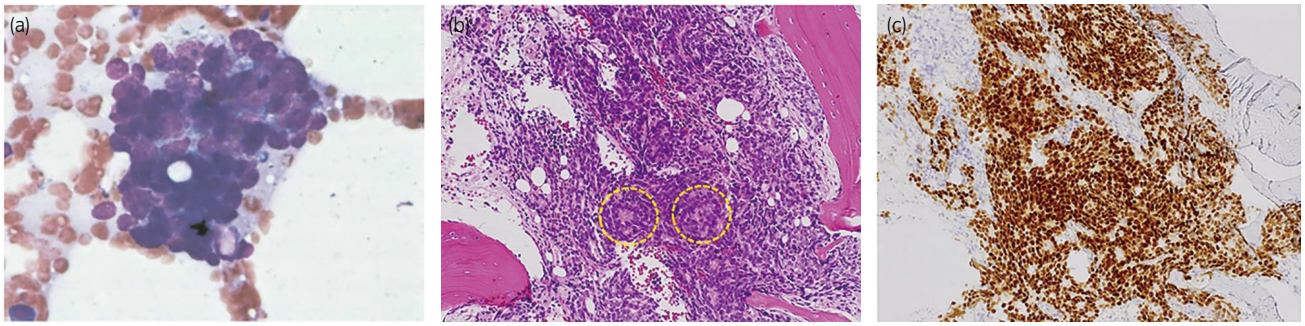

Fig. 1 (a) A cluster of atypical cells suspicious for adenocarcinoma in bone marrow puncture. (b) Infiltration of atypical cells with glandular structures between the trabecular bone in bone marrow biopsy (HE, ×100). (c) Immunostaining for NKX3.1 strong positive (NKX3.1, ×100).

metastases with super bone scan, respectively (Fig. 2). Computed tomography showed enlarged supraclavicular, mediastinal, para-aortic, and obturator lymph nodes, but there was no obvious visceral metastasis. We diagnosed prostate cancer cT3aN1M1b. The platelet count was low, so ultrasound-guided transrectal prostate biopsy including one target biopsy of a right lobe nodal lesion was performed at six sites 1 week after hormonal therapy. Digital rectal examination again detected the same nodule in the right lobe as in the initial examination. A very small number of atypical glands with cribriform growth were found in one of the six sites. These stained negative for p63, but definitive diagnosis was difficult because of the sparsity of atypical glands (Fig. 3).

Treatment was started with platelet transfusion, bicalutamide and degarelix, with concomitant use of zoledronic acid. Despite the steady decline of PSA, the treatment was changed to docetaxel (75 mg/m^2, every 3 weeks) after 3 months because of progression to castration-resistant prostate cancer. PSA then decreased to nadir 0.021 ng/mL, and a total of 27 courses were continued over about 2 years. From the start of degarelix treatment until this point, the lymph nodes and bone metastases had remained small. Although PSA re-elevation was confirmed and treatment was switched to cabazitaxel (25 mg/m^2 every 3 weeks), cerebral neuropathies including the oculomotor, trigeminal, and facial nerves, soon appeared. Cerebrospinal fluid examination could not be performed owing to the patient's poor condition, but MRI showed a contrast effect in the ventral side of the lower part of the pons, and the multiple cerebral neuropathies were diagnosed as intraparenchymal infiltration due to carcinomatous meningitis. PSA decreased after four courses of cabazitaxel, but neuroendocrine differentiation markers were markedly elevated (pro-gastrin releasing peptide 39 247 pg/mL, neuron-specific enolase 681 ng/mL). On imaging, bone metastases remained unchanged, but lymph node metastases increased and lung, pleural, liver, and right obturator muscle

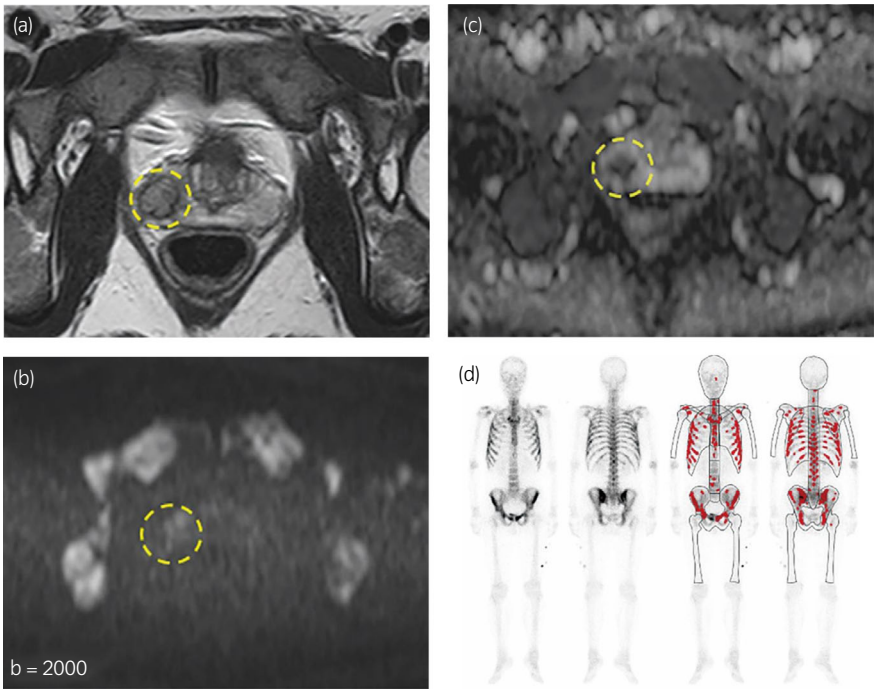

Fig. 2 (a) MRI (T2-weighted image) showing a nodular lesion in the right peripheral zone. (b) MRI (diffusion-weighted image) showing a nodular lesion in the right peripheral zone. (c) MRI (apparent diffusion coefficient) showing a nodular lesion in the right peripheral zone. (d) Bone scintigraphy showing multiple metastases with super bone scan.

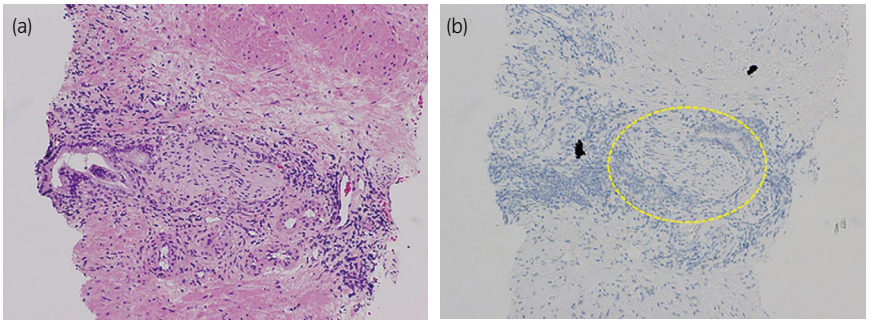

Fig. 3 (a) Very few atypical glands with cribriform growth (HE, ×100). (b) Immunostaining for p63 negative (p63, ×100).

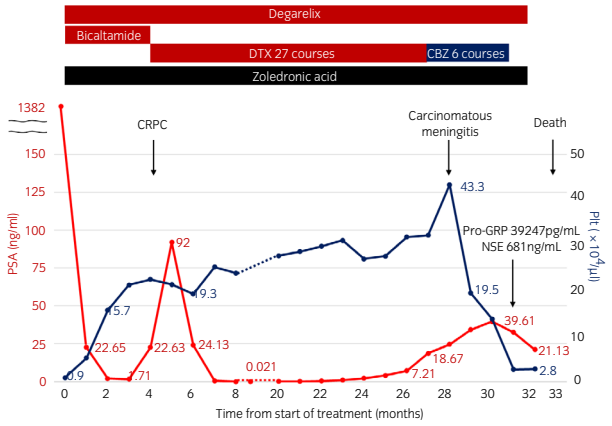

Fig. 4 Course of treatment.

metastases were newly observed. Ultimately, the patient died of respiratory failure due to carcinomatous pleural effusion 33 months after the start of treatment.

Discussion

DCBM is diffuse invasion of the bone marrow by cancer cells, accompanied by hematologic disorders, such as leukopenia, anemia, and thrombocytopenia. Bone marrow metastasis from solid tumors is especially common in gastric, prostate, and breast cancers.[1,2]

In a summary of previous reports, the median overall survival of 24 patients with prostate cancer diagnosed with DCBM at the first presentation was 8 months, while our case had a relatively long survival of 33 months.[3–5] Cytopenia was only thrombocytopenia and not disseminated intravascular coagulation, which may suggest that the present patient was in a relatively early stage of DCBM. Although there is no evidence that zoledronic acid suppresses skeletal-related events and prolongs survival in metastatic hormone-sensitive prostate cancer, this patient's long-term survival could be attributed to the early introduction of docetaxel and the initial use of zoledronic acid. Zoledronic acid induces apoptosis of osteoclasts and directly inhibits tumor cell growth, so it may have been particularly effective in the present case with bone marrow metastasis.[6] Also, radium-223 is captured into the sites with increased bone metabolism, such as bone metastases. The distance from the cortical bone to the bone marrow is beyond the reach of alpha rays, so radium-223 cannot exert its full anti-tumor effect in the bone marrow, and it is unlikely to be effective against DCBM.[7] We proposed that PSA decline after four courses of cabazitaxel was suggestive of effectiveness of treatment after the flare up (Fig. 4). However, based on the elevation of pro-gastrin releasing peptide and neuron-specific enolase, it is likely that there was neuroendocrine differentiation. If tumor markers had been measured at least once before the start of cabazitaxel, further long-term survival could have been achieved by change of treatment.

One reason for failure to diagnose prostate cancer at the primary site is a burned-out tumor. However, there was no scar tissue or fibrosis indicative of a burn-out tumor in the prostate biopsy specimen. Recently, the concept of 'metastasis to metastasis seeding' was proposed based on studies in which both the primary tumor and multiple metastases sites were genetically analyzed for mutations.[8,9] In other words, all metastases were conventionally considered to be metastases from the primary tumor, but metastases can also come from sites of metastasis. The accumulation of genetic mutations in repeated metastases increases the malignancy. Our patient had metastatic prostate cancer with relatively low tumor volume at the primary site, so we suggest that the patient may have followed 'metastasis to metastasis seeding' pathway. In addition, previous studies reported 10 cases in which prostate cancer was undiagnosed despite repeated prostate biopsies with different approaches and additional biopsies, although these studies did not include DCBM.[10,11] In all cases, PSA was markedly elevated during the period of repeated biopsies, and prostate cancer was finally confirmed by biopsies of the metastatic lymph nodes or bones. Guidelines for cancers of unknown primary tumor recommend completing the evaluation of the primary tumor as early as possible due to the poor prognosis.[12] Considering that PSA staining or NKX3.1 staining have high sensitivity and specificity for the diagnosis of metastatic sites in prostate cancer, biopsy of metastatic sites is more important if the primary site cannot be definitively diagnosed.

In conclusion, even in metastatic prostate cancer with DCBM, the tumor volume at the primary site may be quite low. Aggressive biopsy of metastatic sites as well as the primary site should be considered because metastatic prostate cancer is likely to progress during the period of repeated prostate biopsies.

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Conflict of interest

The authors declare no conflicts of interest.

Approval of the research protocol by an institutional reviewer board

Not applicable.

Informed consent

Not applicable.

Registry and the registration no. of the study/trial

Not applicable.

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