CASE REPORT

Pneumothorax After Denosumab Injection in a Graft Versus Host Disease Patient

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ABSTRACT

Prolonged use of bisphosphonates for osteoporosis may risk occurrences of adverse events. Non-bisphosphonate agents such as denosumab is a potential alternative for high-risk osteoporosis patients. Occurrences of denosumab adverse effects were rare in patients with graft versus host disease. We report a case of severe pneumothorax secondary to recurrent pneumonia after denosumab injections which may exemplify a potential risk for pneumonia and pneumothorax in the use of denosumab in a transplant patient complicated by graft versus host disease.

Keywords: Denosumab; Pneumonia; Pneumothorax; Transplant patient; Graft versus host disease

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INTRODUCTION

Bisphosphonate is a mainstay in osteoporosis treatment. Osteonecrosis of jaw and atypical fracture are the issues of concern with prolonged use of bisphosphonate therapy, thus making the treatment more challenging. These adverse events resulted in discontinuation of therapy [1]. Sequential therapy with a non-bisphosphonate agent such as denosumab might be a better alternative for high risk osteoporosis patients. Denosumab has demonstrated efficacy in increasing bone mineral density (BMD) in patients who were previously on oral bisphosphonates [1]. In this case report, we discuss a case of pneumothorax after recurrent pneumonia which occurred shortly upon denosumab injection.

CASE PRESENTATION

A 54-year-old Chinese gentleman who had an allogenic stem cell transplant in 2004, subsequently experienced severe chronic graft versus host disease (GVHD). He was treated with long-term prednisolone since 2005 and not on any chemotherapy for chronic GVHD with no evidence of relapse. Although he was immunocompromised due to prednisolone, patient did not develop any opportunistic infections or pneumonia. After he sustained multiple rib fractures, he was treated for glucocorticoid-induced osteoporosis. He had fractures of the right 7th to 10th and left 6th to 8th ribs. Oral alendronate 70 mg weekly was started in December 2009 until January 2016. Alendronate therapy was stopped as he lost dentation. Table I shows the patient's bone mineral density (BMD). Patient's laboratory parameters such as calcium, inorganic phosphate, testosterone and 25-hydroxyl Vitamin D were within normal range. Following this, the patient was started on subcutaneous denosumab 60 mg in February 2016. He started to display symptoms of pneumonia after a week of denosumab treatment. As a result, he was given standard treatment for pneumonia. Since then, he became dependent on oxygen therapy. In April 2016, patient had pneumonia and fungaemia and was treated with antifungal and antibacterial agents in the private hospital. There was no full blood count from the private hospital. He was also treated for several episodes of mild pneumonia with oral antibiotics before his next denosumab injection. Nevertheless, his haematological parameters were normal during his routine follow-up with the haematologists. Six months later which was in August 2016, he received his second dose of denosumab injection. He was subsequently hospitalized in October 2016 for the diagnosis of bronchiolitis obliterans and needed long term oxygen therapy (LTOT). His chest X-ray (CXR) for the diagnosis is shown in Fig. 1. In February 2017, the patient was admitted again to the hospital for pneumonia for 3 days for which he missed the follow-up for the third dose of denosumab. Then, he had three hospitalizations for right pneumothorax for 30 days, 9 days and 11 days in February 2017, April 2017 and

Table I : Bone Mineral Density and Treatment of Osteoporosis

Date	T-score lumbar spine	T-score hip	Osteoporosis therapy
Feb 2014	-3.1	-2.4	Alendronate 70mg plus cholecalciferol 140mcg weekly (started since Dec 2009)
Aug 2014	-3.3	-2.4	Alendronate 70mg plus cholecalciferol 140mcg weekly
Aug 2015	-3.2	-2.1	Alendronate 70mg plus cholecalciferol 140mcg weekly (stopped in Jan 2016)
Sep 2017	-3.3	-2.3	Denosumab 60mg 6- monthly (February 2016 and August 2016)
Sep 2018	-4.6	-2.7	Vitamin D_3 1000 units and calcium carbonate 500mg daily (since October 2017)
Feb 2020	-4.6	-2.9	Vitamin D_3 1000 units and calcium carbonate 500mg daily
Apr 2021	-4.6	-3.0	Vitamin D_3 1000 units and calcium carbonate 500mg daily

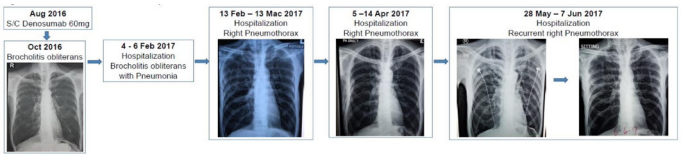

Figure 1 : Patient's chest x-ray from denosumab administration until occurrence of pneumothorax.

May 2017 respectively (Fig. 1). The decision to stop denosumab was made in June 2017, after which he was able to stop LTOT since Oct 2017 and had not had any episode of pneumonia. The occurrence of pneumothorax secondary to pneumonia coincided after each denosumab injection which might suggest drug-induced pneumonitis. Other osteoporosis treatment option was offered to him but he was not keen to try. Nevertheless, he did not have any fracture and was able to do his routine exercise daily since stopping denosumab.

DISCUSSION

Denosumab, a human monoclonal antibody with high affinity for the receptor activator for nuclear factor kappa B ligand (RANKL) has a mechanism of action distinct from the bisphosphonates. Sixty milligram is administered every 6 months via a subcutaneous route [1].

Denosumab was approved by the FDA for treatment of osteoporosis in men based on evidence from the ADAMO (A multicenter, randomized, Double-blind, placebo-controlled study to compare the efficacy and safety of Denosumab versus placebo in Males with Osteoporosis) trial [2]. ADAMO showed that denosumab was efficacious in increasing bone mineral density at the lumbar spine, total hip, femoral neck, hip trochanter, and one-third radius. In the trial, denosumab was generally well tolerated and most adverse effects were mild or moderate in severity. The most common adverse event (≥ 5% incidence) included back pain, arthralgia, nasopharyngitis, and constipation. The trial did not report of any severe deleterious events such as atypical femoral fracture, hypocalcemia, adjudicated osteonecrosis of the jaw, or complications in fracture healing.

On the other hand, Huang et al reported a significantly increased risk of infections with denosumab therapy during the first 2 years of treatment, but the risk diminished thereafter. These infections include pneumonia and influenza, urinary tract infection, tuberculosis, fungal infection, candidiasis, herpes zoster infection and sepsis. It was postulated that RANKL inhibition might enervate the systemic immune response by suppressing dendritic cells which mediates T-cell activation and differentiation [3]. Additionally, the inhibition of the immunomodulatory effect of RANKL might increase the risk of infection in hematopoietic stem cell transplant patients. However, further study on the use of denosumab in hematopoietic stem cell transplant patients need to be conducted to confirm this theory [4]. Nevertheless, to the best of our knowledge, no safety data on the use of denosumab in men who have received transplants as well as GVHD men has been provided. In addition, hitherto, there was no reported adverse event of pneumothorax secondary to recurrent pneumonia after denosumab administration.

Meanwhile, it has been reported that 10% of patients with chronic GVHD experienced progressive bronchiolitis obliterans within 3 months to 2 years after marrow or blood-derived hemopoietic stem cells transplantation procedures [5]. However, in our patient, episodes of pneumonia, pneumothorax and bronchiolitis obliterans were observed after the commencement of denosumab, and they resolved after denosumab was discontinued. This suggested that denosumab was most likely the triggering factor.

CONCLUSION

This case report provides anecdotal evidence of a potential risk for pneumonia and pneumothorax with the use of denosumab particularly in a transplant patient with chronic GVHD background. Therefore, denosumab should be used with caution in chronic GVHD patients and immunocompromised patients in general.

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