

Central nervous system aspergillosis with negative serum fungal biomarkers after sequential teclistamab and talquetamab for multiple myeloma: a case report and review of the literature

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Case Report

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Abstract

Bispecific antibodies directed against B-cell maturation antigen (BCMA) and G protein-coupled receptor class C group 5 member D (GPRC5D) have improved outcomes in relapsed multiple myeloma but are associated with a high burden of infection. Invasive mould infection of the central nervous system (CNS) has rarely been described in this setting. We report a 70-year-old woman with heavily pretreated IgG-kappa myeloma who received teclistamab, complicated by immune effector cell-associated neurotoxicity syndrome (ICANS) treated with corticosteroids, followed by talquetamab. She received antiviral and anti-*Pneumocystis* prophylaxis and intravenous immunoglobulin, without mould-active cover. Shortly after starting talquetamab, she developed cough and confusion, with cavitating pulmonary lesions initially attributed to bacterial abscesses. Serum galactomannan remained 0.1 on serial testing and β -D-glucan was negative. Computed tomography-guided lung biopsy confirmed pulmonary aspergillosis, and voriconazole was started. Failure to regain her functional baseline and progressive weakness, initially difficult to separate from her previous ICANS, led to brain magnetic resonance imaging, which showed a 10-mm ring-enhancing occipital lesion. Biopsy confirmed CNS aspergillosis. A literature review identified few published cases of invasive aspergillosis during bispecific therapy for myeloma, and serum galactomannan was positive in those with reported results. Negative fungal biomarkers should not exclude invasive aspergillosis in patients receiving bispecific antibodies, and new neurological decline warrants imaging and tissue diagnosis even after ICANS. Patients who require corticosteroids for ICANS during bispecific therapy, particularly after sequential bispecific exposure, may warrant individualised assessment of invasive mould risk and consideration of azole prophylaxis, pending prospective evaluation.

Introduction

Teclistamab, a bispecific antibody targeting B-cell maturation antigen (BCMA) and CD3, and talquetamab, which targets G protein-coupled receptor class C group 5 member D (GPRC5D) and CD3, have shown activity in heavily pretreated, triple-class-exposed multiple myeloma [1, 2]. Their use is associated with a substantial infectious burden. A meta-analysis of 1666 trial participants reported any-grade infection in 56% and grade ≥ 3 infection in 24%, with higher rates for BCMA-directed agents and combination regimens [3]. Most infections are viral or bacterial, and fungal infections accounted for 6% of microbiologically confirmed events in observational studies [3]. Guidelines from the European Conference on Infections in Leukaemia (ECIL) do not support antifungal prophylaxis in myeloma, including during bispecific therapy [4], and expert consensus reserves it for selected patients [5].

Invasive aspergillosis is therefore uncommon in this population and may not be considered early, particularly when pulmonary imaging resembles bacterial infection or when neurological symptoms overlap with immune effector cell-associated neurotoxicity syndrome (ICANS). We describe biopsy-proven pulmonary and central nervous system (CNS) aspergillosis with persistently negative serum fungal biomarkers in a patient treated sequentially with teclistamab and talquetamab, and review published cases of invasive aspergillosis during bispecific therapy for myeloma.

Case presentation

A 70-year-old woman was diagnosed with IgG-kappa multiple myeloma in April 2015, with a haemoglobin of 10.8 g/dL and 40% bone marrow plasma cells. She received cyclophosphamide, bortezomib and dexamethasone (CyBorD), followed by autologous stem-cell transplantation. She relapsed in 2019 and received further lines of therapy (Table 1).

On 25 November 2024, teclistamab was started for progressive disease with a pleural effusion and a rib plasmacytoma. Before the second dose, she developed ICANS, with cognitive deterioration that improved with corticosteroids, and teclistamab was held. Teclistamab was restarted on 20 January 2025 with regular intravenous immunoglobulin (IVIg). Prophylaxis comprised valaciclovir, trimethoprim–sulfamethoxazole and nystatin, without a mould-active antifungal. In December 2025, she relapsed, with a haemoglobin of 9.0 g/dL, creatinine of 112 μ mol/L and IgG of 47.50 g/L, and was admitted to the intensive care unit with acute kidney injury. Teclistamab was stopped, and talquetamab was commenced in January 2026.

Later that month, she developed a productive cough and confusion. Chest radiography showed multifocal air-space opacification, with persistent left lung consolidation despite antibiotics. Thoracic computed tomography (CT) in February 2026 demonstrated bronchiectasis, cavitating right lung nodules measuring 1–2 cm (Fig. 1a) and a 3.8-cm subpleural cavitating lesion with an air–fluid level (Fig. 1b), initially considered bacterial abscesses. Serum galactomannan remained 0.1 on serial testing from February to July 2026, and β -D-glucan was 29 pg/mL; both were reported as negative. CT-guided lung biopsy confirmed pulmonary aspergillosis. Intravenous voriconazole was started and subsequently changed to therapeutic-dose oral treatment.

She remained neurologically stable but did not regain her previous functional baseline and entered rehabilitation in late April 2026. By 20 May, persistent mobility impairment and progressive generalised weakness prompted further investigation. Recurrent ICANS was considered, and her previous ICANS complicated interpretation of the neurological symptoms. Brain magnetic resonance imaging (MRI) on 25 May 2026 showed a 10-mm ring-enhancing posteromedial left occipital lesion (Fig. 1c), initially considered an infarct or metastatic disease. Biopsy confirmed intracranial aspergillosis, establishing pulmonary and CNS involvement following sequential bispecific antibody therapy. At the latest follow-up, she was clinically stable, able to verbalise and receiving voriconazole as an inpatient.

Table 1
Clinical timeline

Date	Event
April 2015	IgG-kappa multiple myeloma diagnosed (haemoglobin 10.8 g/dL; 40% plasma cells); CyBorD, then autologous stem-cell transplantation
2019	Relapse; further lines of therapy
25 November 2024	Teclistamab started for progressive disease with pleural effusion and rib plasmacytoma
Before dose 2	ICANS with cognitive deterioration; corticosteroids; teclistamab held
20 January 2025	Teclistamab restarted with regular IVIG
December 2025	Relapse; intensive care admission with acute kidney injury; teclistamab stopped
January 2026	Talquetamab started
Late January 2026	Productive cough and confusion; consolidation persisting despite antibiotics
February 2026	Thoracic CT: cavitating lung lesions; CT-guided biopsy: pulmonary aspergillosis; voriconazole started
February–July 2026	Serum galactomannan 0.1 on serial testing; β -D-glucan 29 pg/mL
Late April 2026	Rehabilitation; functional baseline not regained
20 May 2026	Impaired mobility and progressive generalised weakness
25 May 2026	Brain MRI: 10-mm ring-enhancing left occipital lesion; biopsy: CNS aspergillosis

CNS central nervous system, CT computed tomography, CyBorD cyclophosphamide, bortezomib and dexamethasone, ICANS immune effector cell-associated neurotoxicity syndrome, IVIG intravenous immunoglobulin, MRI magnetic resonance imaging

Literature review

PubMed, Europe PMC (including open-access full texts), Embase, Scopus and Web of Science Core Collection were searched on 14 October 2026 without language restrictions. Search terms combined teclistamab, talquetamab, elranatamab, linvoseltamab, bispecific antibody or T-cell engager with aspergillosis, invasive fungal infection, mould or mucormycosis, and multiple myeloma. Reports describing invasive aspergillosis in patients with myeloma during or after bispecific antibody

therapy were eligible, and full texts were reviewed for case-level detail. The main search returned 44 records in PubMed, 34 in Embase (including conference abstracts), 20 in Scopus and 7 in Web of Science. Searches restricted to CNS involvement returned 3 records in Embase, 2 in Scopus and none in Web of Science, and none of these described CNS aspergillosis in myeloma. The additional Embase and Scopus records were cohort studies, reviews or guidelines without further case-level reports. Conference abstracts were identified through Embase only, so cases presented solely at meetings may have been missed.

Three previously published cases contained sufficient clinical detail for comparison (Table 2) [6, 7]. Two further cohorts reported aspergillosis without case-level data: *Aspergillus* respiratory infection occurred in 2 of 80 patients receiving teclistamab, both during IVIG replacement [8], and grade 1–2 aspergillosis in 6 of 101 patients receiving elranatamab [9]. Outside myeloma, combined aspergillosis and mucormycosis has been reported after epcoritamab and severe cytokine release syndrome (CRS) in diffuse large B-cell lymphoma [10]. No antemortem, biopsy-proven CNS aspergillosis and no case following sequential BCMA- and GPRC5D-directed therapy was identified.

Table 2
Published cases of invasive aspergillosis during bispecific antibody therapy for multiple myeloma, compared with the present case

Case	Patient	Bispecific antibody	Additional risk factors	Sites	Serum GM	Diagnosis	Outcome
Present case	70 F; autologous transplant	Teclistamab, then talquetamab	Corticosteroid-treated ICANS; IVIG; no mould-active prophylaxis	Lung; brain	0.1 (negative), February–July 2026	Proven: lung and brain biopsy	Clinically stable on voriconazole
Monzo-Gallo et al [6]	60 M; autologous transplant	Teclistamab	Dexamethasone; influenza A co-infection	Lung; brain lesions on CT	Index 9.3 (positive)	Azole-resistant <i>A. fumigatus</i> in bronchoaspirate; confirmed at necropsy	Died
Aparicio-Minguijón et al [7]	Myeloma	Bispecific antibody	CRS and ICANS treated with corticosteroids and anti-IL-6	Lung	Positive	Probable: <i>A. fumigatus</i> in sputum	–
Aparicio-Minguijón et al [7]	Myeloma	Bispecific antibody	COVID-19; mechanical ventilation; corticosteroids	Lung	–	Probable: <i>A. nidulans</i> in bronchoalveolar lavage	–
– not stated in the source publication. CRS cytokine release syndrome, CT computed tomography, F female, GM galactomannan, ICANS immune effector cell-associated neurotoxicity syndrome, IL-6 interleukin-6, IVIG intravenous immunoglobulin, M male							

Discussion

To our knowledge, this is the first reported case of antemortem, biopsy-proven CNS aspergillosis during sequential BCMA- and GPRC5D-directed bispecific antibody therapy for myeloma. Two features complicated the diagnosis. The cavitating pulmonary lesions were initially treated as bacterial abscesses, and the later neurological decline was difficult to separate from previous ICANS. Serum fungal biomarkers remained negative throughout, and tissue was required at both sites.

Infection is frequent with bispecific antibodies. In MajesTEC-1, 80.0% of patients treated with teclistamab had an infection and 55.2% had a grade 3/4 infection [11]. Talquetamab was associated with fewer grade 3/4 infections, although the rate was highest in patients previously exposed to T-cell redirection (27.5%, compared with 21.7% and 15.9% in the weekly and every-other-week cohorts) [12]. Grade 3/4 infections occurred in 64% of patients receiving talquetamab with teclistamab [13]. Fungal infection is less common. In a single-centre cohort of 98 bispecific courses, fungal aetiology accounted for 2.8% of

infectious episodes, including two cases of invasive aspergillosis [7]. After BCMA-directed chimeric antigen receptor T-cell (CAR-T) therapy, the 1-year cumulative incidence of proven or probable invasive fungal disease was 1.72% [14].

Several features of this case correspond to reported risk factors. In the same cohort, previous bispecific exposure (adjusted hazard ratio 1.75) and ICANS (adjusted hazard ratio 3.23) were independently associated with infection, whereas IVIG was protective (adjusted hazard ratio 0.68) [7]. A recent systematic review published in this journal identified neutropenia, corticosteroid or tocilizumab exposure and hypogammaglobulinaemia as recurrent risk factors after T-cell-redirecting therapy [15]. The present patient had sequential BCMA- and GPRC5D-directed exposure and corticosteroid-treated ICANS, and developed aspergillosis despite IVIG replacement. A single case cannot establish causality, and cumulative immunosuppression from earlier lines of therapy is likely to have contributed.

Negative fungal biomarkers did not exclude invasive disease. Serum galactomannan had a pooled sensitivity of 0.71 for proven invasive aspergillosis in a meta-analysis [16], and sensitivity was 29.5% in a cohort of non-neutropenic patients with invasive pulmonary aspergillosis [17]. Expert consensus notes that β -D-glucan may be falsely positive in patients receiving IVIG [5]; in this case it remained negative despite IVIG. By contrast, serum galactomannan was positive in both previously described myeloma cases with reported results [6, 7]. Proven invasive fungal disease requires histopathological or culture evidence from tissue [18], and cerebrospinal fluid galactomannan has a pooled sensitivity of 69.0% for CNS aspergillosis [19]. When imaging suggests a mould infection, biopsy should not be deferred because biomarkers are negative.

CNS aspergillosis carries a mortality exceeding 50% in immunocompromised patients, and voriconazole remains the cornerstone of treatment because of its CNS penetration [20]. Voriconazole is a recommended first-line agent for invasive aspergillosis in both the Infectious Diseases Society of America and the European ESCMID-ECMM-ERS guidelines [21, 22]. The only comparable myeloma case with cerebral involvement, caused by azole-resistant *Aspergillus fumigatus*, was fatal within days, with dissemination confirmed at necropsy [6]. In the present case, tissue diagnosis at both sites allowed targeted therapy, and she remained clinically stable on voriconazole.

Current guidance does not support routine antifungal prophylaxis in myeloma treated with bispecific antibodies [4], and expert consensus reserves it for patients with previous fungal infection, prolonged neutropenia or prolonged high-dose corticosteroid exposure [5]. These criteria appear too narrow for patients who develop ICANS. ICANS is recognised as a contributor to infection risk after T-cell-redirecting therapy [23] and was independently associated with infection in a bispecific cohort, in which one of the two cases of invasive aspergillosis followed corticosteroid and anti-interleukin-6 treatment for CRS and ICANS [7]. After CAR-T therapy, a comparable setting of T-cell-mediated toxicity and corticosteroid exposure, ECIL guidelines already endorse anti-mould prophylaxis for high-risk patients [4]. We therefore propose that patients receiving bispecific antibodies who require corticosteroids for ICANS or CRS, particularly after sequential bispecific exposure, undergo individualised assessment of invasive mould risk, taking into account corticosteroid dose and duration, neutropenia, previous T-cell-redirecting therapy and other host factors. In patients judged to be at high risk, mould-active azole prophylaxis, such as posaconazole or voriconazole, could be considered while corticosteroids are continued, with infectious diseases input on azole drug interactions and therapeutic drug monitoring. This proposal is hypothesis-generating: a single case cannot establish benefit, and the balance of benefit against toxicity, drug interactions and cost should be evaluated prospectively, for example in registries or cohort studies of patients treated with bispecific antibodies.

Conclusions

Invasive aspergillosis, including CNS disease, can occur during bispecific antibody therapy for myeloma despite persistently negative serum galactomannan and β -D-glucan. Cavitating lung lesions and new or persistent neurological decline in this setting warrant investigation for invasive mould infection, with tissue diagnosis where clinically appropriate, and previous ICANS should not preclude a search for an alternative cause. For patients who require corticosteroids for ICANS or CRS during bispecific therapy, particularly after sequential BCMA- and GPRC5D-directed therapy, we propose individualised assessment of invasive mould risk, with mould-active azole prophylaxis considered for those at high risk, and suggest that this strategy be evaluated prospectively.

Declarations

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

Institutional ethics approval was not required for this single-patient case report in accordance with local policy. The report was prepared in line with the principles of the Declaration of Helsinki.

Consent to participate

Informed consent was obtained from the patient.

Consent to publish

Informed consent was obtained from the patient for publication of the clinical information and images.

Author contributions

Aly Samy Aly: data curation, writing – original draft, writing – review and editing. Elly Hanis Che Othman: data curation, validation, writing – review and editing. Aoibheann Davis: methodology, data curation, writing – review and editing. Patrick Thornton: conceptualization, validation, supervision, writing – review and editing. All authors read and approved the final manuscript.

Data availability

The clinical data supporting this report are contained within the article. No additional dataset was generated.

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Figures

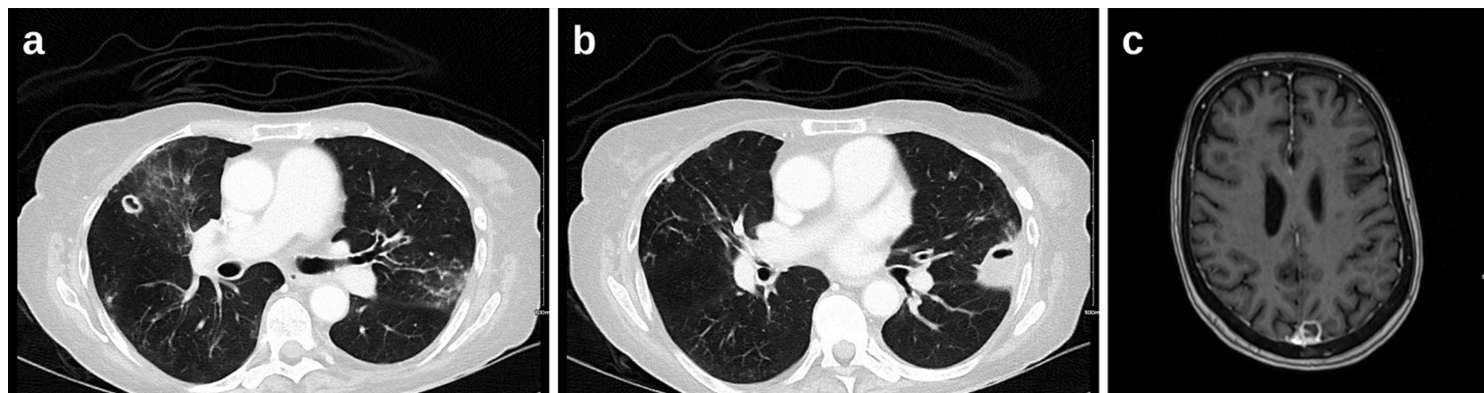


Figure 1

Imaging findings. **a** Axial thoracic CT (lung window), February 2026, showing a cavitating right lung nodule. **b** Subpleural cavitating lesion with an air–fluid level. **c** Axial T1-weighted post-gadolinium brain MRI, 25 May 2026, showing a ring-enhancing posteromedial left occipital lesion, confirmed as aspergillosis on biopsy. CT computed tomography, MRI magnetic resonance imaging