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Case Report

Two Cases of Exacerbation of Asthma during Treatment with Enfortumab Vedotin

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Enfortumab vedotin · Urothelial carcinoma · Asthma · Nectin-4 · Antibody-drug conjugate

Abstract
Enfortumab vedotin is an antibody-drug conjugate against nectin-4 that is recently being used in the management of patients with urothelial carcinoma. The common adverse events include rashes, peripheral neuropathy, and hyperglycemia. Only a few cases of associated respiratory symptoms have been reported. Herein, we describe 2 patients with advanced urothelial carcinoma who experienced asthma exacerbation after initiating enfortumab vedotin treatment. Both patients improved with inhalation therapy. Since nectin-4 is expressed in the tracheal epithelium, its association with asthma is likely. This study highlights that clinicians should caution patients with a history of asthma against the worsening of respiratory symptoms when enfortumab vedotin is administered.

Introduction

In addition to platinum-containing chemotherapy and programmed cell death protein-1/programmed death-ligand 1 (PD-1/PD-L1) inhibitors, various other target molecules such as nectin-4 and fibroblast growth factor receptor have recently been developed for the treatment of urothelial cancer [1]. Enfortumab vedotin (EV) is an antibody-drug conjugate (ADC) against nectin-4 that is administered after platinum-containing chemotherapy and PD-1/PD-L1 inhibitor treatment to patients with advanced urothelial cancer [2].

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Nectin-4 is a type 1 transmembrane protein and immunoglobulin-like adhesion molecule that is involved in intercellular adhesion and is highly expressed in patients with urothelial carcinomas [3]. EV, which is a fully humanized monoclonal ADC, delivers the microtubule-disrupting agent monomethyl auristatin E to cells that express nectin-4, resulting in apoptotic death [3].

The main adverse events of EV include rashes, peripheral neuropathy, and hyperglycemia. Although EV-related pneumonitis has been reported [2, 4–6], only a few cases of respiratory symptoms associated with EV have been reported. Herein, we describe 2 patients who experienced asthma exacerbation after initiation of EV treatment.

Case Report

Case 1

A 67-year-old man, with a history of childhood asthma, fatty liver disease, kidney stones, hypothyroidism, and smoking presented with hematuria. The patient had not experienced asthma symptoms during adulthood. He underwent transurethral resection of the bladder tumor and was diagnosed with a muscle-invasive urothelial carcinoma with multiple lymph node metastases in October 2019. He was unresponsive to three cycles of gemcitabine plus cisplatin and was treated with pembrolizumab in February 2020. The patient was prescribed oral prednisolone for 4 weeks for immune-related enteritis in May 2020, and pembrolizumab treatment was discontinued in August 2020. Pembrolizumab treatment was resumed in October 2021; however, after 10 cycles, his cancer progressed.

In January 2022, the patient was administered EV (1.25 mg/kg). Since April 2022, he had experienced nocturnal dyspnea and increased sputum production (Fig. 1a). No other asthma risk factors such as exposure to allergens or respiratory infection were found. On June 30, 2022, computed tomography revealed numerous ground-glass opacities in both the lungs (Fig. 2). However, this was not considered to cause respiratory symptoms. Further, the eosinophil count was elevated. Spirometry yielded the following results: forced vital capacity (FVC) of 3,340 mL (97.4% of the predicted), forced expiratory volume in 1 s (FEV1) of 2,240 mL (84.8% of the predicted), and FEV1/FVC of 67.1%. Moreover, FEV1 increased by 760 mL following β2-agonist inhalation, with a fraction of exhaled nitric oxide (of 207.0 ppb. He was diagnosed with bronchial asthma, which was managed with inhaled budesonide 640 μg and formoterol fumarate 18 μg, and a 3-day course of oral prednisolone (5 mg). His eosinophil count decreased and his respiratory symptoms disappeared (Fig. 3). However, the patient continued cigarette smoking.

Case 2

A 46-year-old male with a history of atopic dermatitis and smoking was diagnosed with non-muscle invasive urothelial carcinoma in July 2016. He underwent repeated transurethral resection of the bladder tumor, followed by intravesical instillation of pirarubicin and bacillus Calmette-Guérin. Lymph node metastases were detected, and he underwent six cycles of gemcitabine and cisplatin in January 2019.

In January 2020, he was treated with 15 cycles of pembrolizumab due to the presence of increased right axillary and mediastinal lymph node metastases. Due to the presence of umbilical masses and peritoneal dissemination, he received an additional 10 courses of gemcitabine plus cisplatin.

In March 2022, his lymph node metastasis and peritoneal dissemination worsened. He was administered EV (1.25 mg/kg). Since April 2022, he experienced nocturnal cough, dyspnea, and wheezing (Fig. 1b). However, no abnormalities were observed on thoracoabdominal computed tomography. No other asthma risk factors such as exposure to allergens or respiratory infection

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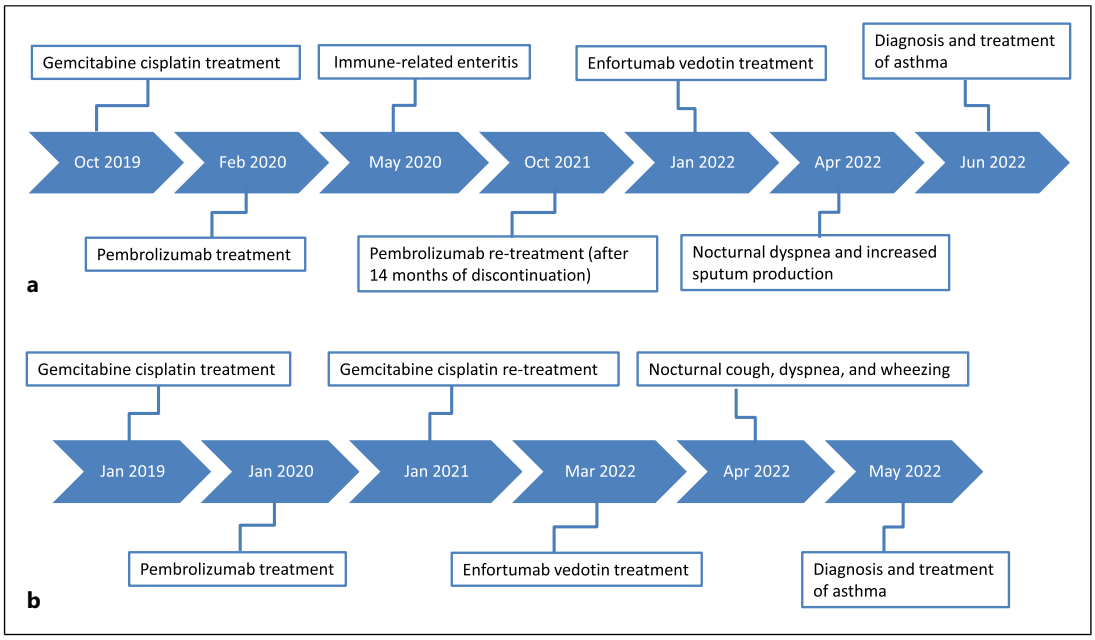

Fig. 1. a Timeline of events in Case 1. **b** Timeline of events in Case 2.

were found. His spirometry yielded the following results: FVC of 2,680 mL (75.5% of the predicted), FEV1 of 1,000 mL (34.7% of the predicted), and FEV1/FVC of 37.3%. His FEV1 increased by 220 mL of absolute volume after β2-agonist inhalation, with a fraction of exhaled nitric oxide of 47.0 ppb. No eosinophilia was observed in this patient. He was diagnosed with asthma and was managed with inhaled fluticasone furoate 200 μg/vilanterol trifenatate 40 μg. The patient stopped cigarette smoking at the start of his treatment. His symptoms improved and his wheezing disappeared.

Discussion

Although coughing and dyspnea have been reported as side effects in EV trials, the development of bronchial asthma has not been reported [2, 4, 5]. The main side effect of EV is rashes caused by increased monomethyl auristatin E delivery to nectin-4-expressing tissues, such as the epidermis and epithelium of sweat glands and hair follicles [7]. Nectin-4, a cell adhesion molecule, is also expressed in tracheal tissue and is involved in the spread of measles in the trachea [8, 9]. Nectin-4 is also implicated in airway inflammation; some reports suggest it may be a potential therapeutic target in asthma [10, 11]; thus, suggest that EV, which targets nectin-4, may trigger asthma exacerbations.

However, EV therapy for urothelial carcinoma is often administered after using immune checkpoint inhibitors (ICIs), and the involvement of immune-related adverse events must be considered. Although rare, asthma-related side effects have been reported with ICI use [12–14].

In the first case, eosinophils were slightly elevated after pembrolizumab initiation, and eosinophils were reported to increase with the use of ICIs [15]. However, the count increased to 2,000 cells/μL only after EV was initiated. The effect of EV was not considered negligible. In the second case, approximately 17 months had passed since the last pembrolizumab treatment. The median off-treatment interval for immune-related adverse events is reported to be 6 months [16]. Therefore, the possibility of asthma caused by ICIs was unlikely.

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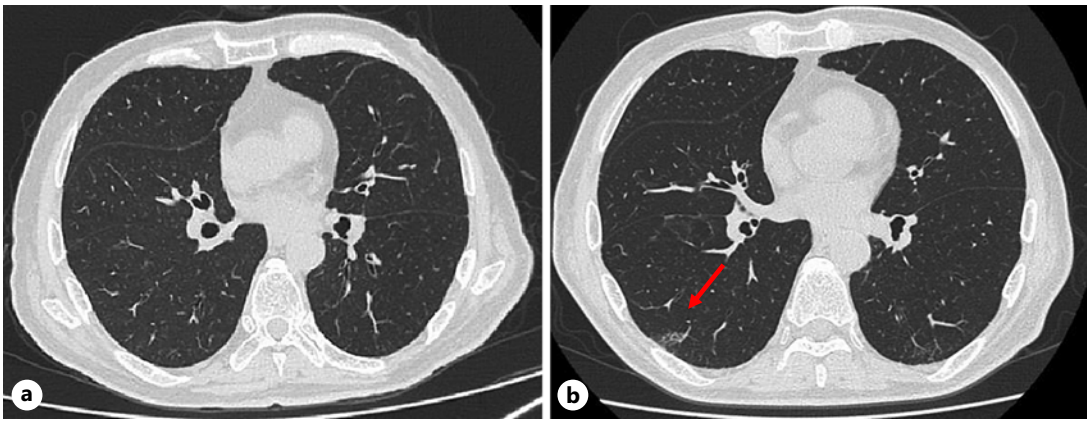

Fig. 2. Chest computed tomography (CT) findings of case 1, after 3 months (April 2022) (**a**), and 5 months (June 2022) (**b**) of enfortumab vedotin treatment. CT revealed minor ground-glass opacities.

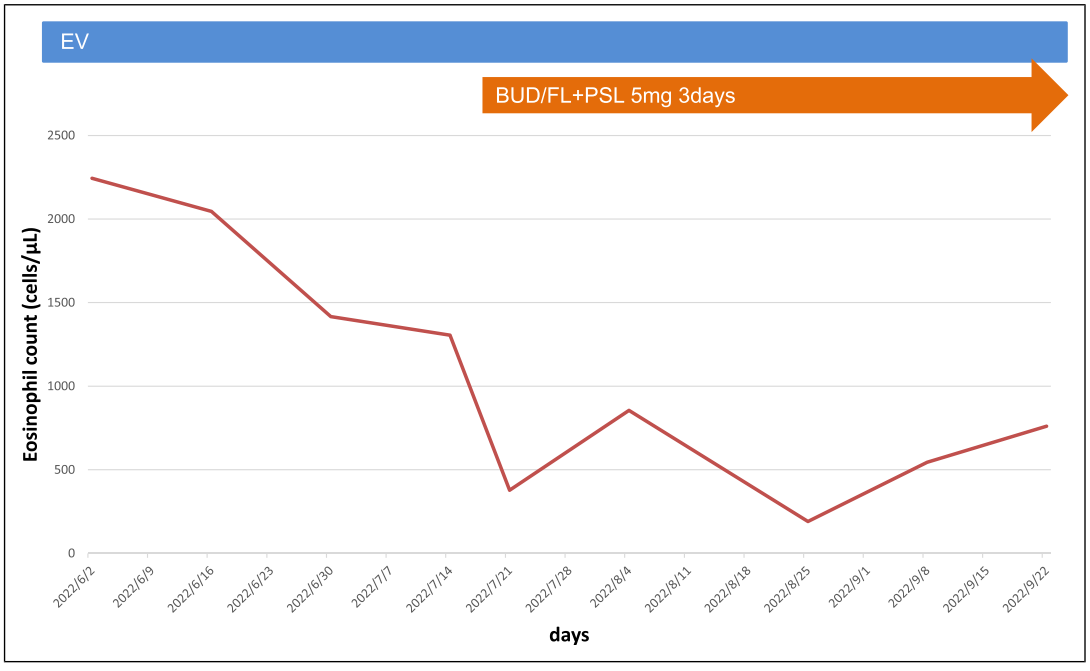

Fig. 3. A decrease in eosinophil count is observed after starting asthma treatment in the patient in case 1. BUD/FL + PSL, budesonide/formoterol fumarate + prednisolone.

These 2 cases suggest the possibility of exacerbation of asthma symptoms in patients treated with EV. Our report noted that both patients were smokers with a history of childhood asthma and atopic dermatitis and had an asthma exacerbation within 3 months of EV administration. Therefore, careful attention should be paid to the occurrence of respiratory symptoms in the initial stages of treatment when EV is administered to patients with a history of asthma or those at a high risk of asthma.

Ultimately, the number of patients with urothelial carcinoma treated with EVs is expected to increase, with the inclusion of recent clinical trials such as combination therapy with ICIs underway [17]. However, currently, reports on nectin-4 and its ADC, EV, and asthma are limited. The current findings highlight the necessary precautions that should be taken, regarding adverse respiratory events, when administering EV; nonetheless, further research and reports are needed. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534150).

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Statement of Ethics

Written informed consents were obtained from the patients for publication of this case report and any accompanying images. This study was reviewed and approved by the Ethics Committee of Kariya Toyota General Hospital, approval number 860.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Takamasa Homma wrote the manuscript; Naoya Takeda, Shota Torii, Hideki Esaki, Takashi Sakakibara, and Norio Takimoto supervised and corrected the manuscript; and Kuniaki Tanaka and Yu Okada were the physicians in charge of the patients. All authors read and approved the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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