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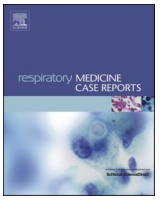

Case report

Myeloperoxidase-antineutrophil cytoplasmic antibody-associated diffuse alveolar hemorrhage caused by denosumab

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ABSTRACT

Denosumab is a bone anti-resorptive drug, commonly used for treating osteoporosis. Pulmonary involvement has rarely been reported as a possible serious adverse effect of this medication. Herein, we report the case of a 67-year-old woman who presented with non-massive hemoptysis, anemia, and extensive pulmonary opacities on a chest radiograph for 3 days after receiving denosumab. The patient was diagnosed with myeloperoxidase-antineutrophil cytoplasmic antibody-associated pulmonary hemorrhage secondary from denosumab. She was treated with high doses of intravenous methylprednisolone and cyclophosphamide combined with plasmapheresis. Subsequently, her clinical and radiological findings improved without residual abnormalities after treatment.

Abbreviations

DAH	Diffuse alveolar hemorrhage
RANKL	Receptor activator of nuclear factor kappa-B ligand
RANK	Receptor activator of nuclear factor kappa-B
ARDS	Acute respiratory distress syndrome
COVID-19	Coronavirus disease of 2019
WBC	White blood cell
ESR	Elevated erythrocyte sedimentation rate
CRP	C-reactive protein
PaO2	Partial pressure of oxygen
FiO2	Fraction of inspired oxygen
CT	Computed tomography
BAL	Bronchoalveolar lavage
ANA	Antinuclear antibody

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MPO-ANCA	Myeloperoxidase antineutrophil cytoplasmic antibody
PR3-ANCA	Proteinase 3 antineutrophil cytoplasmic antibody
AAV	ANCA-associated vasculitis
MPA	Microscopic polyangiitis
RPGN	Rapidly progressive glomerulonephritis
DIV	Drug-induced vasculitis
TNF	Tumor necrosis factor
DRESS	Drug reaction with eosinophilia and systemic symptoms
ILD	Interstitial lung disease

1. Introduction

Diffuse alveolar hemorrhage (DAH) is a life-threatening clinical syndrome causing hypoxemic respiratory failure, with approximate mortality rate ranging from 20 to 50% [1]. The syndrome is recognized by the triad of hemoptysis, anemia, and diffuse radiographic pulmonary opacities. Once DAH is diagnosed, the etiologies must be investigated in order to guide appropriate treatment. The most common cause of DAH is immune-associated vasculitis, but DAH may also result from non-immune-directed causes such as drugs, inhalation injuries, infectious, coagulopathy, radiation, or transplantation [1,2].

Denosumab is a human monoclonal antibody (IgG2) that specifically binds to receptor activator of nuclear factor kappa-B ligand (RANKL), competitively inhibiting stimulation of receptor activator of nuclear factor kappa-B (RANK), for treatment of osteoporosis. The most common adverse effects of denosumab are back pain, pain in extremity, hypercholesterolemia, and cystitis. There are few case reports regarding serious adverse events associated with denosumab such as hypersensitivity, osteonecrosis of the jaw, serious infections, and vasculitis [3–8]. Among these serious side effects, the pulmonary complication in a denosumab-treated patient is extremely rare, especially potentially life-threatening pulmonary hemorrhage with acute respiratory distress syndrome (ARDS) that has not yet been reported.

Herein, we report a patient who developed severe DAH after receiving denosumab therapy. The patient showed marked clinical and radiological improvements after administrating high doses of pulsed intravenous methylprednisolone and cyclophosphamide together with plasmapheresis.

2. Case report

A 67-year-old woman who worked as a government officer was admitted to our hospital with complaint of non-massive hemoptysis for 3 days. Her medical history included essential hypertension, well-controlled asthma, and severe osteoporosis. Due to severe postmenopausal osteoporosis, denosumab had been administered every six months since May 2019. Three days after the sixth dose of denosumab, she presented with frequently blood-stained expectorations and worsening shortness of breath over a period of 3 days. She denied fever, chest pain, extremity edema, paroxysmal nocturnal dyspnea, and orthopnea. She had never been hospitalized or had an emergency department visit for asthma or pneumonia. The patient did not take any medicine other than prescribed. She denied a history of close contact with a probable or confirmed case of coronavirus disease of 2019 (COVID-19), smoking, recent travel history, nor known environmental exposure to pollutants or pets.

Upon physical examination, she was marked by the appearance of respiratory distress. Vital signs included a temperature of 37 °C, blood pressure of 167/84 mmHg, heart rate of 98/minute, and respiratory rate of 48/minute. Her pulse oximetry showed an oxygen saturation of 84% at ambient air. She had marked pale conjunctivae. Respiratory examination revealed bilateral bronchial breath sound and crackles at both lower lungs. Cardiovascular examination was unremarkable. She had no pedal edema, joint line tenderness,

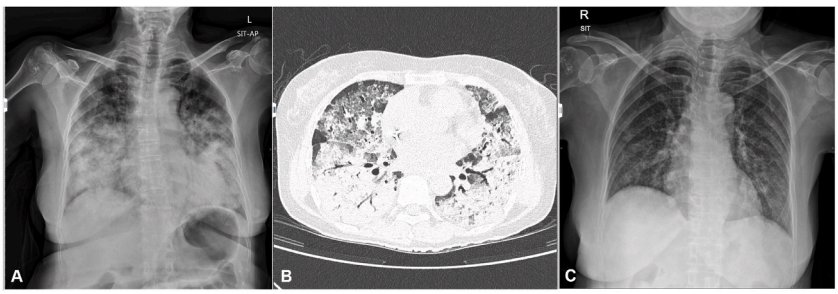

Fig. 1. A-C
A. Initial chest radiograph showing extensive multifocal airspace consolidation in both lower lobes.
B. Axial chest CT scan with lung-window setting showing diffuse widespread peribronchovascular ground-glass opacities and dense consolidation more in both lower lobes.
C. The follow-up chest radiography obtained after receiving pulsed corticosteroids, cyclophosphamide, and completed six sessions of plasmapheresis showing a marked decrease in the size of alveolar opacity at the bilateral lower lobes.

or abnormal skin lesion. On that day, the patient established deteriorating respiratory symptoms requiring intubation and was transferred to the intensive care unit.

The complete blood count showed hemoglobin level of 5.7 g/dL (11.6 g/dL in the previous eleven months), a white blood cell (WBC) count of 17,490 cells/μL (91% neutrophil, 5% lymphocyte, 4% monocyte), and platelet count of 635,000 cells/μL. The liver function and coagulation tests were unremarkable. Her serum creatinine was 1.24 mg/dL which was comparable to a baseline of 1.0–1.3 mg/dL since 2019. Urinalysis showed neither overt proteinuria nor microscopic hematuria. Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were found at 119 mm/hr and 141 mg/L respectively. Despite high ventilator setting with a fraction of inspired oxygen (FiO2) of 0.6, her arterial blood gas revealed a pH of 7.37, partial pressure of oxygen (PaO2) of 79 mmHg, and partial pressure of carbon dioxide of 42 mmHg.

Initial chest radiography (Fig. 1A) showed new extensive bilateral coalescent alveolar opacities with lower lungs predominance. Computed tomography (CT) scan of the chest (Fig. 1B) demonstrated diffuse bilateral widespread peribronchovascular ground-glass opacities and dense consolidation more in both lower lobes. An echocardiogram revealed normal size and functions of the right and left ventricles with a left ventricular ejection fraction of 60% without valvular abnormality. The patient was provisionally diagnosed with moderate ARDS with pulmonary hemorrhage, together with a ratio of PaO2 to a FiO2 of 131. The causes of pulmonary hemorrhage that we initially considered on this patient consisted of pulmonary vasculitis and pulmonary infection. Hence, flexible bronchoscopy was then performed to confirm the diagnosis of DAH and to investigate the potential organisms for pulmonary infection. The procedure revealed minimal blood staining at both basal bronchi. Sequential bronchoalveolar lavage (BAL) was performed and showed progressively more bloody effluent in the serial samples that was highly suggestive of alveolar hemorrhage (Fig. 2A). BAL fluid analysis showed an increase in red blood cells of 313,000 cells/μL and WBC of 1265 cells/μL (82% neutrophil, 18% monocyte). Cytology of BAL fluid showed mild inflammation. Histopathologic sections of transbronchial biopsies revealed organizing diffuse alveolar damage (Fig. 2B). Anti-GBM antibodies, antinuclear antibody (ANA), antiphospholipid antibodies, rheumatoid factor, complement 3 and 4, myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA), and proteinase3 ANCA (PR3-ANCA) were tested to screen autoimmune associated vasculitis. The nasopharyngeal swab test was negative for COVID-19.

The patient received lung-protective ventilation, neuromuscular blocking agent and was placed on broad-spectrum antibiotics. The patient's gas exchange continued to deteriorate despite mentioned treatments. We decided to attempt prone positioning to the patient.

Afterward, MPO-ANCA result turned back strongly positive at 106.65 RU/mL (normal <20 RU/mL), whereas neither PR3-ANCA nor the serology for other autoimmune panels were detected. BAL fluid showed no organisms on Gram-, acid-fast bacilli and Gomori methenamine silver stains. Respiratory 33 pathogens real-time polymerase chain reaction panel, as well as cytomegalovirus, and herpes simplex virus were undetectable from BAL fluid. Cultures of BAL fluid were also negative for bacterial and fungal growth.

After the infectious causes of DAH were excluded, the initial diagnosis of MPO-ANCA associated DAH was approved. Also, denosumab has the potential to cause drug-induced ANCA-associated vasculitis (AAV).

The patient was treated with high dose intravenous pulse methylprednisolone (1,000 mg a day) for three days plus a single dose of cyclophosphamide (15 mg/kg). She was soon treated with a complete 6 sessions of plasmapheresis. Following the intensive immunosuppressive therapy, the patient showed clinical improvement evidenced by a decrease in the need for oxygen and ventilatory support along with gradually improved radiological findings allowing her to be extubated and discharged on the eighth and twentieth hospital days respectively (Fig. 1C). Upon follow-up, the patient subsequently had a significant amelioration of dyspnea and hemoptysis accompanied by a normalized CRP level and substantial improvement of chest radiography. Then, she received prednisone at a dose of 1 mg/kg per day, followed by gradual tapering.

3. Discussion

The etiologies of DAH can be simply divided into immune and nonimmune mediated disorders. Most cases of DAH were immune-mediated vasculitis, either primary (idiopathic) or secondary to drugs, infection, or connective tissue diseases. The diagnosis depends on a compatible basis of clinico-histopathological and serological evidence, along with exclusions of other potential causes of vasculitis [1,2]. In our case, the presence of clinical DAH confirmed by the bronchoscopic finding and a strongly MPO-ANCA serologic positivity, in the absence of infectious evidence led to a diagnosis of AAV. In the view of MPO-ANCA pattern, microscopic polyangiitis (MPA) was

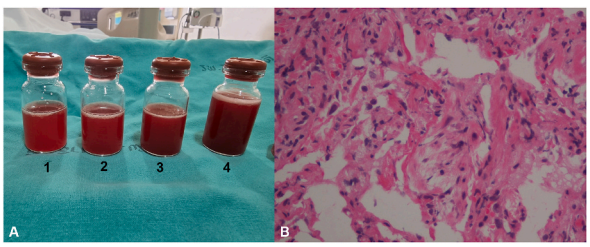

Fig. 2. A-B
A. Sequential bronchoalveolar lavage (BAL) starting left to right showing progressively more bloody effluent in the serial samples that suggestive of alveolar hemorrhage.
B. Histopathologic sections of the right lower lobe biopsies reveal organizing diffuse alveolar hemorrhage, no evidence of vasculitis or granuloma, or malignancy (H&E stain, 400x).

decidedly suspected. MPA is a systemic inflammation of small vessels that can affect multiple organs, mostly involving the kidneys and the lungs. However, the majority of patients with MPA have an insidious onset of constitutional symptoms prior to diagnosis and almost all patients experience some form of glomerulonephritis, in particular rapidly progressive glomerulonephritis (RPGN) [9]. In contrast, our patient manifested acute onset of pulmonary symptoms, she had neither subtle systemic symptoms nor evidence of active renal involvement. Temporal relationship between the onset of clinical DAH and the use of denosumab had led us to consider the diagnosis of drug-induced vasculitis (DIV). Additionally, most patients reported with drug-induced AAV have MPO-ANCA, frequently in very high titers [10].

The diagnosis of DIV is challenging due to quite nonspecific clinical presentation and laboratory marker that can mimic primary AAV. Thus, the diagnosis of DIV must rely on a careful clinical evaluation, the temporal relationship between symptoms and administration of culprit drugs, and exclusion of other mimic conditions [11,12]. There have been cases with the disease of targeted biologic therapy-induced ANCA increasingly published in the literature, mostly related to tumor necrosis factor (TNF) inhibitors. As we are all aware of, there is a scarce number of studies comparing biologic agent-induced AAV with idiopathic disease in contrast to cases involved with anti-thyroid medication, the most common form of drug-induced AAV. Therefore, we may relate our case characteristics to those with drug-induced forms in order to expand the information about the difference between drug-induced and primary AAVs. Patients with drug-induced AAV generally have a milder manifestation, especially constitutional symptoms, and fewer vital organ involvements, in companies with lower levels of creatinine, urine protein, and CRP compared to those with the primary form. With the suspension of the offending drug, the prognosis of these patients is generally good and relapse is rare. The mortality rate was lower than that of primary AAV, and long-term immunosuppressive agents might not be required [10,11]. In this case, even though her symptoms were severe and life-threatening, the onset occurred within a few days after exposure to the offending drug, and obvious rapid improvement observed after receiving a few doses of immunosuppressants supported the diagnosis of MPO-ANCA-associated DAH secondary from denosumab. However, the patient should be closely monitored and long-term follow-up is necessary to confirm a complete remission with the causative agent discontinued. Denosumab should be no longer used once DIV is suspected and drug rechallenge should be avoided in favor of fatal adverse reaction prevention.

Denosumab is a RANKL inhibitor. The binding between denosumab and RANKL suppresses osteoclastogenesis, thus decreasing bone resorption and increasing bone density. Nowadays, denosumab is approved for several indications, including treatments of postmenopausal osteoporosis, osteoporosis in men at high risk of fracture as well as to increase bone mass in individuals at high risk for fracture receiving hormonal deprivation therapy and corticosteroids [5–7]. RANKL, one of the TNF superfamily, is a transmembrane protein mostly expressed in bone and bone marrow, as well as lymphoid tissues, and brain. RANK is expressed not only in osteoclastic cells but also in other cells, including cells of the macrophage-monocyte series, activated T and B cells, dendritic cells, microglia, and fibroblasts. The RANK–RANKL interaction, therefore, plays an essential role in the regulation of bone cells as well as immune cells as a part of bone-immune system cross-talk, in terms of osteoimmunology [3,4]. Hence, denosumab may have other unfavorable effects beyond those in the skeletal system.

Denosumab-related extra-musculoskeletal major adverse drug effects have been increasingly reported such as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome [13], minimal change disease [14], and RPGN [15].

At present, there are only three case reports having pulmonary adverse effects complicating denosumab therapy. The first reported two cases with interstitial lung disease (ILD), presented with new diagnoses of ILD after the third dose of denosumab [16]. Another published a study of a case with rheumatoid arthritis-related ILD having a severe exacerbation of interstitial pneumonia after a long course of denosumab administration [17]. The last one reported a case with newly diagnosed C-ANCA-associated RPGN and DAH one month after initiation of denosumab [15]. Pulmonary toxicity associated with denosumab involving lung parenchyma and vasculature may have been idiosyncratic and still unpredictable so far. We speculated that denosumab can alter the function of alveolar macrophage and T cell-mediated immunity which may be at least in part responsible for development of autoantibodies, causing lung injury and vasculopathy. However, this hypothesis still remains unproven, and future research about the pathogenesis of denosumab-induced lung injury is further needed. Published case series of denosumab-related side effects have been accumulated over time which indirectly helps monitor and raises awareness of serious adverse events of this medication.

4. Conclusion

With an advanced treatment with new targeted biological agents, more cases of evolving DIV have been reported in the literature. We report the first case of MPO-ANCA associated vasculitis in form of acute life-threatening DAH with ARDS in patients treated with denosumab. Clinicians should consider the possibility of this condition and keep this drug-related effect on their list of differential diagnoses. Early recognition and prompt diagnosis and management had a favorable outcome as shown in the presented case. The exact effects on the immune system of this drug class should be a topic of interest that needs a thorough investigation in the near future.

Ethic and consent statement

This case report was approved by the Ethics Committee on Human Rights related to research involving human subjects at the Faculty of Medicine Ramathibodi Hospital. The written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Financial disclosure

The authors have indicated that they have no financial relationships relevant to this study to disclose.

Declaration of competing interest

The authors declare that they have no competing interests.

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