

New-Onset Sarcoidosis During B-cell Maturation Antigen (BCMA)-Directed T-cell Engager Therapy With Teclistamab in Relapsed/Refractory High-Risk Multiple Myeloma: A Case Report and Mechanistic Insight

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Abstract

Teclistamab is a bispecific T-cell engager targeting the B-cell maturation antigen (BCMA) on myeloma cells and CD3 on T cells, leading to potent immune activation and durable responses in relapsed/refractory multiple myeloma. Although many immune-mediated complications have been described with teclistamab, granulomatous inflammation or sarcoidosis has not been associated. We present a patient with relapsed/refractory multiple myeloma receiving teclistamab who developed new hypermetabolic lymphadenopathy on positron emission tomography/computed tomography six months after therapy initiation. The patient was asymptomatic with normal pulmonary function, borderline-elevated angiotensin-converting enzyme (ACE) levels, and mild hypercalcemia. Lymph node biopsy revealed nonnecrotizing granulomas without evidence of myeloma or infection. Extensive evaluation excluded fungal, mycobacterial, and opportunistic pathogens. Given clinical stability and sustained myeloma remission, teclistamab was continued without corticosteroid therapy. The patient remained asymptomatic with stable radiographic findings on follow-up. This represents the first reported case of sarcoidosis developing during teclistamab therapy. Recognition of this phenomenon is essential to prevent misinterpretation as myeloma progression or infectious lymphadenitis—diagnostic pitfalls that may lead to unnecessary treatment changes. This case underscores the need for heightened pharmacovigilance, systematic reporting of granulomatous toxicities associated with BCMA-directed therapies, and future immune profiling to identify patients at risk of atypical immune-mediated adverse events.

Categories: Pathology, Internal Medicine, Oncology

Keywords: bcma, granuloma, immune-related adverse event, sarcoidosis, teclistamab

Introduction

Multiple myeloma is a hematological malignancy driven by the clonal proliferation of malignant plasma cells in the bone marrow. It is widely considered incurable, which highlights the pressing need for the development of novel therapeutic agents in the setting of relapse. The transmembrane glycoprotein receptor B-cell maturation antigen (BCMA), expressed on myeloma cells, is increasingly used as a key target for novel therapeutic modalities, including bispecific T-cell engagers (BiTEs) such as teclistamab [1].

The BiTE teclistamab is a breakthrough immunotherapeutic agent for multiple myeloma. BiTEs, also known as bispecific antibodies or bispecifics, are composed of fusion proteins of specific regions of the immunoglobulin heavy and light chains, connected by a peptide linker sequence [2]. This structure facilitates teclistamab's unique mechanism of action by activating native T-cells to lyse BCMA+ myeloma cells through simultaneous targeting of CD3 (a T-cell surface protein complex) and BCMA, respectively [3]. By harnessing the patient's own immune system, teclistamab represents a paradigm shift in cutting-edge immunotherapeutics for myeloma with durable clinical outcomes; however, it is not without inherent risks.

BiTE toxicities well characterized in the literature include immune-related adverse events (irAEs), such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome, mediated by proinflammatory cytokines released by activated immune cells [4]. Additionally, teclistamab heralds an increased risk of opportunistic infection with microorganisms [5]. This is attributed to T-cell exhaustion, hypogammaglobulinemia, and pancytopenia because of T-cell activation and unintended toxicities in the bone marrow [6].

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Sarcoidosis, a diagnosis of exclusion, is a rare noninfectious inflammatory disease characterized by clusters of white blood cells termed granulomas. It is often difficult to diagnose because of its heterogeneous presentation and alternative etiologies of granuloma formation, such as infection. Sarcoidosis, like irAE, has immune-mediated mechanistic implications that are yet to be elucidated.

To our knowledge, there are no previous reports of sarcoidosis or granulomatous inflammation in the setting of teclistamab, in which immune-related side effects are possible. However, there are well-documented granulomatous and sarcoid-like reactions (SLRs) to other immune-modulating agents such as tumor necrosis factor-alpha (TNF- α) inhibitors and immune checkpoint inhibitors [7].

Here, we present a case report where one of our patients developed new-onset sarcoidosis during treatment with teclistamab for relapsed and refractory multiple myeloma.

Case Presentation

We present the case of a 67-year-old woman with high-risk IgG kappa multiple myeloma, complicated by plasma cell leukemia and extramedullary disease involving the skin, soft tissue, and spleen, who presented for further evaluation and treatment. Her initial bone marrow biopsy and aspirate revealed that 95% of the bone marrow cells were atypical plasma cells. Cytogenetic studies revealed a normal female karyotype (46, XX) with hyperploidy and a t(14;16)(q32;q23) translocation, consistent with high-risk myeloma biology.

Her treatment course included multiple lines of therapy. She initially received VD-PACE induction with plans for stem cell collection on day 1 (Velcade (bortezomib or "V," 1 mg/m² administered subcutaneously on days 1, 4, 8, and 11), dexamethasone (or "D," 40 mg given orally or intravenously (IV) on days 1, 2, 3, and 4), cisplatin (Platinol or "P," 10 mg/m²/day as a continuous intravenous infusion over days 1-4), doxorubicin (Adriamycin or "A," 10 mg/m²/day as a continuous intravenous infusion over days 1-4), cyclophosphamide (or "C," 400 mg/m²/day as a continuous intravenous infusion over days 1-4), etoposide (or "E," 40 mg/m²/day as a continuous intravenous infusion over days 1-4), resulting in a significant response and successful collection of 16.3 million CD34+ stem cells per kilogram. This was followed by Daratumumab-KRD on day 32 (daratumumab or "D," given IV weekly for initial cycles and subsequently less frequently); carfilzomib or "K," given IV 56 mg/m² on specific days (e.g., days 1, 8, and 15), lenalidomide or "R," 15 mg taken orally 21 days out of a 28 day cycle and dexamethasone or "D," 20 mg), which produced a mixed response. She subsequently underwent a fractionated melphalan (40 mg/m² for four days)-based autologous stem cell transplant on day 164 and later received cyclophosphamide 600 mg by mouth once weekly with pomalidomide 4 mg days 1-21, seven days off, and dexamethasone 40 mg by mouth weekly as bridging therapy until chimeric antigen receptor T-cell (CAR-T) infusion. She ultimately proceeded to CAR-T therapy with ciltacabtagene autoleucel (Carvykti) on day 351. Due to delayed hematologic recovery, she received an additional stem cell boost on day 373. Most recently, she was started on teclistamab on day 486 with step-up dosing and experienced grade 1 CRS during therapy initiation.

At the time of evaluation in the August of 2025, the patient reported feeling well and was completely asymptomatic. She denied cough, dyspnea, fever, rash, or fatigue. Restaging positron emission tomography/computed tomography (PET/CT) imaging on day 554 revealed new mediastinal lymphadenopathy, including several enlarged right paratracheal lymph nodes with standardized uptake values of 4.7-4.8 and sizes of 1-1.3 cm, new bilateral hilar lymphadenopathy, and fluorodeoxyglucose (FDG) uptake in the right mandible without evidence of bone destruction.

Laboratory evaluation demonstrated an angiotensin-converting enzyme (ACE) level of 82 U/L (upper limit of normal 85 U/L), mild hypercalcemia at 10.5 mg/dL (reference: 8.6-10.2 mg/dL), and low vitamin D levels of 10.8 ng/mL (reference: 20-50 ng/mL). Given the PET/CT findings, the patient underwent endobronchial ultrasound-guided transbronchial needle aspiration of the 4R (Figure 1), 11R and 7 (Figure 2), and lymph node stations for further investigation of the pathologic lymphadenopathy.

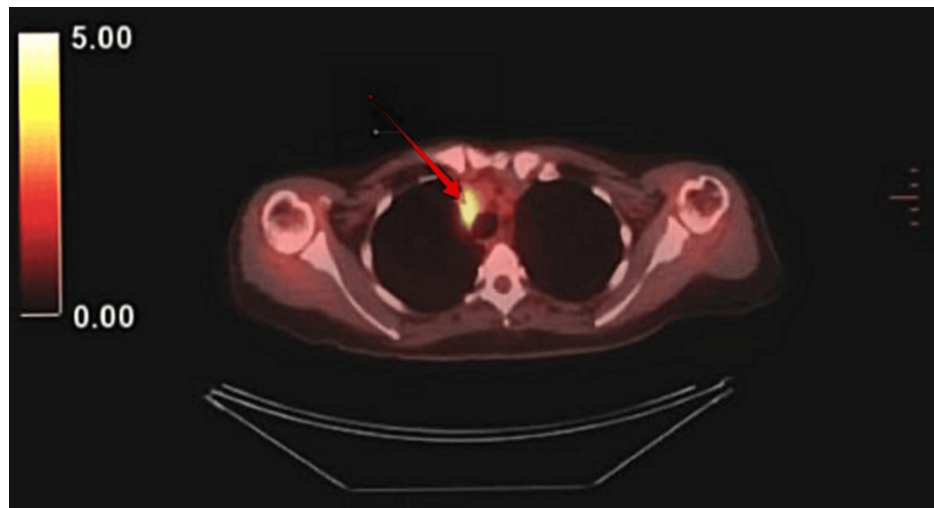


FIGURE 1: Station 4R lymph node on PET/CT scan (red arrow), which was biopsied during EBUS. Note the FDG avidity with SUV significantly above the background

PET/CT: positron emission tomography/computed tomography; EBUS: endobronchial ultrasound; FDG: fluorodeoxyglucose; SUV: standardized uptake value

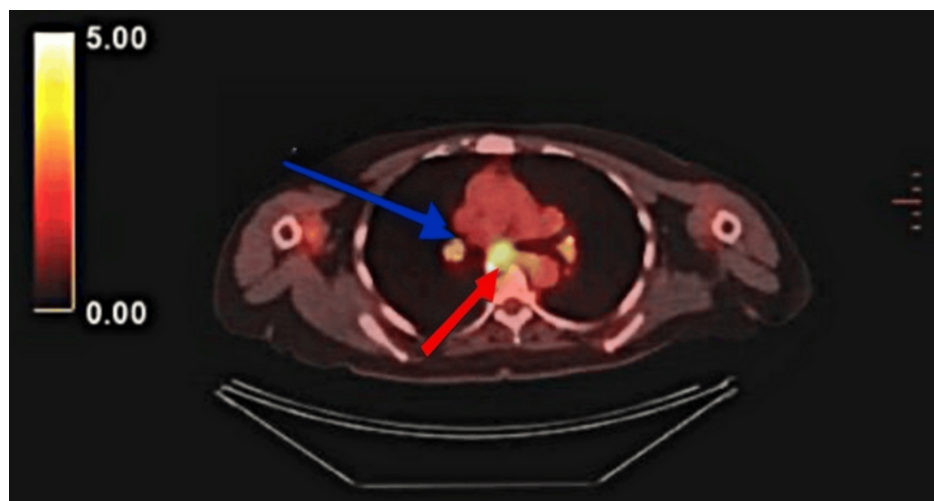


FIGURE 2: Station 11R (blue arrow) and station 7 (red arrow) lymph nodes on PET/CT scan, which were biopsied during EBUS. Note the FDG avidity with SUV significantly above the background

PET/CT: positron emission tomography/computed tomography; EBUS: endobronchial ultrasound; FDG: fluorodeoxyglucose; SUV: standardized uptake value

The pathologic specimens revealed nonnecrotizing granulomatous inflammation with no malignant cells on cytology; Gram stain, acid-fast bacilli (AFB) stain, and fungal stain were negative, as well as their respective cultures, as shown in Figures 3-8. Polymerase chain reaction testing for broad-range bacterial, fungal, and AFB was negative.

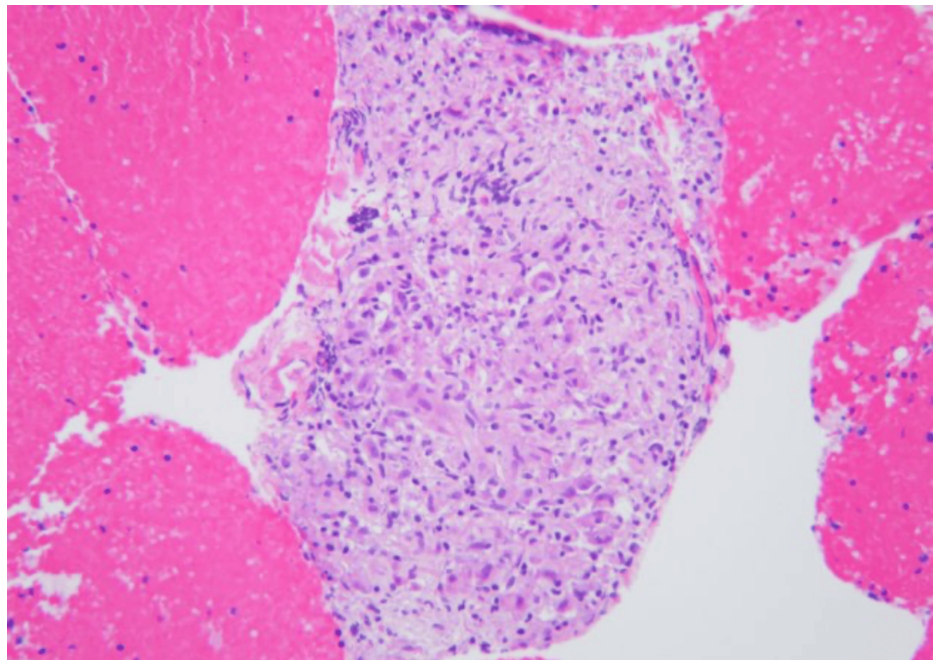


FIGURE 3: H&E section of the submitted cell block 4R at 20× magnification, revealing several collections of histiocytes forming nonnecrotizing granulomas mixed with mature lymphocytes

H&E: hematoxylin and eosin

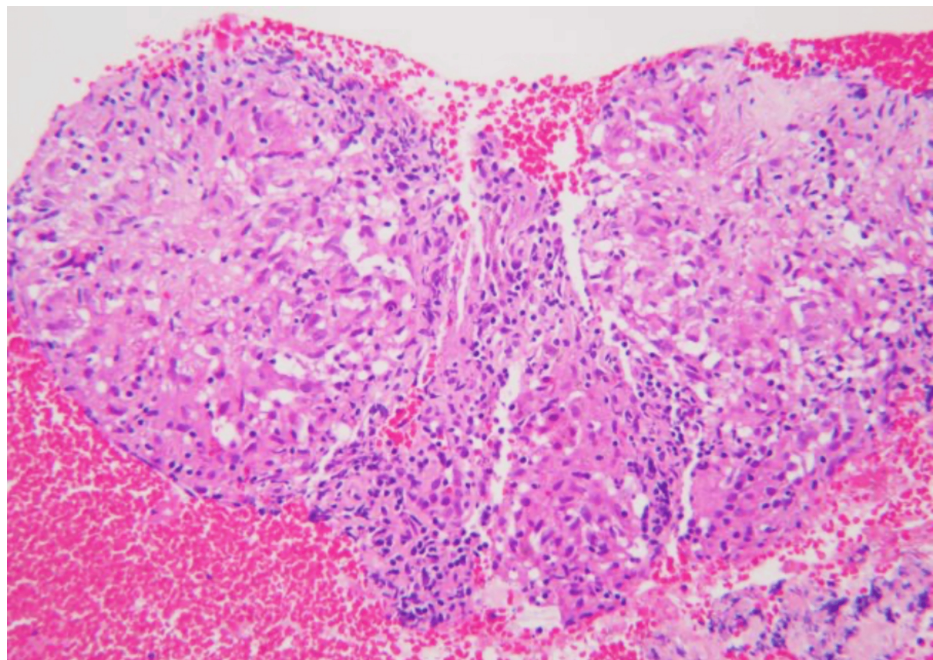


FIGURE 4: H&E section of the submitted cell block of lymph node station 7 at 20× magnification revealing several collections of histiocytes forming nonnecrotizing granulomas mixed with mature lymphocytes

H&E: hematoxylin and eosin

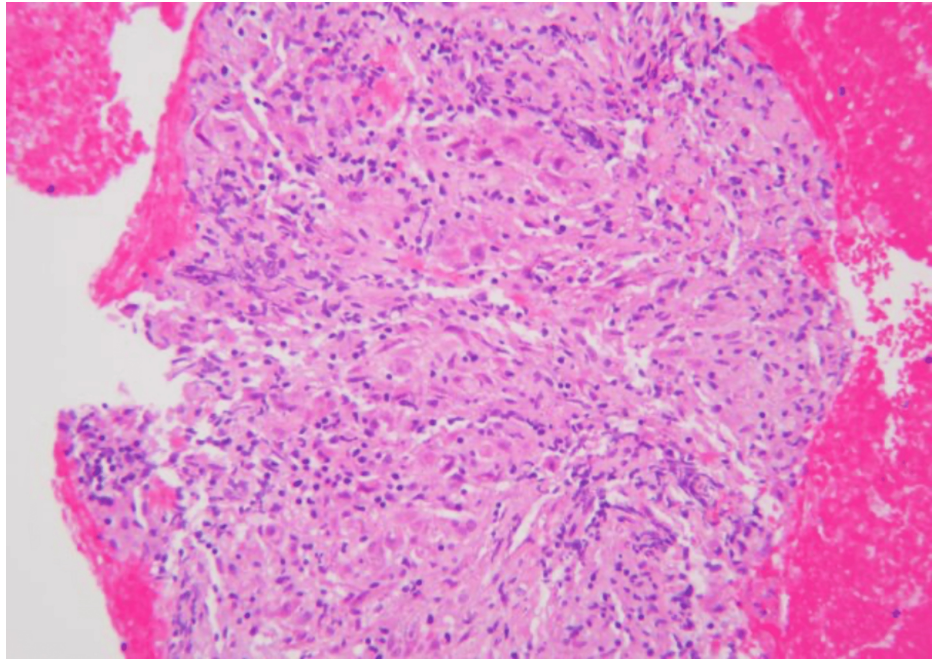


FIGURE 5: H&E section of the submitted cell block of the 11R lymph node station at 20× magnification revealing several collections of histiocytes forming nonnecrotizing granulomas mixed with mature lymphocytes

H&E: hematoxylin and eosin

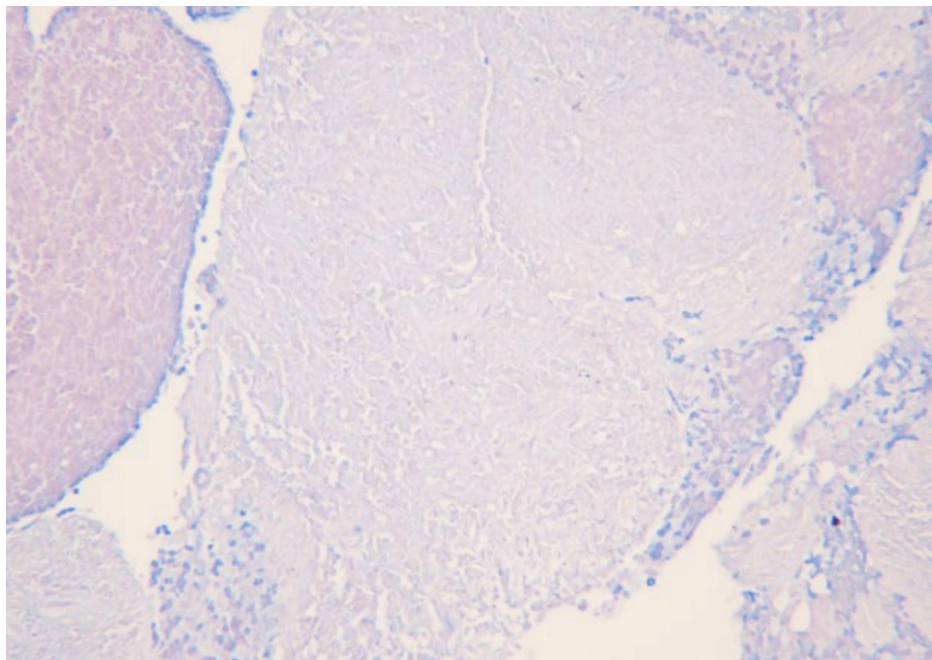


FIGURE 6: AFB special stains performed on the 4R lymph node resulting negative for acid-fast and fungal organisms

AFB: acid-fast bacilli

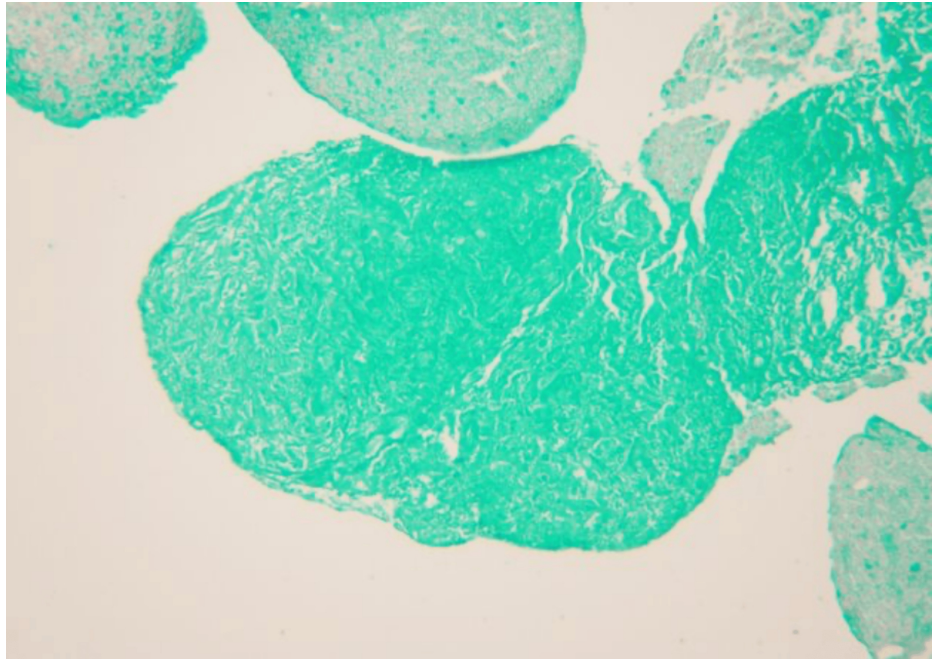


FIGURE 7: GMS special stain performed on the 4R lymph node resulting negative for acid-fast and fungal organisms

GMS: Grocott-Gomori methenamine silver

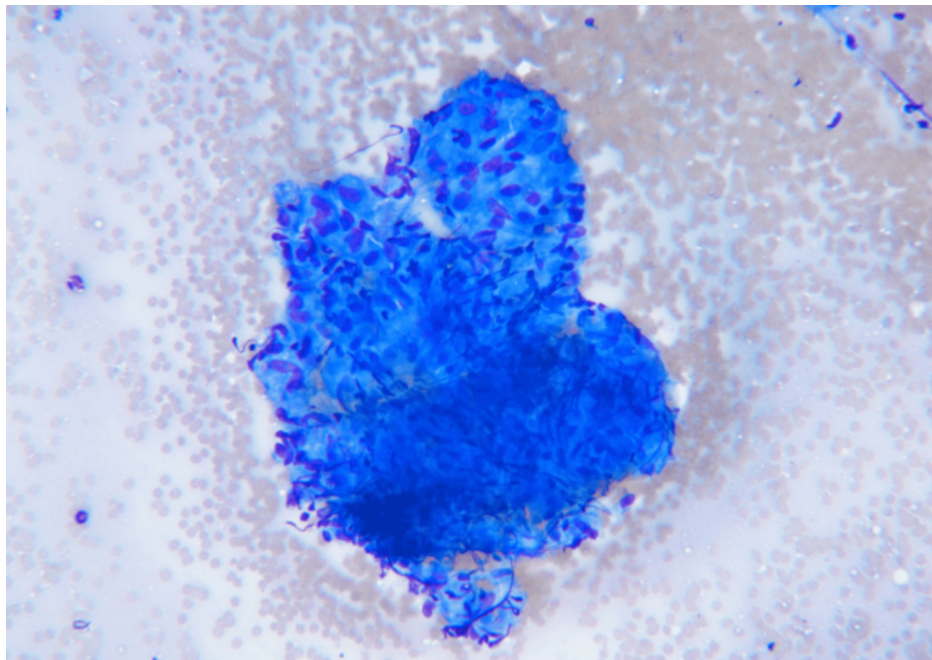


FIGURE 8: Diff-Quik stains performed during rapid on-site assessment revealing clusters of histiocytes forming nonnecrotizing granulomas

Overall, the imaging pattern, laboratory data, and granulomatous pathology were most consistent with stage I sarcoidosis. As the patient remained asymptomatic without evidence of end-organ involvement, an observational management strategy was adopted. This approach aligns with current American Thoracic Society and British Thoracic Society guidelines, which recommend observation for asymptomatic stage I pulmonary sarcoidosis, even in the presence of mild hypercalcemia, because most cases resolve spontaneously. The patient remained asymptomatic in remission from myeloma for a total of six months. She remained radiographically stable during this time period, with stable laboratory findings. She continued

teclistamab without interruption.

Discussion

Teclistamab is a bispecific antibody that has shown remarkable efficacy in treating relapsed or refractory multiple myeloma. It works by targeting BCMA on plasma cells and CD3 on T cells, leading to potent T cell activation, cytokine release, and proliferation [8]. This immune activation can potentially lead to granulomatous inflammation. Sarcoidosis is characterized by the activation of Th1- and Th17-mediated cellular responses along with the activation of CD4 T cells and macrophages. This interaction ultimately leads to a clustering of immune cells culminating in granuloma formation [9]. Granulomas are formed by a combination of the proinflammatory cytokines IL-10, TNF- α , interferon-gamma, and IL-17 along with macrophages [10]. Bispecific antibodies such as teclistamab can perpetuate a high cytokine environment that leads to the release of IL-6, IFN- γ , TNF- α , and granulocyte-macrophage colony-stimulating factor. These cytokines create overlapping pathways that can cause granuloma formation. In the literature, reports have associated activation of nontubercular mycobacteria with a very similar phenomenon, but using a different set of cytokines [11].

There are a few case reports that hypothesize that CRS after CAR-T infusion triggers expansion of Th17 T cells that lead to sarcoid-like manifestations [11,12]. There is also evidence that immune checkpoint inhibitors are associated with sarcoid granuloma formation [13], but teclistamab is not widely associated with granulomatous toxicity. However, its pharmacologic immune-activation profile provides a plausible mechanism for sarcoid-like pathology that may emerge during treatment.

Distinguishing between true myeloma and sarcoid granulomas can be difficult on PET/CT scans, as both show high 18-FDG uptake. Tumors in the initial phase of therapy can also increase in size, which is often coined “pseudoprogression” [14]. Another manifestation resembling pseudoprogression is the development of a granulomatous reaction rather than actual disease progression [15]. Therefore, it is important to recognize these changes to make the correct management decision for the patient. In this patient, prior exposure to cilta-cel could potentially lead to a sequential immune-stimulating effect due to similarity between these pathways. The absence of symptoms, elevated level of normal values of ACE, mild hypercalcemia, and the presence of nonnecrotizing granulomas with a negative infectious workup further support sarcoidosis as the diagnosis, rather than progression of multiple myeloma or infection in this case.

Awareness of benign granulomatous reactions in heavily pretreated myeloma patients is essential to prevent misclassification of immunotherapy-related inflammatory findings as disease progression, which could lead to unnecessary treatment changes. SLRs, also known as drug-induced sarcoidosis-like reactions, are increasingly observed in patients undergoing immune-modulating therapies. While the etiology of classic sarcoidosis remains unclear, reports have described the emergence of new granulomatous lesions associated with drugs such as immune checkpoint inhibitors, interferons, TNF- α antagonists, BRAF/MEK inhibitors, and other biologic agents [16]. A recently reported case also described Th17 cell-driven inflammation following anti-BCMA CAR T-cell therapy (Idecabtagene vicleucel) in a patient with multiple myeloma, further supporting that a heightened Th1/Th17 pathway can precipitate sarcoid-like granulomatous inflammation [12]. Opportunistic infections, including mycobacterial and fungal pathogens, must be carefully excluded, as they can produce nonnecrotizing granulomas that are indistinguishable from sarcoidosis on imaging alone [17]. In patients receiving teclistamab, disease progression in the form of extramedullary relapse is also a common concern. Therefore, histological confirmation remains essential. Infectious lymphadenitis should also be considered due to underlying hypogammaglobulinemia, immune system exhaustion, and T-cell dysfunction associated with BCMA therapies. Treatment strategies should be tailored to the individual; if organ-threatening involvement occurs, corticosteroids or immunosuppressants used to treat sarcoidosis may be warranted [18].

Systemic corticosteroids remain the primary initial treatment for autoimmune diseases such as sarcoidosis. Sarcoidosis is characterized by four radiological stages, based on lymph node and pulmonary involvement [19]. Most patients with stages 1-3 or those who are asymptomatic often recover without the use of corticosteroids. Asymptomatic patients should be closely monitored for any changes, and corticosteroids may be administered if pulmonary dysfunction develops [20]. Rechallenging corticosteroids may be feasible in mild cases after a thorough assessment, imaging, and laboratory testing; however, risks include the reactivation of sarcoidosis via T-cell activation. Limited data are available on rechallenge after BCMA-targeted therapy for sarcoidosis. In our case, a multidisciplinary team elected to continue treatment with teclistamab due to sustained remission and the absence of symptoms. Additionally, patients receiving teclistamab are susceptible to infections due to immune suppression, which is exacerbated by corticosteroid use. Preventive strategies include prophylaxis with antiviral, antifungal, and antibacterial agents as well as prophylaxis against *Pneumocystis jirovecii*. Managing granulomatous inflammation while maintaining therapeutic efficacy necessitates individualized, closely monitored treatment plans to ensure safety and tolerability.

As BCMA-targeted therapies become increasingly prevalent, it is imperative to recognize rare immune-mediated complications, such as sarcoidosis or sarcoid-like granulomatous inflammation, for pharmacovigilance. These adverse reactions can mimic disease progression or infection, thereby

confounding diagnosis and leading to inappropriate modifications of therapy. Awareness of these potential complications can prevent unwarranted discontinuation and assist in accurate diagnosis. Systematic data collection and the establishment of registries are essential to better understand the incidence, clinical course, outcomes, genetic predispositions, biomarkers, and optimal management strategies, including the safety of rechallenge. As the utilization of immunotherapeutics such as bispecific antibodies and CAR T-cell therapies continues to grow, integrating real-world safety data into postauthorization safety studies and research networks is essential. Multidisciplinary collaboration can elucidate underlying mechanisms, such as Th1/Th17 immune dysregulation, and facilitate the development of guidelines for their recognition and management. Incorporating postmarketing safety data into ongoing assessments and guidelines will serve to optimize patient care.

Conclusions

To the best of our knowledge, our case represents the first documentation of sarcoidosis as a hypothesized consequence of teclistamab therapy. This implies the importance of recognition of atypical immune toxicities from novel immunotherapeutic agents, which can easily be overlooked or confused. The field of immunotherapy continues to evolve, with BiTEs, including teclistamab, becoming increasingly utilized in a variety of settings. As BiTEs undergo widespread adaptation, the profile of their immune toxicities is becoming increasingly discovered and documented. This altogether could suggest a future need for immune profiling to stratify those individuals at higher risk for immune toxicities including sarcoidosis.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Stefan A. Longobardi

Acquisition, analysis, or interpretation of data: Stefan A. Longobardi, Shoon Oo, Manpreet Saini, Anup Trikkannad, Logan Meurer, Sharmilan Thanendrarajan

Drafting of the manuscript: Stefan A. Longobardi, Shoon Oo, Manpreet Saini, Anup Trikkannad

Critical review of the manuscript for important intellectual content: Stefan A. Longobardi, Shoon Oo, Manpreet Saini, Anup Trikkannad, Logan Meurer, Sharmilan Thanendrarajan

Supervision: Sharmilan Thanendrarajan

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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