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Eosinophilic Pneumonia Putatively Induced by Vancomycin: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 65
Final Diagnosis: Eosinophilic Pneumonia putatively induced by vancomycin
Symptoms: Dyspnea • fatigue • fever • hypoxia
Medication: Vancomycin
Clinical Procedure: Discontinuation of vancomycin and administration of prednisolone
Specialty: General and Internal Medicine

Objective: Adverse events of drug therapy

Background: Herein, we describe a case of eosinophilic pneumonia that was likely to have been induced by vancomycin.

Case Report: A 65-year-old man on maintenance hemodialysis presented with chest pain and dyspnea. He subsequently developed methicillin-resistant *Staphylococcus aureus*-positive acute pleural empyema in an evacuated right-sided pneumothorax. Surgical thoracoscopic curettage was ultimately performed, but dyspnea recurred post-operatively. Computed tomography depicted widespread reticular shadowing of the left lung, and peripheral eosinophilia was detected. The proportion of eosinophils found in bronchoalveolar lavage fluid was also remarkable (43%). All symptoms and the results of laboratory tests immediately improved after the discontinuation of vancomycin and initiation of prednisolone therapy.

Conclusions: We attribute this case of eosinophilic pneumonia to vancomycin, because all other candidate causes were ruled out, and only vancomycin fulfilled the criteria of both drug-induced eosinophilic pneumonia and drug-induced lung injury. If confirmed, this constitutes the first reported case of vancomycin-induced eosinophilic pneumonia.

MeSH Keywords: Hemodialysis • Methicillin-Resistant *Staphylococcus aureus* • Pulmonary Eosinophilia • Vancomycin

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Background

Vancomycin (VCM) is a glycopeptide antibiotic used to treat staphylococcal infections, particularly those involving methicillin-resistant *Staphylococcus aureus* (MRSA) [1]. Previously reported lung conditions associated with VCM include drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, anaphylaxis, and red man syndrome, among others [2]. Herein, we describe what is, to the best of our knowledge, the first reported case of VCM-induced eosinophilic pneumonia (EP).

Case Report

A 65-year-old man undergoing maintenance hemodialysis for end-stage renal disease was admitted to the hospital with chest pain and dyspnea. His medical history included IgA nephropathy (hemodialysis was started for chronic renal failure at the age of 58 years), angina pectoris (at the age of 59 years, with coronary artery bypass surgery performed 6 years prior), pneumothorax (once on the right side and once on the left, both at the age of 60 years), and cholesteatoma in the right ear (at the age of 42 years). He smoked approximately 30 cigarettes a day from age 20 to 36 years and had no history of allergies or immune disease. His medication regimen included aspirin, mosapride citrate hydrate, precipitated calcium carbonate, ferric citrate hydrate, lanthanum carbonate hydrate, carvedilol, olmesartan medoxomil, amlodipine besilate, alfacalcidol, and esomeprazole magnesium hydrate.

Chest X-ray imaging and computed tomography (CT) revealed a right-sided pneumothorax (Figure 1A, 1B) prompting immediate thoracic drainage. On day 7 of hospitalization, intermittent fever commenced, and the drainage fluid became turbid on day 9. On day 9, laboratory tests revealed leukocytosis with a white blood cell (WBC) count of 11 800/μL (normal range 3300–8600/μL), neutrophil count of 86.2% (normal range 48–61%), and elevated C-reactive protein (CRP; 15.42 mg/dL, normal levels ≤0.14 mg/dL) with a normal eosinophil count of 2.3% (normal range 1–5%). On day 10, MRSA was isolated from pleural fluid obtained on day 9. Surgery was performed for acute pleural empyema due to MRSA with pneumothorax. The patient was then started on intravenous VCM (0.5 g every 2–3 days after dialysis, intravenously) and piperacillin/tazobactam (PIPC/TAZ; 4.5 g twice daily, intravenously). VCM was targeted at MRSA, and PIPC/TAZ was started as a broad-spectrum antibiotic because the patient was a compromised host. Flow cytometry before VCM administration was not performed because immediate antibiotic administration was necessary to treat the MRSA infection, and flow cytometry tests are limited to the diagnosis of hematological diseases (for example, malignant lymphoma) in clinical practice in Japan. On day 12, the patient's eosinophil count rose to 26.0% and CRP was 25.84 mg/dL. Because the sole bacterial isolate was MRSA, PIPC/TAZ was discontinued on day 16. On day 16, the eosinophil count was 27.9%, CRP was 12.18 mg/dL, and the WBC count was 11 900/μL. During days 18–27, meropenem (MEPM; 0.5 g daily, intravenously) was added to VCM due to an increase in the WBC count (14 400/μL), although CRP dropped to 9.19 mg/dL on day 18 and 4.19 mg on day 23. The eosinophil count exceeded 30% thereafter, and fatigue developed on day 26. On day 27, MEPM was discontinued, given improved clinical symptoms and laboratory test results (WBC count 8140/μL, eosinophil count 30.7%, and CRP 2.38 mg/dL). On day 28, SpO_2 (room air) was satisfactory (96–99%), but on day 30, it dropped to 95%, at which time a chest x-ray image revealed expansive consolidation of the left lung (Figure 1C). On day 32, a further decline in SpO_2 (91%) was noted and a chest CT depicted widespread reticular shadowing and ground-glass opacification of the left lung in addition to a pleural effusion (Figure 1D), so MEPM (0.5 g daily, intravenously) was restarted. Thoracentesis was also performed and cultures were obtained, but an infective etiology was never proven. On day 34, laboratory test results were: WBCs 7220/μL, eosinophils 23.8%, CRP 5.03 mg/dL, procalcitonin 0.20 ng/mL (normal levels ≤0.05 ng/mL), and a serum sialylated carbohydrate antigen Krebs von den Lungen – 6 level of 216.0 U/mL (normal levels <500.0 U/mL). Arterial blood gas analysis revealed oxygen and carbon dioxide partial pressures of 57.6 torr and 32.8 torr, respectively. During days 10–30, there was intermittent fever (up to 38.0°C) despite continuous loxoprofen sodium hydrate or acetaminophen administration for pain.

Lymphocyte transformation tests (LTT) directed at VCM, PIPC/TAZ, and acetaminophen in peripheral blood were consistently negative. Analysis of bronchoalveolar lavage (BAL) fluid on day 45 revealed 43% eosinophils, 24% macrophages, 24% lymphocytes, and 9% neutrophils (Figure 2). There was also an abundance of eosinophils in sputum (eosinophils 55%, macrophages 10%, lymphocytes 12%, neutrophils 23%). Fiberoptic bronchoscopy did not yield any remarkable observations. Histamine levels were unknown because urine was not available as the patient was on dialysis.

Because drug-induced lung injury was suspected as well as bacterial pneumonia, on day 34, VCM and MEPM were discontinued and linezolid (LZD; 600 mg daily, intravenously) and PIPC/TAZ were started. LZD, used instead of VCM, was targeted at MRSA, and the broad-spectrum antibiotic combination PIPC/TAZ was substituted for MEPM because the patient was a compromised host and the possibility of bacterial pneumonia could not be ruled out. At this point it was determined that PIPC/TAZ did not induce adverse effects based on the clinical course after day 16 and negative LTT results. On discontinuation of VCM after day 34, the eosinophil count decreased unilaterally. On day 37, the WBC count was 7880/μL

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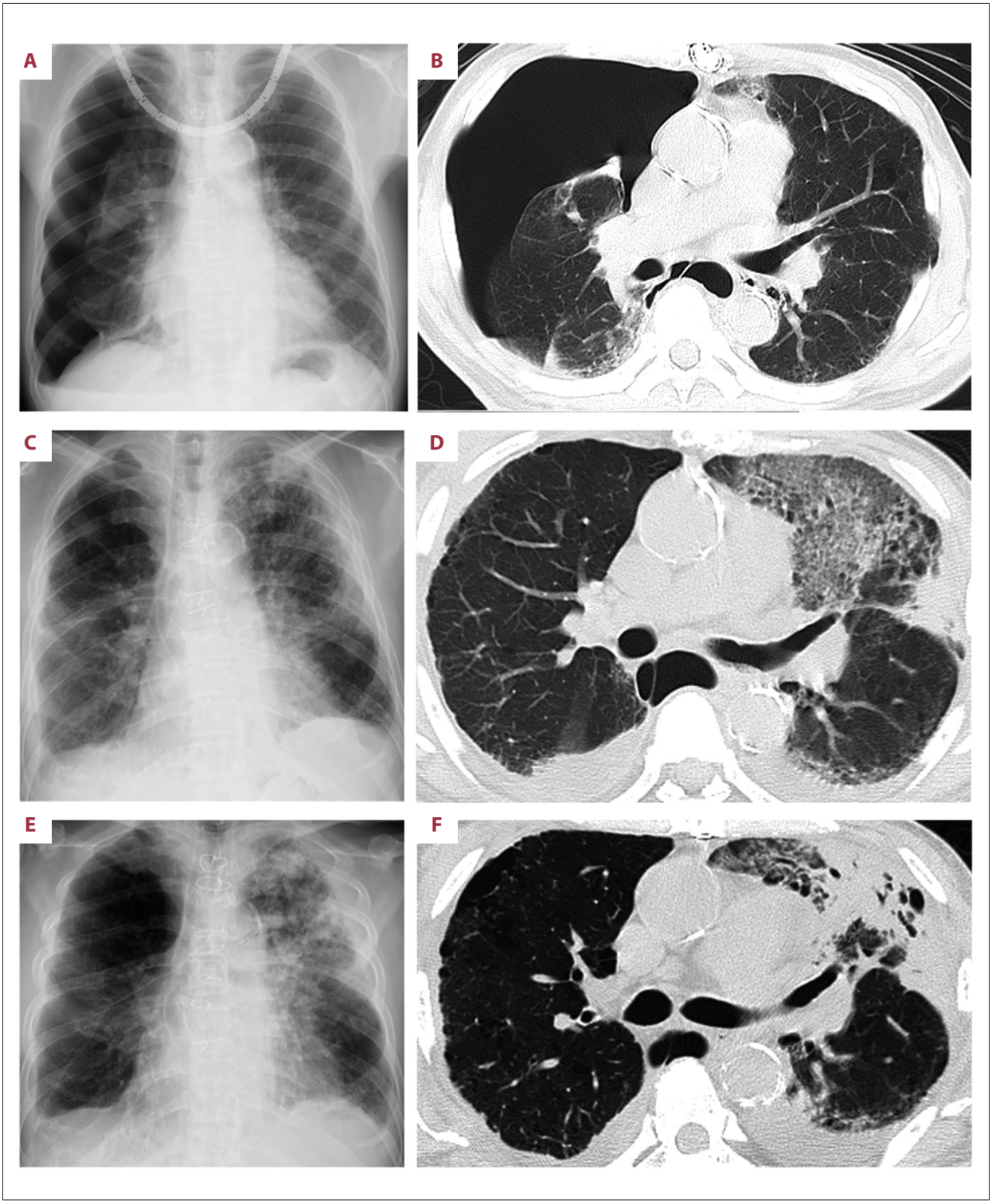

Figure 1. Chest imaging. (**A**) X-ray and (**B**) computed tomography on admission (day 0), showing right-sided pneumothorax. (**C**) X-ray on day 30 showing expansive consolidation of the left lung. (**D**) Computed tomography on day 32 showing widespread reticular shadows and ground-glass opacification of the left lung, with pleural effusion. (**E**) X-ray on day 45 showing exacerbated consolidation of the left lung in the same location as on day 32. (**F**) Computed tomography on day 45 showing exacerbated shadows and consolidation of the left lung, with pleural effusion in the same location as on day 32.

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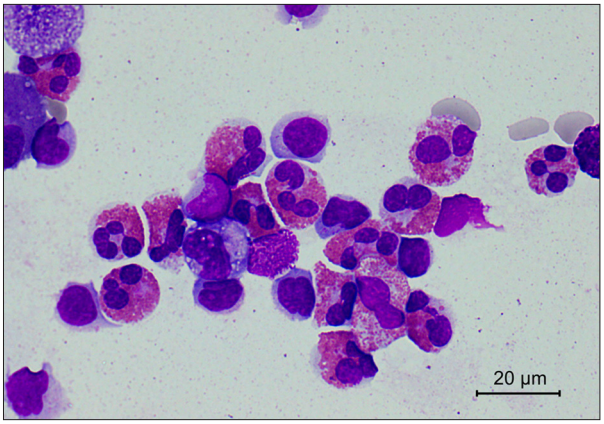

Figure 2. Giemsa staining of bronchoalveolar lavage fluid on day 45 revealed an abundance of eosinophils.

and eosinophils dropped to 17.1%; however, the dyspnea persisted. On day 41, WBCs were 7230/μL and eosinophils were 11.8%. On day 45, a chest CT revealed an exacerbated shadow in the lingula of the left upper lobe in the same location as on day 32, although eosinophils had decreased. No other new abnormal finding was detected on chest X-ray and CT on day 45 (Figure 1E, 1F). Hence, BAL was obtained from the lingula of the left upper lobe. Acute EP was diagnosed from BAL findings, and prednisolone (30 mg daily, oral administration) was initiated on day 45.

The patient's eosinophil count normalized on day 46 and remained normal thereafter. On day 46, WBCs were 4340/μL and eosinophils dropped to 0%. Expectorated pink sputum collected on day 47 yielded *Klebsiella oxytoca* and *Pseudomonas aeruginosa* cultures. LZD was subsequently discontinued, and faropenem (400 mg daily, oral administration) was added to the ongoing prednisolone treatment. Radiography and CT findings of the chest had not changed, yet the patient improved sufficiently for discharge on day 66. The patient's clinical course is summarized in Figure 3. No recurrence was observed after discharge. He did not have any symptoms other than fever and chest symptoms. Written informed consent for the publication of this case was obtained from the patient and his spouse, and it was approved by the Kindai Nara University Hospital Ethics Committee.

Discussion

The present case suggests that VCM can induce EP, and that the LTT may be an unreliable indicator of reactions to VCM. Camus et al. [3] established the following criteria to justify a diagnosis of drug-induced lung injury: 1) correct identification of the drug; 2) singularity of the drug; 3) temporal eligibility; 4) characteristic clinical, imaging, BAL, and pathologic patterns of the reaction to the specific drug; and 5) exclusion of other causes of the condition. According to the Japanese Respiration Society [4], at least 1 of 3 additional provisions must also be met when diagnosing drug-induced EP: abnormal diagnostic chest imaging with eosinophilia, eosinophilic infiltration of transbronchial or open-lung biopsy specimens, or inordinate numbers of eosinophils (≥25%) in BAL fluid.

In the present patient, non-VCM causes, including surgical intervention, pneumothorax, and pleural empyema (all contralateral), were reasonably ruled out. There had been no change in the dialyzer membrane (polyethersulfone) that could have provoked allergy, and MRSA was an unlikely source. Eosinophils in the peripheral blood were 2.3% on day 9, MRSA empyema was present on day 9, and on day 32 the pleural fluid was clear of MRSA. Combined PIPC/TAZ treatment was excluded as a cause due to a lack of relapse upon its reintroduction on day 34. Furthermore, the time-frames in which MEPM, LZD, faropenem, and other medications were administered did not coincide chronologically with the increase in eosinophils. VCM was the only medication administered consistently, concurrent with increasing eosinophilia. His medical history, including

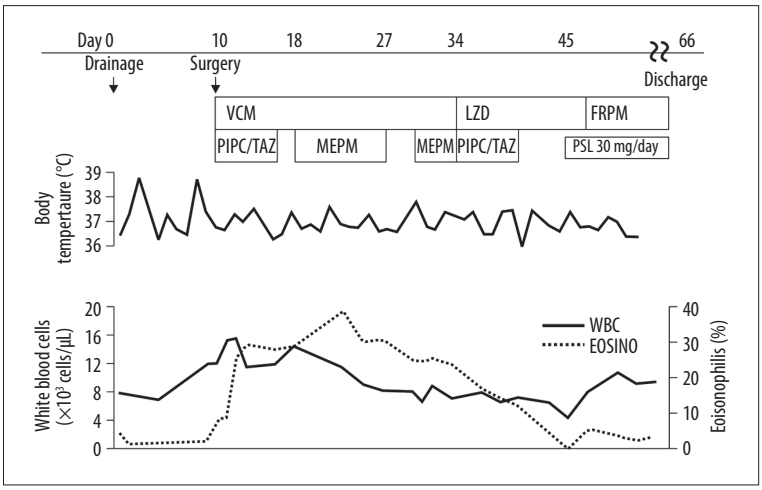

Figure 3. Clinical course in the present case. Steroid therapy and vancomycin withdrawal resulted in the improvement of respiratory failure and resolved eosinophilia. VCM – vancomycin; LZD – linezolid; FRPM – faropenem; PIPC/TAZ – tazobactam/piperacillin; MEPM – meropenem; PSL – prednisolone; EOSINO – eosinophils; WBC – white blood cells.

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IgA nephropathy (decomposition of IgA in the kidney was not likely to induce EP or any allergic reactions), angina pectoris (cured with surgery), pneumothorax (cured), and cholesteatoma (cured with surgery), seemed to be pathologically unrelated with EP. Lastly, the patient had no remarkable history of allergies. This case ultimately satisfied all criteria for drug-induced lung injury and drug-induced EP, with VCM being the most likely suspected candidate.

The patient exhibited fever despite the administration of acetaminophen, hypoxia from day 30, widespread reticular shadows, ground-glass opacification of the left lung with pleural effusion of the left lung in chest CT imaging on days 32 and 45, and high eosinophil counts in BAL fluid. These observations satisfy the fourth criteria described above for drug-induced lung injury, namely "characteristic clinical, imaging, BAL, and pathologic patterns of the reaction to the specific drug" [3]. In EP, shadowing is usually bilateral, not unilateral, as it was in the present patient. However, some cases of drug-induced EP with unilateral shadowing have been reported [5], and Rhee et al. [6] reported that 14 of 121 patients with acute EP exhibited unilateral pleural fluid, so unilaterality does not rule out a diagnosis of EP.

Notably, drugs such as antibiotics and NSAIDs are already well-known causes of EP. In an analysis of a collation of drug-induced EP case reports spanning nearly 30 years (1990–2017, N=196), Bartal et al. [7] identified 67 problematic drugs, including daptomycin, mesalamine, sulfasalazine, minocycline, NSAIDs, hydantoin/phenytoin, and risperidone. While antibiotics are known causes of EP, this is, to the best of our knowledge, the first published case of VCM-induced EP. However, it is peculiar in that an unexplained and uncharacteristic 18-day lag occurred between the eosinophilic surge (day 12) and the development of hypoxia (day 30). Yi et al. [8] reported that eosinophilic infiltration was induced by secretion of the chemokine ligands (CCLs) CCL17 and CCL12 from cDC1-lineage dendritic cells in the presence of nitric oxide (a product of $CD24^{-}$ $CD11b^{+}$ DC2 subpopulations), whereas transforming growth factor beta-1 (TGF-beta1), produced by CD24+ cDC2s, inhibit this process. Interruption of this molecular cascade may effectively impose a blockade. For instance, levels of TGF-beta1 may have been elevated in this patient. These higher levels of TGF-beta1 would then have repressed cDC1 cells from releasing CCL17 and CCL22 to recruit abundant eosinophils, which were already increased by VCM, from the vessels to the lung. TGF-beta1 is elevated in bacterial pneumonia [9], including MRSA [10], giving rise to the possibility that the patient had higher TGF-beta1 levels, which could thus enable the blockade described above. The delayed diagnosis in the present case was due to a preoccupation with containing the right-sided perioperative MRSA empyema. Increased attention to rising eosinophil counts may have resulted in earlier recognition of EP and earlier initiation of treatment.

The time required to resolve eosinophilia after discontinuation of VCM may have been more than expected, from days 34 to 46. In this period, eosinophils decreased unilaterally, and the interstitial shadow that appeared in the lingula of the left upper lobe on the chest CT taken at day 32 (before discontinuation of VCM) was retained at day 45 (before initiation of PSL), and no new abnormal finding appeared; thus, this was recognized as the characteristic sequence of the medical condition. Thus, no new disease, other than VCM-induced EP, had developed and other etiological candidates, including LZD and PIPC/TAZ, could be ruled out in this period. On day 45, we detected 43% eosinophils from BAL. These eosinophils may have moved from peripheral blood to the lung. On day 46, eosinophils were 0%. This was because of prednisolone administration on day 45 after BAL.

The LTT is widely used to identify drugs implicated in allergic reactions. However, such testing has a number of associated technical issues and limitations, and its reliability depends on the agent targeted. Although Enomoto et al. [11] reported LTT positivity in 56% of patients exhibiting Japanese herbal medicine-induced pneumonitis, previously reported data indicate that some drugs (including VCM) can prompt nonspecific lymphocyte stimulation *in vitro*, causing false-positive results [12]. In the present patient, the LTT was negative. A potential explanation for the negative result may be that LTT, which is used to detect an allergy type IV, T cell mediated immune response, followed the MRSA infection. The infection induced Th17 and regulatory T cells (Tregs), which regulate the inflammatory response [13,14]. When the LTT was performed, the MRSA infection and inflammatory response were well controlled, so high levels of Tregs may have existed. Tregs may have then controlled not only the inflammatory response by Th17 to bacterial infection, but also caused the negative response to nonspecific stimulation of lymphocytes (T cells) by VCM.

VCM can trigger DRESS syndrome [15], Stevens-Johnson syndrome/toxic epidermal necrosis [16,17], leukocytoclastic vasculitis [18], agranulocytosis [19], or red man syndrome as adverse reactions [20]. While the mechanisms involved in VCM-induced EP are not entirely clear, VCM promotes degranulation of mast cells and basophils, resulting in the release of histamine [20]. It may be that eosinophils then respond in order to modulate immediate hypersensitivity.

Conclusions

Although VCM-induced EP has not been formally described, an underreporting bias is possible. It is our view that EP due to VCM is a valid consideration, particularly if life-threatening respiratory failure ensues.

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Conflicts of interest

None.

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