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Breathless after brentuximab: Unmasking a rare adverse reaction

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Abstract

Brentuximab Vedotin (BV) is an antibody-drug conjugate used in the treatment of CD30-positive malignancies such as Hodgkins lymphoma. While generally well tolerated, BV has been rarely associated with severe pulmonary toxicity, including pneumonitis. We report the case of a 25-year-old male with relapsed Hodgkins lymphoma who presented with high-grade fever, generalized skin rash, cough, and dyspnea two weeks after receiving BV. The patient rapidly progressed to respiratory failure, necessitating mechanical ventilation and prone positioning for severe acute respiratory distress syndrome (ARDS) .Chest imaging showed bilateral infiltrates and empirical antibiotics were started. After ruling out probable infection and other common causes, corticosteroid therapy was started in suspicion of BV induced pneumonitis. Patient had gradual improvement in oxygenation, subsequently weaned off ventilator and recovered completely. BV-induced pneumonitis is a rare but serious adverse effect. The underlying mechanisms may involve direct cytotoxicity or immune-mediated injury. Diagnosis requires a strong suspicion and exclusion of other etiologies. Management typically includes discontinuation of BV and initiation of corticosteroids and immunosuppressant's. This case underscores the importance of high index of suspicion, early recognition and prompt management of BV-induced pneumonitis. Clinicians should consider this diagnosis in patients presenting with new-onset respiratory symptoms following BV therapy, especially when other causes have been excluded.

Introduction

Drug-induced pneumonitis represents a significant challenge in the management of cancer patients. Several chemotherapeutic drugs have well-documented potential to cause pulmonary toxicity. These complications are most often attributed to direct cytotoxic effects, infections secondary to immunosuppression, and immune-mediated mechanisms. Here we present one such patient with Brentuximab Vedotin (BV) induced pulmonary toxicity.

Case Presentation

A 25-year-old male with a known history of Hodgkin's lymphoma initially achieved remission following treatment with the standard ABVD chemotherapy regimen (Adriamycin, Bleomycin, Vinblastine, and Dacarbazine). However, subsequent Positron Emission Tomography (PET) scans indicated a relapse, for which

he was treated with Brentuximab Vedotin (BV). Two weeks after receiving BV, the patient presented with high-grade fever, a generalized skin rash, cough, and difficulty in breathing. On physical examination, patient was tachypneic, tachycardic, hypoxemic with cervical lymphadenopathy. The patient had severe respiratory failure requiring intubation and mechanical ventilation. Empirical antibiotics were initiated after obtaining appropriate cultures.

High Resolution Computed Tomography (HRCT) of thorax showed confluent areas of peribronchovascular consolidations with ground glass opacities in bilateral lungs. Subsequently patient underwent 3 sessions of proning in view of severe Acute Respiratory Distress Syndrome (ARDS). A comprehensive evaluation for infections, including opportunistic pathogens such as *Pneumocystis carinii*, Epstein-Barr virus, and Cytomegalovirus, yielded negative results. An autoimmune workup was also carried out and the results were negative as well. Patient showed no signs of improvement despite on antibiotics and proning. He was started on corticosteroid therapy in view of suspected BV induced pneumonitis as a diagnosis of exclusion on day 4. He received Inj. Methylprednisolone 1 mg kg IV OD. The patient's oxygenation gradually improved and he was extubated after 8 days of mechanical ventilation. Steroids were gradually tapered following clinical improvement over 6 weeks.

Discussion

Brentuximab Vedotin (BV) is an antibody-drug conjugate (ADC) that selectively targets the CD30 membrane receptor, a member of the tumor necrosis factor receptor superfamily. Its high expression on specific tumor cells makes CD30 an ideal candidate for ADC-based therapy.[1] BV is primarily used in the treatment of CD30-positive malignancies such as Hodgkin lymphoma and anaplastic large-cell lymphoma.[2]

Clinical trials have shown that BV is generally well tolerated. The most commonly reported adverse events include peripheral neuropathy, neutropenia, nausea, vomiting, and fatigue. Though the incidence of BV induced pulmonary toxicity is only about 2-5 %, it has emerged as serious complication.[3-4]

The pathogenesis of drug-induced lung injury may involve either direct cytotoxic effects or immune-mediated mechanisms.[5-6] In rare instances, the condition may present as cryptogenic organizing pneumonia.[7]

Symptoms of BV-induced pneumonitis may include cough, dyspnea, wheezing, chest discomfort, and exertional breathlessness. Symptoms can emerge any time after treatment, from days to weeks or even months later. It is a diagnosis of exclusion. There is no specific investigation to confirm the diagnosis. Radiological patterns in computed tomography (CT) thorax are non-specific and it ranges from interstitial infiltrates, diffuse alveolar damage, non-specific interstitial pneumonia, eosinophilic pneumonia, pulmonary hemorrhage to pulmonary edema and pulmonary hypertension. HRCT thorax in our case had features suggestive of atypical pneumonia with ARDS. In some cases, a reduction in the diffusing capacity of

the lungs for carbon monoxide (DLCO) may be observed. Risk factors for BV-induced pneumonitis include the concurrent use of bleomycin, which is known for its pulmonary toxicity.

Management involves immediate BV discontinuation and initiation of systemic corticosteroids, typically prednisone 1 mg/kg daily or equivalent, as per European Society of Medical Oncology (ESMO) guidelines. Steroids help counteract both cytotoxic and immune-mediated mechanisms. Steroids are tapered over 4–6 weeks following clinical and radiological recovery.[7] In more severe cases, additional immunosuppressive agents such as infliximab, tocilizumab, or mycophenolate mofetil may be necessary. However, standardized guidelines for steroid tapering are lacking, highlighting the need for further research. Prompt recognition and timely intervention are essential to reduce morbidity and prevent potentially fatal outcomes.[8]

The rarity of this condition, absence of clear guidelines, and the need for extensive evaluation to exclude other potential causes make its diagnosis and treatment a significant challenge for clinicians.

Conclusion

Due to the potential severity of BV-induced pneumonitis, early recognition with high index of suspicion is vital to initiate timely diagnostic evaluation and distinguish it from other possible etiologies. Swift and appropriate management is crucial to prevent clinical decline and minimize the risk of irreversible lung damage, unnecessary antibiotic usage or fatal outcomes including mortality.

Source of Funding

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Conflict of Interest

None.

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