Journal of Blood Medicine

Dovepress
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CASE REPORT

Teclistamab-Induced Localized Pleural Cavity Cytokine Release Syndrome in a Multiple Myeloma Patient Managed with Intrapleural Dexamethasone Administration

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Abstract: Teclistamab, a B-cell maturation antigen (BCMA) × CD3 bispecific T-cell engager, has shown significant efficacy in patients with refractory multiple myeloma (MM). However, the clinical characteristics and optimal management strategies for localized cytokine release syndrome (CRS) remain poorly defined compared with systemic CRS. We report the case of a 57-year-old woman with refractory MM who developed both systemic and localized CRS following teclistamab therapy. She initially presented with grade 3 systemic CRS during step-up dosing phase, which partially resolved with intravenous methylprednisolone. However, interleukin-6 remained elevated in pleural effusions but not in serum, indicating localized pleural cavity CRS. Management with pleural fluid drainage combined with intrapleural dexamethasone successfully controlled the localized CRS. At two months, the patient achieved a partial response and continued teclistamab therapy. To our knowledge, this is among the first reported cases of teclistamab-associated localized pleural cavity CRS effectively managed with intrapleural dexamethasone.

Keywords: teclistamab, cytokine release syndrome, multiple myeloma, dexamethasone, bispecific T-cell engager

Introduction

The development of T-cell redirected therapies, including chimeric antigen receptor T (CAR-T) cells and bispecific antibodies, has revolutionized the treatment landscape for multiple myeloma (MM).[1] Among these, teclistamab, a B cell maturation antigen (BCMA) × CD3 bispecific T-cell engager (BiTE), has demonstrated remarkable efficacy in patients with triple-class refractory MM-defined as disease resistant to proteasome inhibitors, immunomodulatory drugs, and anti-CD38 monoclonal antibodies.[2] In the pivotal MajesTEC-1 trial, with a median follow-up of 14.1 months, teclistamab achieved a high overall response rate (ORR) of 63%, including a complete response (CR) or better rate of 39.4%, and a median duration of response of 18.4 months.[3]

The most common adverse event associated with teclistamab is cytokine release syndrome (CRS), with an incidence of 72.1%.[4] Most CRS events typically arise during the initial step-up dosing phase. The median time to CRS onset is 2 days (range, 1–6 days), with a median duration of 2 days (range, 1–9 days).[3] CRS is predominantly mild to moderate in severity, with common presenting symptoms including fever, hypoxia and hypotension. The standard management for CRS often involves steroids and tocilizumab.

Compartmental CRS occurs within natural body cavities, especially in cases of malignant involvement, where T-cell redirected therapies trigger a localized inflammatory response and the subsequent release of cytokines in situ. Specifically, when manifesting in the pleural cavity, it primarily presents with respiratory symptoms such as cough, dyspnea, and chest pain.[5] Compartmental CRS is often mild and self-limiting; its symptoms frequently overlap with those of systemic CRS, infection, or malignant involvement, thereby leading to potential under-recognition. The ratio of pleural effusion to serum IL-6

https://doi.org/10.2147/JBM.S588402
Received: 12 December 2025
Accepted: 23 March 2026
Published: 23 April 2026

may be utilized to evaluate localized CRS within pleural lesions and assist in differential diagnosis.[5] While research primarily focuses on systemic CRS, there have been rare reports of compartmental CRS after T-cell redirection therapy.[6–8] We present a case of local CRS within pleural cavity after teclistamab treatment in a MM patient who was successfully treated with pleural drainage and intrapleural administration of dexamethasone. In cases where pleural symptoms persist despite control of systemic CRS, clinicians should consider compartmental CRS and initiate prompt medical intervention.

Case Presentation

In July 2023, a 57-year-old woman who initially presented with an asymptomatic cranial mass was diagnosed with IgG kappa MM, Revised International Staging System stage III. Fluorescence in situ hybridization (FISH) analysis revealed high-risk cytogenetic abnormalities, including t (4;14) and 1q21 amplification.

The patient received induction therapy consisting of two cycles of bortezomib, lenalidomide, and dexamethasone (VRD), followed by two cycles of bortezomib and dexamethasone (VD) due to concerns that prolonged lenalidomide exposure could adversely impact subsequent stem cell collection, and achieved CR based on the International Myeloma Working Group consensus criteria. In February 2024, she underwent autologous stem cell transplantation (ASCT) with high-dose melphalan conditioning and subsequently received maintenance therapy with ixazomib and lenalidomide.

One year after ASCT, her immunofixation returned positive, with detectable M-protein (57.1 g/L). Positron emission tomography/computed tomography (PET/CT) revealed a posterior mediastinal mass and multiple lytic bone lesions, with a maximum standardized uptake value (SUVmax) of 15.17 (Supplementary Figure 1). CT-guided biopsy of the mediastinal lesion confirmed extramedullary plasmacytoma, with plasma cells staining positive for CD38, CD56, CD138, BCMA, and cytoplasmic kappa light chain on immunohistochemistry. Concurrently, bone marrow flow cytometry detected 8.1% abnormal plasma cells, indicating relapse both in the bone marrow and at extramedullary sites. As the patient was ineligible for clinical trial enrollment, she was started on carfilzomib, pomalidomide, and dexamethasone (KPD) as second-line therapy. However, within one month, she developed chest tightness and dyspnea. Chest CT showed massive right pleural effusion, and thoracentesis drained 4200 mL of fluid, in which cytology revealed predominantly abnormal plasma cells. Despite a regimen switch to daratumumab, lenalidomide, and dexamethasone (DRD), her disease progressed rapidly, with worsening clinical symptoms.

Considering the triple-class refractory status of her disease, subcutaneous teclistamab was initiated with a first step-up dose of 3.3 mg (0.06 mg/kg) on day 1. Twenty-six hours after injection, she developed a fever of 39.2 °C and mild shortness of breath without an identifiable infectious cause (Figure 1A). The serum interleukin-6 (IL-6) level was 501 pg/mL. Grade 2 systemic CRS was diagnosed according to the American Society for Transplantation and Cellular Therapy (ASTCT) criteria.[9] She received non-steroidal anti-inflammatory drugs (NSAIDs) and low-flow nasal cannula oxygen, which led to partial symptom relief with a normal temperature. On day 3, an ultrasound revealed significant bilateral pleural effusions. Thoracentesis was performed, draining 700 mL of pleural fluid, which again showed abnormal plasma cells as well as a markedly elevated IL-6 level of 7171 pg/mL (Figure 1B). As scheduled, subsequent step-up doses of teclistamab were given at 16 mg (0.3 mg/kg) on day 4 and 82 mg (1.5 mg/kg) on day 8. On day 5, she developed a high fever of 39.1 °C and progressive dyspnea requiring oxygen via facemask, consistent with grade 3 CRS. She received methylprednisolone 40 mg twice daily for seven days, which led to resolution of fever, a hallmark of systemic CRS. However, intermittent dyspnea persisted. Notably, interleukin-6 levels remained markedly elevated in the pleural effusion compared with serum, suggesting localized CRS within the pleural cavity. Dexamethasone 5 mg daily was administered via the drainage tube, resulting in complete resolution of respiratory symptoms and significant reductions in both pleural fluid volume and interleukin-6 levels by day 13. Teclistamab therapy was continued as scheduled, and the patient achieved a very good partial response after 2 months, remaining on treatment thereafter. The patient's treatment timeline and chest CT scans of mass change are presented in Figure 2A and B, respectively.

Discussion

Despite advances in novel anti-myeloma agents and immunotherapies, MM remains incurable, and triple-class refractory disease continues to pose a significant therapeutic challenge.[10] Teclistamab has demonstrated a promising response in this population. The most common adverse event associated with teclistamab is CRS, which is typically grade 1–2 and occurs

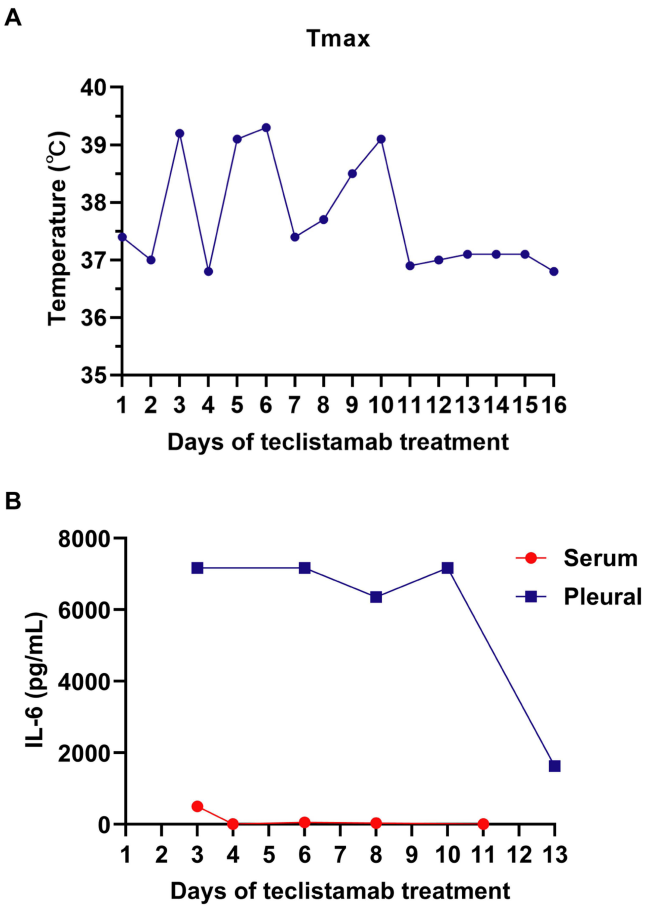

Figure 1 (**A**) The fever curve of with maximum daily temperatures from day 1 to day 16. (**B**) Serum and pleural fluid interleukin-6 (IL-6) level.

mainly during the initiation period.[4] Recent studies have supported the use of tocilizumab prophylaxis prior to bispecific antibodies, demonstrating a reduction in the incidence of CRS without compromising efficacy; however, further research is needed to confirm these findings.[11] Early recognition and appropriate management of CRS are critical for treatment efficacy and patient safety.

Compared with systemic CRS, localized CRS is often underestimated in both incidence and clinical severity. Localized CRS at the tumor site had been reported in the early stage of CAR T-cell therapy, which was thought to result from localized activation of CAR-T cells and subsequent induction of inflammatory responses.[12] Pleural cavity CRS typically presents with progressive effusions, markedly elevated IL-6 levels, and respiratory compromise. The specific underlying mechanisms of localized CRS remain unclear. Here, we describe a rare case of teclistamab-induced grade 3 systemic CRS, which was complicated by localized CRS in the pleural cavity, in a patient with refractory MM. Sporadic cases of pleural CRS have been reported in patients receiving bispecific antibody or CAR T therapy. For example, in a patient with relapsed/refractory B-cell lymphoma treated with epcoritamab, a CD3/CD20 BiTE, pleural CRS was refractory to both tocilizumab and corticosteroids, ultimately leading to fatal pyothorax.[8] Two additional cases of compartmental CRS following CAR T-cell therapy were successfully managed with systemic treatment and pleural drainage.[6,13] In our case, IL-6 levels were markedly elevated in pleural fluid compared with serum, whereas tumor necrosis factor-α and interferon-γ only slightly increased (Supplementary Figure 2A and B). Together, these findings support the diagnosis of teclistamab-induced localized pleural CRS, likely attributable to localized T-cell activation and cytokine secretion.

Systemic CRS initially responded well to intravenous methylprednisolone, with a rapid decline in serum IL-6 levels and resolution of fever. However, IL-6 levels remained elevated in the pleural effusion, and dyspnea persisted despite systemic corticosteroid therapy and daily pleural drainage. Intrapleural dexamethasone administration was subsequently attempted,

https://doi.org/10.2147/JBM.S588402

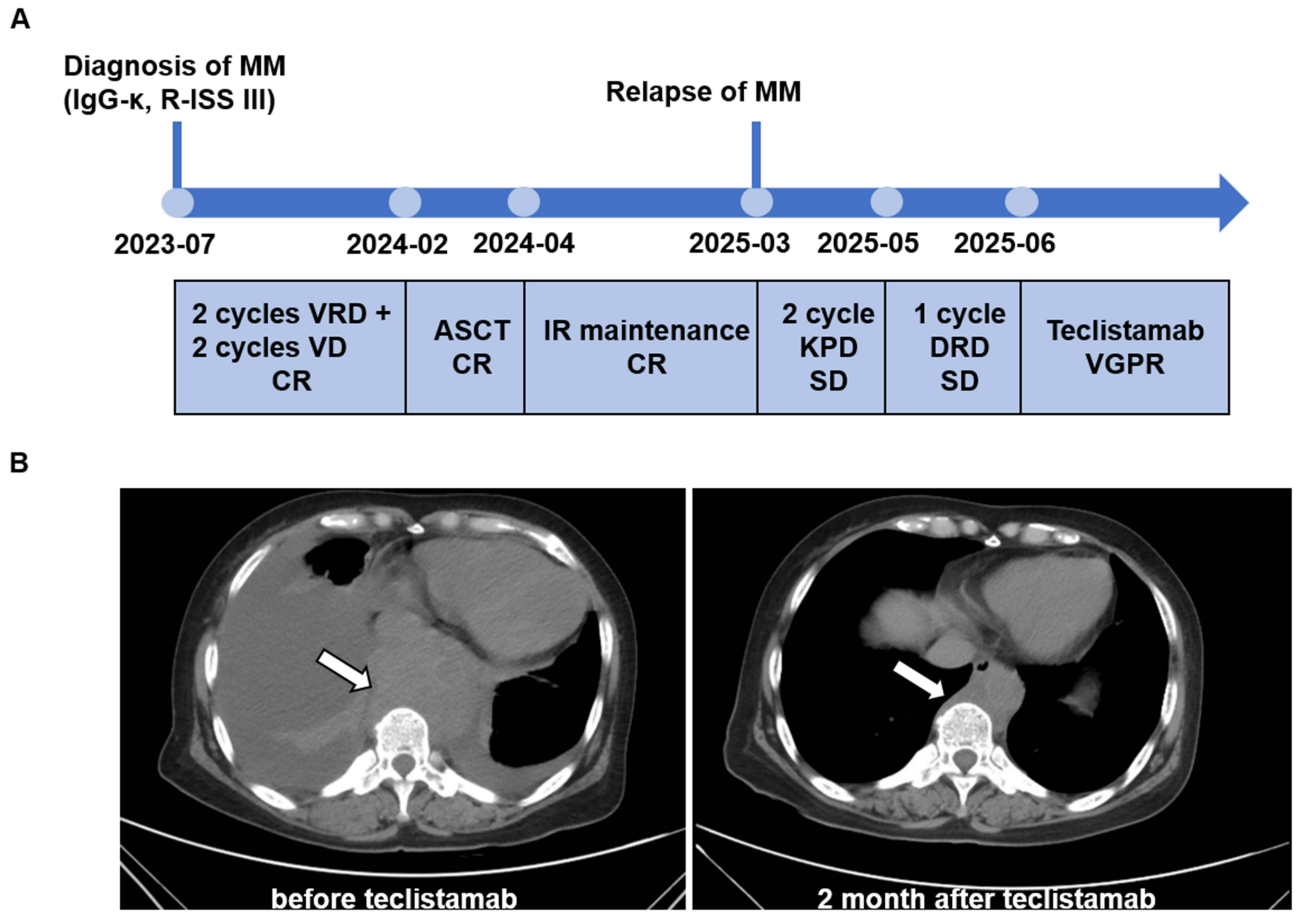

Figure 2 (**A**) Timeline of patient's diagnosis and treatment. (**B**) CT scan of plasmacytoma changes 2 months post teclistamab therapy, the white arrow indicates the extramedullary plasmacytoma.

resulting in immediate resolution of pleural cavity CRS. This suggests that localized corticosteroid delivery may be effective when systemic therapy is insufficient; however, its safety, optimal dosing and efficacy require further investigation through larger case series. Patients with pleural or intrapleural tumor involvement appear to be at increased risk of developing pleural CRS during treatment with bispecific antibodies or CAR-T therapy. The onset of systemic CRS and local CRS may not be synchronous, and further case-based evidence is needed to clarify their pathogenesis and clinical characteristics. While these findings may not be widely generalizable, pleural effusions during T-cell redirected therapies of myeloma require early differential diagnosis and intervention. Once pleural cavity CRS is suspected, serial paired pleural/serum measurements and broader inflammatory panels can facilitate the diagnosis.

Conclusion

This case highlights the successful management of teclistamab-induced localized pleural cavity CRS by prompt pleural drainage and localized dexamethasone therapy following failure of systemic interventions. While this finding is limited to a single case, further case series are needed to establish diagnostic criteria and standardize treatment approaches for compartmental CRS.

Data Sharing Statement

No datasets were generated or analysed during the current study.

Ethics Approval and Consent to Publish Statement

The consent process and publication of the case details were approved by the Human Ethics Committee of the Second Affiliated Hospital, School of Medicine, Zhejiang University, China. Written informed consent to publish case details and any accompanying images was obtained from the patient.

Acknowledgments

We would like to thank the researchers and patients for their contributions.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was funded by National Natural Science Foundation of China (No.82400217).

Disclosure

The authors declare that they have no conflicts of interest in this work.

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