Case Report

Bone marrow metastasis in a patient with non-seminomatous testicular germ cell tumor

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Abbreviations & Acronyms
AFP = alfa-fetoprotein
BEP = bleomycin, etoposide, cisplatin
CBC = complete blood count
CT = computed tomography
ExGCT = extragonadal germ cell tumor
GCT = germ cell tumor
Hb = hemoglobin
hCG = human chorionic gonadotropin
IGCCC = international germ cell consensus classification
IrN = irinotecan, nedaplatin
IrP = irinotecan, cisplatin
MRI = magnetic resonance imaging
PET-CT = positron emission tomography-computed tomography
PLT = platelet
RBC = red blood cell
RPLND = retroperitoneal lymph node dissection
TGCT = testicular germ cell tumor
TGN = paclitaxel, gemcitabine, nedaplatin
TGO = paclitaxel, gemcitabine, oxaliplatin
TIN = paclitaxel, ifosfamide, nedaplatin
TIP = paclitaxel, ifosfamide, cisplatin
WBC = white blood cell

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Introduction: Metastasis to the bone marrow is rare in testicular germ cell tumor patients. We report a case of a patient with a non-seminomatous testicular germ cell tumor who presented with bone marrow metastases after intensive chemotherapy.
Case presentation: A 36-year-old man was admitted to the hospital with pancytopenia. Previously, he had received intensive care for an advanced left testicular germ cell tumor. Although multidisciplinary treatments including several regimens of salvage chemotherapy, desperation retroperitoneal lymph node dissection, and focal radiotherapy were performed, the serum tumor marker alfa-fetoprotein was not normalized and there were no findings of relapse by several imaging modalities. Bone marrow aspirate, conducted to diagnose a cause of pancytopenia, revealed metastatic germ cell tumors in the bone marrow.
Conclusion: Bone marrow metastasis should be considered as a differential diagnosis in patients with germ cell tumors whose serum tumor makers are not normalized without any radiographic finding of recurrence.

Key words: AFP, bone marrow metastasis, desperation RPLND, salvage chemotherapy, testicular germ cell tumor.

Keynote message

Metastases to the lymph nodes, lungs, liver, and brain are commonly observed in germ cell tumors. The bone marrow is an extremely rare site where germ cell tumors metastasize and are difficult to diagnose using radiographic examination. We report the first case of a patient with non-seminomatous testicular germ cell tumors who presented with bone marrow metastases after intensive therapy.

Introduction

TGCTs are the most common cancer in young adult men.[1] Although advanced TGCTs commonly metastasize to the lymph nodes, lungs, liver, and brain, metastases to the bone marrow in TGCT patients are rare.[2,3] Standard treatment for advanced TGCT is cisplatin-based chemotherapy followed by the resection of residual tumor after normalization of serum tumor markers such as AFP and hCG. Although 80% of patients with advanced TGCT are successfully cured, 20% become refractory to standard therapy, resulting in elevated serum tumor marker.[1,4]

Here, we report the case of a patient with non-seminomatous TGCTs, who were refractory to chemotherapy and exhibited pancytopenia due to metastases in the bone marrow.

Case presentation

A 36-year-old man visited the hospital for monthly follow-up after being refractory to treatment for TGCT treatment. He complained of back pain and dyspnea. About 10 years ago, he was admitted to our hospital for salvage chemotherapy for left TGCT (histological

diagnosis was immature teratoma>embryonal carcinoma>yolk sac tumor, AFP:539 ng/mL, stage IIIA, IGCCC: good prognosis) after induction chemotherapy consisting of BEP. He was treated with multiple chemotherapy regimens, including TIN, TIP, IrP, TGN, IrN, and TGO. Furthermore, he underwent desperation RPLND and focal radiotherapy twice (Fig. 1). Although his serum tumor marker, AFP, had not normalized after the therapy, his radiographic examination, such as contrast-enhanced CT, MRI, bone scintigraphy, and PET-CT showed no evidence of an active region (Fig. 2). He was monitored by AFP and radiographic examination after intensive care. Blood analysis on the day of hospitalization revealed pancytopenia which was not observed a month ago, and he was urgently hospitalized, although his AFP level tended to decrease, and radiographic examination indicated no relapse. His CBC results was as follows: WBC: 2000/mm^3, neutrophil: 600/mm^3, RBC: 1.93×10^6/mm^3, Hb: 6.7 g/dL, PLT (platelet): 2.0×10^3/mm^3. To exclude hematological malignancies induced by cumulative chemotherapy, bone marrow aspiration and bone marrow biopsy from the iliac crest were performed. Histological analysis showed atypical cells having abundant mucus in the cytoplasm were forming ducts and floating diffusely in the fluid of the bone marrow cavity. Though it was the histopathological image of moderate to poorly differentiated adenocarcinoma, it was presumed to be a portion of teratoma with malignant formation from the medical history and normal findings in the upper and lower endoscopy (Fig. 3). The patient required frequent transfusion of packed RBCs and platelets after admission. Since the teratoma is chemoresistant and the general condition was too poor to perform aggressive treatment including myeloablative chemotherapy with bone marrow transplantation and administration of immune checkpoint inhibitors, the patient was moved to palliative and supportive care.

Discussion

GCTs are divided into two groups. The major group, TGCTs, occurs in gonads, and the minor group, ExGCTs, occurs in other regions.[5] ExGCTs are commonly localized to the mediastinum or retroperitoneum. Fundamentally, the principle of treatment for both types of GCT is the same. Patients are treated with chemotherapy aiming for normalization of serum tumor marker, followed by resection of the residual tumor performed as completely as possible.[6] However, the prognosis of each GCT is different. ExGCTs, especially mediastinal GCTs, have worse prognoses than TGCTs.[7] Unlike usual bone metastasis, bone marrow metastasis shows diffuse infiltrate growth in the bone marrow which sometimes causes systemic hematologic disorders such as pancytopenia.[8] Metastases of GCTs to the bone marrow are extremely rare, and all previously reported cases involve metastases to the bone marrow in patients with mediastinal GCT.[2,3] To the best of our knowledge, this is the first case of bone marrow metastasis in a patient with TGCT presenting with pancytopenia.

The mechanism underlying metastasis to the bone marrow in malignant diseases has not yet been discovered. However, it seems that there is a difference in the tendency of bone marrow metastases according to the type of malignancy. In addition to hematological malignancies, neuroblastoma, lung cancer, breast cancer, and prostate cancer have a relatively higher tendency to metastasize to the bone marrow.[9] However, bone metastases in patients with GCTs are rare.[10] In neuroblastoma patients, bone marrow aspirates are the standard examination for staging the disease.[11] These cancers have a high tendency to metastasize to the skeleton. One of the mechanisms of bone marrow metastasis may be a direct invasion from the bones themselves. Another proposed mechanism is hematogenous metastasis to the bone marrow by a study using a model mouse,[12,13] where intracardiac injection

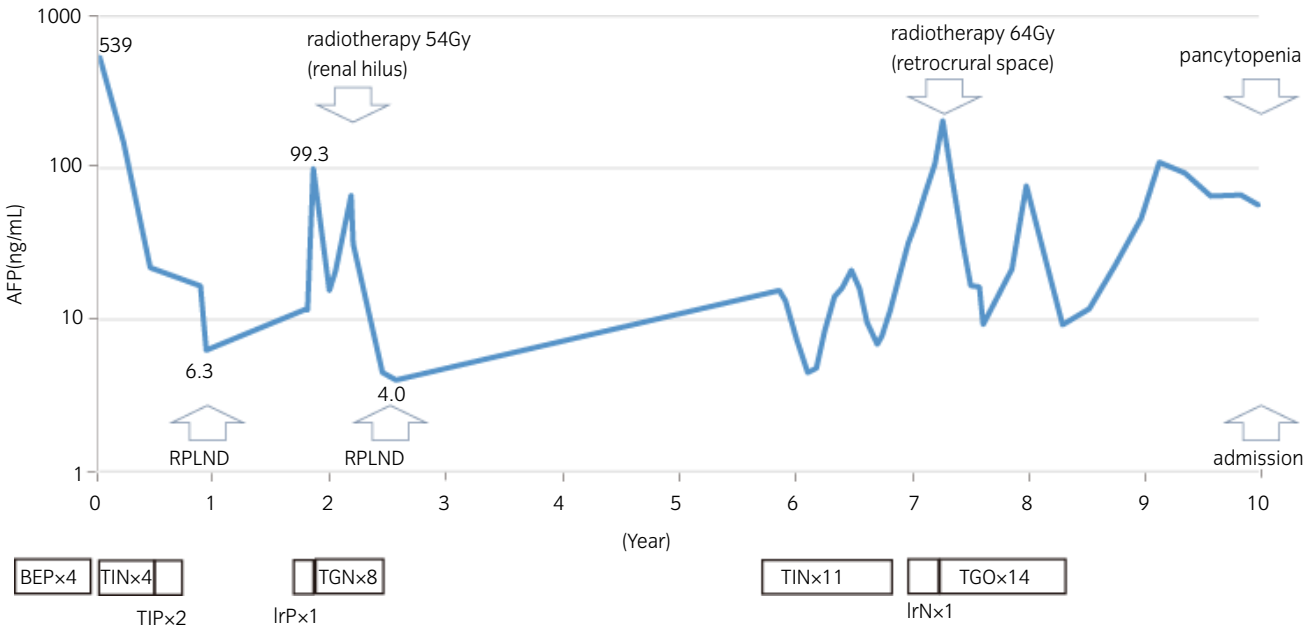

Fig. 1 Clinical course of the patient.

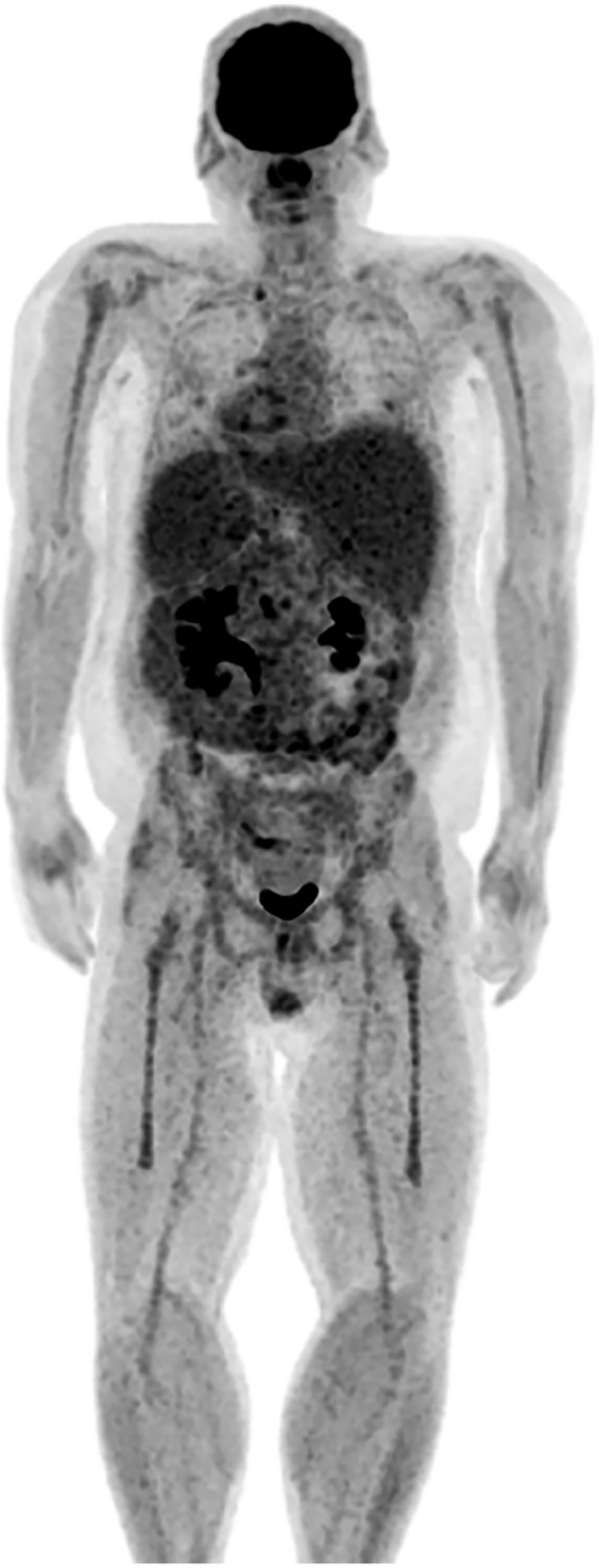

Fig. 2 PET-CT showing no specific result including the bone area.

of tumor cells caused bone marrow metastases while intravenous injection of tumor cells did not, suggesting that arterial distribution of tumor cells bypassing the lungs may lead to bone marrow metastases.

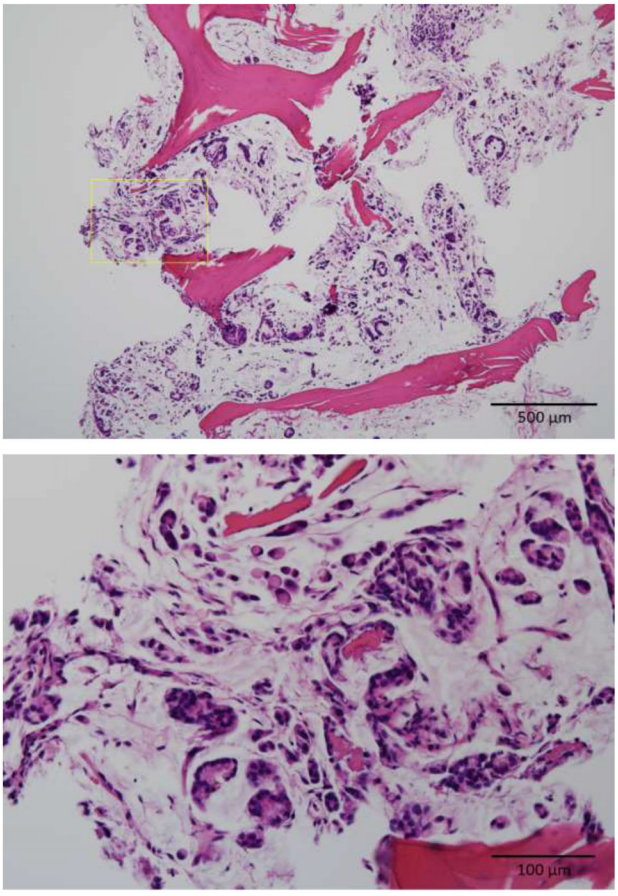

Fig. 3 Histological analysis of the bone marrow aspirate and bone marrow biopsy showed atypical cells having abundant mucus in the cytoplasm were forming duct and floating diffusely in the fluid of bone marrow cavity indicating moderate to poorly differentiated adenocarcinoma.

In our case, pancytopenia, a blood abnormality, led to the diagnosis of bone marrow metastasis by bone marrow aspiration to exclude hematological malignancy. Radiographic examination, including PET-CT, did not indicate GCT metastases to the bone marrow. A previous report on bone marrow metastases in a mediastinal ExGCT patient suggested that PET-CT was useful for the detection of bone marrow metastases in GCT patients.[3] However, PET-CT was not recommended as a follow-up examination for non-seminomatous GCT due to its low sensitivity[14,15] and PET-CT was not useful in our case. Bone marrow metastasis should be considered for the follow-up of GCT patients, whose serum tumor makers are not normalized and whose imaging presents no relapse.

Unfortunately, the reason for the high serum AFP level in this patient had not been clear yet. It could be residual yolk sac tumor or embryonal carcinoma which could not be identified by radiographical findings. Upregulation of AFP level in teratoma is relatively rare.[16,17] Immunohistochemistry using AFP antibody may be future work.

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Author Contributions

Takashi Ueda: Writing – original draft. Ippei Takada: Data curation. Teruki Shimizu: Writing – review and editing. Saya Ito: Writing – review and editing. Atsuko Fujihara: Writing – original draft. Takumi Shiraishi: Writing – review and editing. Terukazu Nakamura: Supervision. Osamu Ukimura: Supervision.

Conflict of interest

The authors declare no conflict 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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