Case Report

Myelodysplastic syndrome occurring after enfortumab vedotin treatment for metastatic urothelial carcinoma

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Abbreviations & Acronyms
ADC = antibody-drug conjugate
AUC = area under the curve
CT = computed tomography
DIILD = drug-induced interstitial lung disease
EV = enfortumab vedotin
GCa = gemcitabine and carboplatin
MDS = myelodysplastic syndrome
t-MNs = therapy-related myeloid neoplasms
UC = urothelial carcinoma

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Introduction: Enfortumab vedotin is an antibody-drug conjugate targeting Nectin-4 for the treatment of advanced urothelial carcinoma in patients previously treated with platinum-containing chemotherapy and immune checkpoint inhibitors. Common adverse events include rashes, peripheral neuropathy, and hyperglycemia. However, there are no reports on the development of myelodysplastic syndrome during enfortumab vedotin therapy in clinical settings.
Case presentation: A 72-year-old male patient experienced prolonged and severe thrombocytopenia 18 weeks after the start of enfortumab vedotin therapy for metastatic urothelial carcinoma, requiring daily platelet transfusions. Bone marrow examination and chromosomal analysis confirmed the diagnosis of myelodysplastic syndrome. Treatment with eltrombopag proved to be effective.
Conclusion: This is the first report of the development of myelodysplastic syndrome during enfortumab vedotin therapy in a clinical setting. Although rare, myelodysplastic syndrome can occur during enfortumab vedotin therapy.

Key words: eltrombopag, enfortumab vedotin, myelodysplastic syndrome, urothelial carcinoma.

Keynote message

This is the first report of the development of myelodysplastic syndrome during enfortumab vedotin treatment in a clinical setting. The patient developed myelodysplastic syndrome 18 weeks after the start of enfortumab vedotin therapy for metastatic urothelial carcinoma, requiring daily platelet transfusions due to severe thrombocytopenia. Significant improvement in thrombocytopenia was observed following treatment with eltrombopag.

Introduction

EV is an ADC that targets Nectin-4 and is an effective third-line therapy for metastatic and advanced UC.[1] EV is linked to treatment-related adverse events, such as skin disorders, peripheral neuropathy, myelosuppression, and hyperglycemia. However, there are no reports on the development of MDS after this treatment in clinical settings. Herein, we report a case of the development of MDS during EV therapy for metastatic UC.

Case presentation

A 72-year-old man with right ureteral and bladder cancers and metastases to the right thigh muscle, para-aortic lymph nodes, and right axillary lymph nodes received EV therapy (1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle). Before receiving EV therapy, the patient had experienced disease progression after two cycles of GCa therapy (unfit for cisplatin due to renal impairment; gemcitabine 1000 mg/m^2 and carboplatin AUC5), eight cycles of avelumab (600 mg/every 2 weeks), two cycles of pembrolizumab (200 mg/every 3 weeks), 10 cycles of GCa therapy retried, and radiation therapy (30 Gy/10 fractions) for thigh muscle metastases. After two cycles of EV therapy, a CT scan showed a partial response by the cancer.

However, 18 weeks after the start of EV therapy, the patient developed a generalized rash and dyspnea. Complete blood count demonstrated thrombocytopenia (platelet; 6.6 × 10^4/μL)

and anemia (hemoglobin; 9.9 g/dL) and biochemistry tests showed elevations of KL-6 (970 U/mL), surfactant protein D (224 ng/mL), surfactant protein A (63.9 ng/mL), and C-reactive protein (16.16 mg/dL). Consolidation in a large area of both lungs was identified on chest CT, leading to a diagnosis of DIILD. High-dose corticosteroid therapy (methylprednisolone, 1000 mg/day) was performed for 3 days, followed by the oral administration of prednisolone. However, thrombocytopenia continued to worsen even 4 weeks after admission, requiring daily platelet transfusions (Fig. 1). No leukopenia or anemia requiring blood transfusion or other treatments was observed. Laboratory findings of peripheral blood were as follows: erythrocyte ($330 \times 10^4/\mu L$), hemoglobin (10.9 g/dL), mean corpuscular volume (98.5 fL), leukocyte (4100/μL; myeloblast 0%, myelocyte 2%, stab 2%, seg 86%, lymphocyte 4%, monocyte 5%, and erythroblast 1%), platelet ($1.9 \times 10^4/\mu L$), and immature platelet fraction (12.8%). Bone marrow examination revealed the following parameters: all marrow nucleated cells ($2.4 \times 10^4/\mu L$), myeloid/erythroid ratio (1.25), myeloid total (48.9%), myeloblast (1.5%), erythroblast (39.0%), and megakaryocyte (<0.1%). The bone marrow was hypoplastic, with pseudo-Pelger-Huët cells (Fig. 2a) and multinucleated megaloblasts (Fig. 2b). Chromosomal analysis showed 45, XY, der(5;17) (p10;q10)[3]/44, idem, -7[2]/46, XY[13] (Fig. 3). These results led to a diagnosis of MDS with multilineage dysplasia. Considering the patient's general condition, neither chemotherapy nor bone marrow transplantation was performed. The administration of eltrombopag, a thrombopoietin receptor agonist, was initiated at a dose of 25 mg/day. The patient required nine platelet transfusions. One month after the last platelet transfusion, thrombocytopenia was resolved. The patient was discharged approximately 1.5 months after admission due to significant improvement in physical and imaging findings of DIILD.

Two weeks later, the patient was readmitted to the hospital because of septic shock associated with pyelonephritis and cholecystitis. Additionally, imaging studies showed a recurrence of DIILD. Antibiotic administration was initiated concurrently with catecholamine. Because the patient was unable to take the drug internally, eltrombopag was discontinued. On the fifth day of admission, the patient experienced cardiopulmonary arrest. Although a return of spontaneous circulation was achieved, the patient experienced a prolonged loss of consciousness and was diagnosed with post-resuscitation encephalopathy. Two months after the second admission, the patient died. Ultimately, the patient showed no exacerbation of metastatic UC.

Discussion

MDS is a group of disorders characterized by the inability of bone marrow stem cells to mature into normally functioning blood cells.[2] Older age and history of hematological or autoimmune diseases have been reported as risk factors for MDS.[3,4] Chemotherapy, immune checkpoint inhibitors, and radiation therapy are also known to be associated with MDS, which was encompassed as t-MNs in the WHO classification in 2017.[2,5,6] Damage to DNA or chromosomes induced by anticancer drugs, molecularly targeted drugs, or irradiation of malignant tumors leads to the development of t-MNs. Although the exact mechanisms and risk factors remain

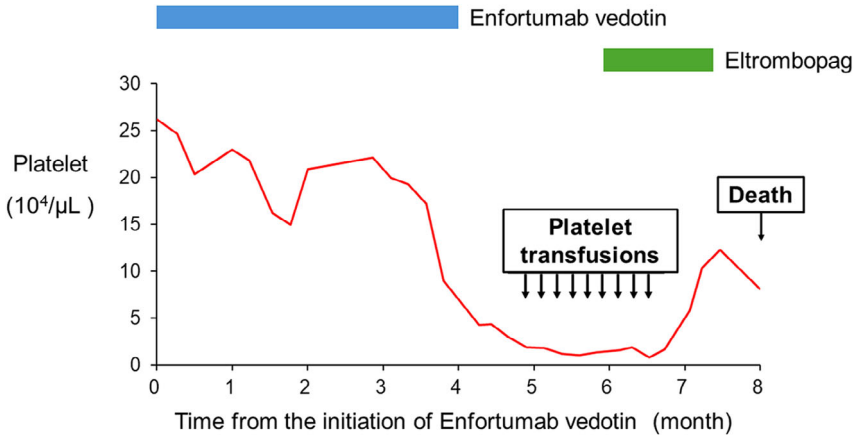

Fig. 1 Chronological changes in platelet. Treatments performed are indicated above the graph.

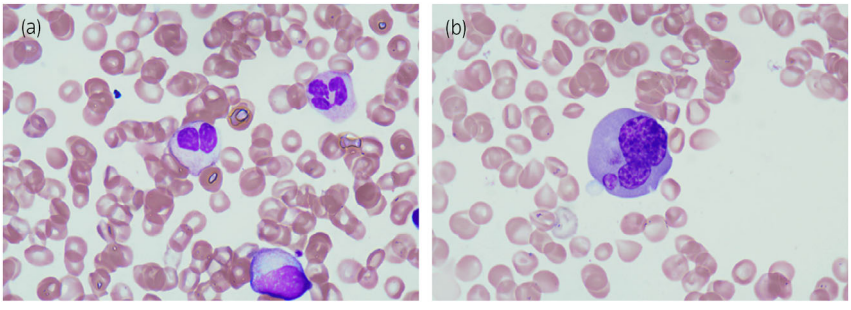

Fig. 2 May–Giemsa staining of bone marrow (original magnification ×1000). Pseudo-Pelger-Huët cells (dysplastic neutrophils with round and peanut-shaped nuclei) (a) and multinucleated megaloblasts (b) are observed.

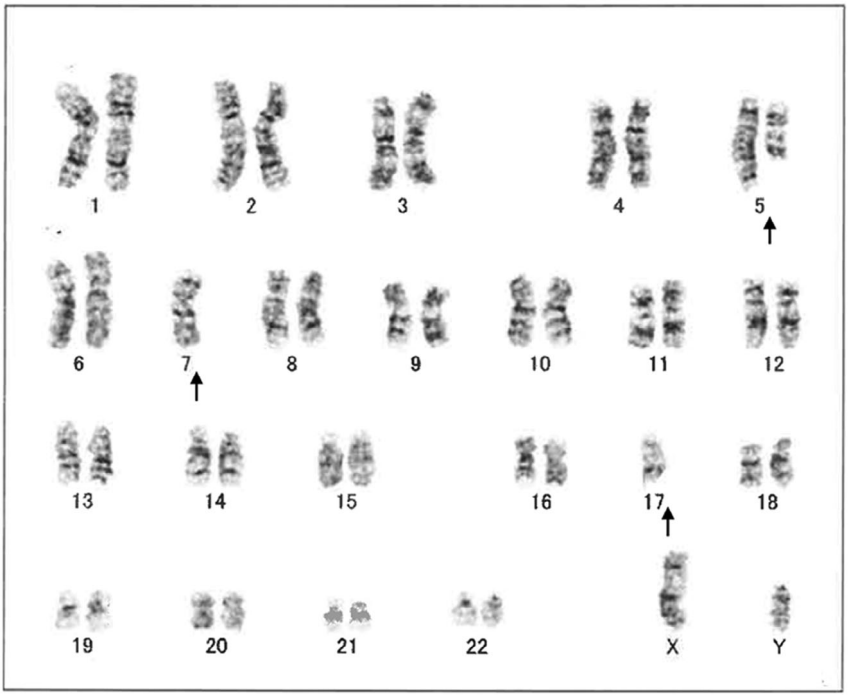

Fig. 3 G-banded karyotypes of the bone marrow cells. The karyotypes are as follows: 45, XY, der(5:17) (p10:q10)[3]/44, idem, -7[2]/46, XY[13].

unknown, three main mechanisms have been proposed.[7] The first is reciprocal translocation via chromosomal breaks. Topoisomerase II is an enzyme involved in DNA cleavage and rejoining. DNA that is inhibited from rejoining by topoisomerase II inhibitors binds to other chromosomes, causing mutual translocation and t-MNs. The second is genomic instability caused by impaired DNA repair mechanisms. Alkylating agents and extensive irradiation disrupt DNA repair mechanisms, destabilize the genome, and cause the accumulation of multiple mutations. Deletion-type chromosomal aberrations, such as del(7q)/- 7 and del(5q), are also frequently observed, and in this case, the deletion of chromosome 7 occurred. Third, radiation leads to the occurrence of DNA damage. Radiation causes base damage, base excision, and DNA strand breaks, and t-MNs develop when the checkpoints and repair mechanisms that detect these abnormalities fail.

Owing to the relatively short history of EV therapy in clinical settings, its adverse effects are not fully understood. This is the first report of MDS development during EV therapy in a clinical setting, although one case has been reported in a phase I trial of EV.[8] To the best of our knowledge, there are no reports of t-MNs in other ADCs.

A limitation of this report is the possibility that MDS may have been induced by factors other than EV, such as past chemotherapy, immune checkpoint inhibitors, or radiation. In the present case, thrombocytopenia appeared as a main manifestation of MDS, but thrombocytopenia may also appear as an immune-related adverse event after administration of pembrolizumab. However, it is presumed that the thrombocytopenia due to MDS in this case differs from immune-related adverse events, as thrombocytopenia as an immune-related adverse event is known to have the mechanism of aplastic anemia rather than MDS.[9] Currently, this possibility that MDS may have been induced by factors other than EV is unavoidable because patients previously treated with chemotherapy and immune checkpoint inhibitors are candidates for EV therapy. This issue is expected to become verifiable in the future if EV becomes available for use as a single-agent, first-line systemic therapy.

In conclusion, we presented a case of MDS during EV therapy for metastatic UC. With advances in anticancer drugs, molecular targeted therapies, ADCs, and irradiation, the need for the treatment of t-MNs is expected to increase. Furthermore, improved outcomes and prolonged cancer prognosis may increase the frequency of t-MNs.

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Author contributions

Kazuki Yanagida: Data curation; writing – original draft. Taketo Kawai: Conceptualization; writing – review and editing. Toyoshi Seito: Data curation; writing – original draft. Kensuke Matsumoto: Supervision; writing – review and editing. Tomoyuki Kaneko: Supervision. Tohru Nakagawa: 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

Written informed consent was obtained from the patient for publication of this case report.

Registry and the Registration No. of the study/trial

Not applicable.

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