Case Report

Cryptococcosis in a patient with multiple myeloma receiving pomalidomide: a case report and literature review

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Abstract: While overall survival with multiple myeloma (MM) has improved, patients suffer from overwhelming tumor burden, MM-associated comorbidities, and frequent relapses requiring administration of salvage therapies. As a result, this vicious cycle is often characterized by cumulative immunodeficiency stemming from a combination of disease- and treatment-related factors leading to neutropenia, T-cell deficiency, and hypogammaglobulinemia. Infectious etiologies differ based on the duration of MM and treatment-related factors, such as number of previous treatments and cumulative dose of corticosteroids. Herein, we present the case of a patient who was receiving pomalidomide without concomitant corticosteroids for MM and was later found to have cryptococcosis, as well as findings from a literature review. Most cases of cryptococcosis are reported in patients with late-stage MM, as well as those receiving novel anti-myeloma agents, such as pomalidomide, in combination with corticosteroids or following transplantation. However, it is likely cryptococcosis may be underdiagnosed in this population. Due to the cumulative immunodeficiency present in patients with MM, clinicians must be suspicious of cryptococcosis at any stage of MM.

Keywords: Cryptococcus, malignancy, multiple myeloma, pomalidomide, thalidomide

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Introduction

Cryptococcus spp. is an encapsulated yeast and opportunistic pathogen that has historically been associated with T-cell immunodeficiency due to untreated HIV infection.[1,2] However, as the number of immunodeficient hosts increases, the incidence of cryptococcosis continues to grow in patients with malignancies, organ transplantation, autoimmune diseases, primary immunodeficiency syndromes, chronic comorbidities such as diabetes mellitus and sarcoidosis, and in those receiving immunosuppressive therapies.[1–5]

Indeed, multiple myeloma (MM) is associated with impaired immunologic function resulting in increased susceptibility to infections.[6] Specifically, immunodeficiency observed in patients with MM is often multifactorial due to mucosal barrier defects, respiratory dysfunction, hypogamma-globulinemia, disrupted lymphocyte function, and treatment-related immunodeficiency.[6] Although most patients with MM respond to initial therapies, many cases progress as conventional treatment options are not curative. Patients who relapse or develop refractory disease suffer from shorter periods of remission and more treatment-related adverse events.

Pomalidomide, a more potent and less toxic derivative of thalidomide, was introduced for patients with MM refractory to lenalidomide and bortezomib. Although infectious diseases have

been reported in patients receiving pomalido-mide, most are viral or bacterial and are often observed when pomalidomide is administered in combination with dexamethasone.[7,8] Herein, we present the case of a patient who was receiving pomalidomide without concomitant corticoster-oids for MM and was later found to have crypto-coccosis. In addition, we present findings from a literature review detailing reports of cryptococco-sis in patients with MM.

Case description

A gentleman in his early 70s was admitted due to right arm and right leg weakness and paresthesia for 2 weeks. He was previously able to walk inde-pendently but was unable to bear weight on his right leg for the last 2 weeks. Other than right-sided weakness, his physical and neurological examination were unremarkable whereby he spe-cifically denied dysarthria, facial paralysis, chest pain, fever, chills, shortness of breath, nausea, vomiting, or trauma in relation to his leg.

He had a history of MM, hypertension, atrial fibril-lation, heart failure with reduced ejection fraction (EF 30% approximately 1 year earlier), automatic implantable cardioverter-defibrillator (AICD) placement, and chronic kidney disease (CKD) stage IV most likely due to a combination of MM and hypertension. He was diagnosed with stage III light chain myeloma in 2012. Notably, he did not undergo stem cell transplantation and was man-aged with maintenance therapy. Due to disease progression and intolerability with previous regi-mens, he was receiving palliative pomalidomide without corticosteroids, his fifth-line therapy, for more than 2 years with normocellular bone mar-row and no evidence of residual myeloma at the time of admission (additional details of MM treat-ment history are provided in Table 1).

Chemistry and hematology laboratories revealed hyperkalemia [5.5 mEq/L (reference range, 3.5–5.0 mEq/L)] and transaminitis [aspartate ami-notransferase (AST) 68 U/L (reference range, 10–40 U/L), alanine aminotransferase (ALT) 81 U/L (reference range, 10–40 U/L), alkaline phosphatase 79 U/L (reference range, 30–120 U/L)], but were otherwise consistent with his baseline (Table 2). He tested positive for SARS-CoV-2 *via* nasopharyngeal swab for which he underwent chest radiograph (CXR) noting ill-defined bilateral perihilar and lower lobe infiltrates, slightly greater on the left than on the right. Computed tomography (CT) of the head without intravenous contrast revealed extensive white matter disease likely related to small vessel occlusive disease. Magnetic resonance imaging (MRI) of the brain was unable to be performed due to incompatibility with his AICD. Chest CT without intravenous contrast revealed non-spe-cific patchy ground glass opacities throughout upper and lower lobes bilaterally and in the right middle lobe. Serologic testing was negative for hepatitis B virus (HBV) surface antigen and core antibody, as well as hepatitis C virus (HCV) antibody.

Upon admission, the neurologic complaints were attributed to a subacute cerebrovascular accident for which neurology recommended conservative management. In addition, pomalidomide was held pending COVID-19 resolution. He was con-sidered not to be a candidate for remdesivir due to his CKD but was started on 6 mg of oral dexa-methasone once daily (Figure 1). In addition, cef-triaxone and azithromycin were administered for 7 days due to concerns for a bacterial pneumonia. His oxygen demand continued to increase over the following 5 days requiring transfer to the intensive care unit (ICU) for receipt of high-flow nasal cannula (HFNC) and blood and urine cul-tures were obtained. Over the next 3 days, he remained on HFNC in no distress. Hematology/oncology was consulted due to his ongoing lym-phopenia and recommended initiation of cefepime and micafungin for as long as he remained on dexamethasone. On day 4 of his ICU admission, his urine culture was noted to be sterile, but Gram stain of his blood cultures revealed yeast. This prompted an infectious diseases consultation resulting in continuation of micafungin and repeat blood cultures ordered for the following morning. Shortly thereafter, he experienced ven-tricular tachycardia and continued to deteriorate, ultimately expiring 24 hours later. Post-mortem examination was not performed.

Yeasts, identified from both sets of blood cultures, grew on Sabouraud Dextrose Agar (Emmons modification) and were identified as *Cryptococcus neoformans via* Thermo Scientific™ RapID™ Yeast Plus System (RapID) (Thermo Fisher Scientific, Lenexa, Kansas, U.S.) post-mortem. Due to limited capacity in the facility's microbiol-ogy laboratory, molecular identification and anti-fungal susceptibility testing were not performed.

Table 1. Reports of cryptococcosis in patients with multiple myeloma.

Case	Age (years)	Sex	Comorbidities	MM history prior to diagnosis of cryptococcosis	Primary site(s) of cryptococcosis	Initial management
Current case	70s	M	Atrial fibrillation, HFrEF, renal dysfunction, COVID-19	• Stage III MM diagnosed 8 years earlier • Initially treated with bortezomib, thalidomide, and dexamethasone but discontinued • Subsequently received bortezomib, cyclophosphamide, and dexamethasone, but discontinued due to progression • Then treated with carfilzomib, but was discontinued due to intolerability • Received pomalidomide and dexamethasone with good response, but dexamethasone was discontinued for undocumented reasons • Stable on palliative pomalidomide for more than 2 years with normocellular bone marrow and no evidence of residual myeloma	• *C. neoformans* isolated from blood cultures	• *C. neoformans* identified post-mortem
Karnad *et al.*[9]	26	M	Newly diagnosed HIV at initial diagnosis of MM	• MM diagnosed 16 months prior following presentation with 4 × 4 cm painless lump on R parieto-occipital aspect of skull with 5 × 5 cm irregular lytic bone lesion underlying the mass • Previous treatments for MM limited to localized radiation therapy	• *C. neoformans* isolated from CSF culture	• Clinical improvement following treatment with amphotericin B • Started vincristine, adriamycin, and dexamethasone for rapid nature of MM but expired 4 weeks later due to sustained hypotension
Mendpara *et al.*[10]	42	F	HIV non-reactive, otherwise NR	• Stage III-B MM (IgGκ) initially treated with vincristine, doxorubicin, and dexamethasone with good response • Underwent SCT without complications for 4 months	• *C. neoformans* isolated from CSF culture • CrAg detected in CSF	• Clinical improvement following treatment with amphotericin B and flucytosine
Fickweiler *et al.*[11]	61	F	NR	• Initially treated with doxorubicin and dexamethasone followed by high-dose melphalan and SCT • Relapsed and started on cyclophosphamide and thalidomide, but discontinued due to pancytopenia • Initiated dexamethasone and thalidomide, but discontinued due to polyneuropathy • Restarted melphalan followed by re-infusion of SCT	• *C. neoformans* isolated from CSF and blood cultures with identification of a cerebellar lesion with mass effect on the fourth ventricle causing hydrocephalus	• Clinical improvement following treatment with amphotericin B and flucytosine
De Oliveira *et al.*[12]	58	M	NR	• MM diagnosed 4 years earlier followed by BMT 1 year later • Relapsed and started on cyclophosphamide and dexamethasone	• *C. neoformans* isolated from an ulcerated plaque on the nasal dorsum • CSF and blood cultures sterile	• Clinical improvement following treatment with oral fluconazole
Cerrati *et al.*[13]	60s	M	NR	• MM diagnosed several years earlier followed by radiation therapy and SCT • Stable on lenalidomide and dexamethasone	• *C. neoformans* isolated from an ulcerated plaque on the nasal dorsum • 2 weeks later *C. neoformans* isolated from CSF culture	• Initially started on fluconazole but changed to amphotericin B plus flucytosine due to dissemination resulting in clinical improvement

(Continued)

Table 1. (Continued)

Case	Age (years)	Sex	Comorbidities	MM history prior to diagnosis of cryptococcosis	Primary site(s) of cryptococcosis	Initial management
Suner and Mathis[14]	77	F	NR	• Stage III MM (IgA-λ) diagnosed 8 years earlier • After multiple relapses, started on corticosteroids, cyclophosphamide, and pomalidomide	• *C. neoformans* isolated from CSF culture	• Started on amphotericin B plus flucytosine but expired 10 days later
Ferraro et al.[15]	64	M	NR	• MM diagnosed 12 years earlier • Stable on bortezomib, lenalidomide, and dexamethasone	• Biopsy of 1.7 × 1.0 × 1.3 cm soft-tissue mass in the L sphenoid sinus revealed *Cryptococcus* spp. • CrAg detected in serum, but not in CSF	• Clinical improvement following treatment with amphotericin B and flucytosine
Bowcock et al.[16]	75	F	HIV non-reactive, otherwise NR	• Bortezomib, cyclophosphamide, and dexamethasone as fourth line treatment	• CrAg detected in CSF and serum	• Clinical improvement following treatment with amphotericin B and flucytosine, but MM relapsed approximately 10 weeks later and expired shortly thereafter
Bowcock et al.[16]	79	M	NR	• Pomalidomide and dexamethasone as sixth line treatment	• *C. neoformans* isolated from blood cultures	• Clinical improvement following treatment with amphotericin B and flucytosine, but expired 5 weeks later due to progression of MM
Sato et al.[17]	62	F	Renal dysfunction	• Stage III MM (IgG-λ) initially treated with bortezomib and dexamethasone but discontinued due to diarrhea • Subsequently started on daratumumab, lenalidomide, and dexamethasone	• *C. neoformans* isolated from CSF and blood cultures	• Started on amphotericin B plus flucytosine but expired approximately 2 weeks later
Stepman et al.[18]	70	M	Diabetes mellitus, hypertension, renal dysfunction	• MM diagnosed several years earlier followed by BMT • Subsequently started on ixazomib, pomalidomide, and prednisone	• *C. neoformans* isolated from CSF culture	• Clinical improvement following treatment with amphotericin B and flucytosine
Sassine et al.[19]	77	M	NR	• Stable on lenalidomide	• *C. neoformans* isolated from intraoperative culture obtained from R femur • CrAg detected in serum, but not CSF • CSF and blood cultures sterile	• Clinical improvement following treatment with amphotericin B
Raheem et al.[20]	60	M	Hepatic cirrhosis	• Initially treated with cyclophosphamide, bortezomib, and dexamethasone for 4 cycles, but changed to pomalidomide and dexamethasone	• *C. neoformans* isolated from CSF culture • CrAg detected in CSF	• Clinical improvement following a loading dose of fluconazole, then amphotericin B and flucytosine

BMT, bone marrow transplant; CrAg, cryptococcal antigen; CSF, cerebrospinal fluid; F, female; HFrEF, heart failure with reduced ejection fraction; L, left; M, male; MM, multiple myeloma; NR, not reported; R, right; SCT, stem cell transplantation.

Table 2. Laboratory values prior to and during hospitalization.

Laboratory parameter	Approximately 2 months prior to hospital admission	Approximately 1 month prior to hospital admission	Day of hospital admission	Day 3 of hospitalization	Day 6 of hospitalization	Day 9 of hospitalization	Day 12 of hospitalization
Serum creatinine, mg/dl	3.67	3.67	3.89	3.33	4.15	3.1	3.26
Blood urea nitrogen, mg/dl	36	41	56	75	104	99	113
White blood cell count, K/μl	2.4	3.0	2	2.6	1.6	4.0	13.7
Neutrophil count, K/μl	1.3	1.5	1.5	1.8	1.1	3.3	12.9
Lymphocyte count, K/μl	0.8	1.0	0.3	0.3	0	0.2	0.3

Baseline laboratory data are presented in relation to the day of hospitalization and include the following: BUN, blood urea nitrogen (range: 8–20 mg/dl); lymphocyte count (range: 1–4 K/μl); neutrophil count (range: 2.5–8 K/μl); SCr, serum creatinine (range: 0.70–1.30 mg/dl); WBC, white blood cell (range: 3.5–10 K/μl).
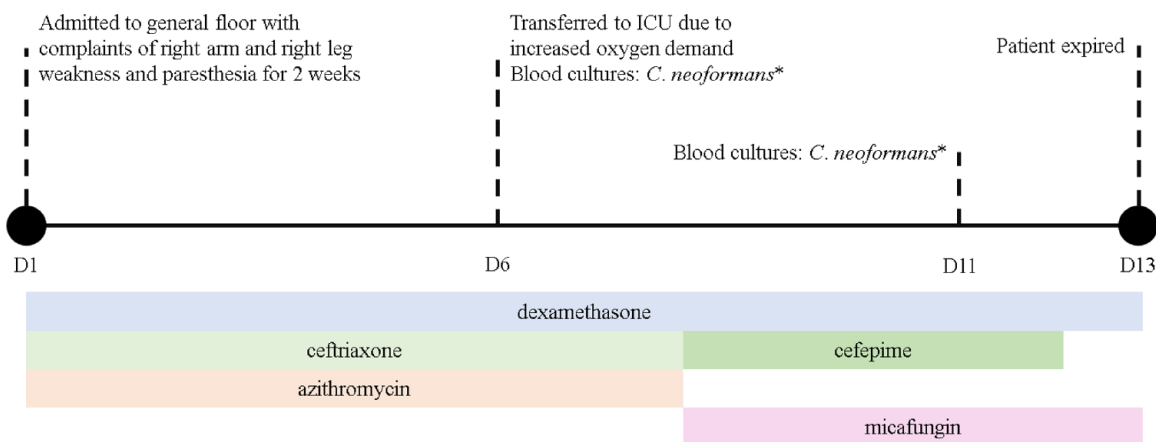

Figure 1. Timeline of hospitalization.
Figure depicts daily (D) timeline of hospitalization.
*Although blood cultures were obtained on D6 and D11, yeasts were not identified on Gram stain until 4 days later in both cases. The yeasts were then plated to Sabouraud Dextrose Agar (Emmons modification) and were eventually identified as *C. neoformans* via Thermo Scientific™ RapID™ Yeast Plus System (RapID) (Thermo Fisher Scientific, Lenexa, Kansas, U.S.). *C. neoformans* was identified after the patient expired.

Additional workup for cryptococcosis [e.g. cerebrospinal fluid (CSF) examination, cryptococcal antigen (CrAg) lateral flow assay (LFA)] was not performed due to low suspicion of *C. neoformans* in this patient.

Discussion

Patients with MM are at an increased risk for infectious diseases due to impaired quantity and function of humoral and cell-mediated immunity.[6] In addition, the degree of immunodeficiency observed in these patients varies from the time of initial MM diagnosis. As expected, infectious etiologies differ based on the duration of MM and treatment-related factors, such as the number of previous treatments and cumulative dose of corticosteroids.[6,21] Compared with bacterial and viral infections, which occur during the first year and again between years 4 and 9 after MM diagnosis, invasive fungal infections occur at much later stages of MM and are associated with cumulative
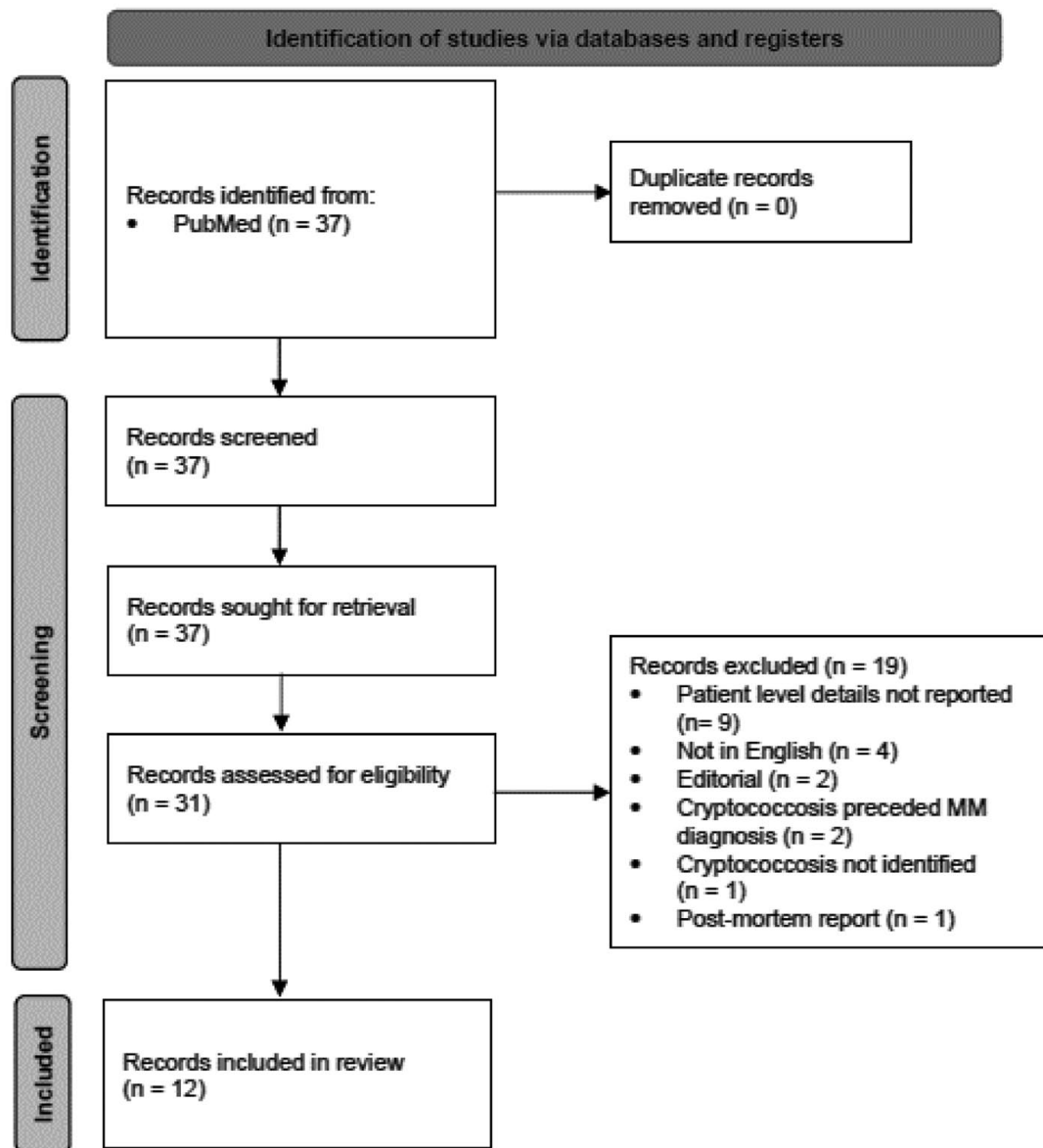
Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

immunodeficiency.[21,22] Invasive aspergillosis is the most common invasive fungal infection among patients with MM due to the administration of high-dose corticosteroids and neutropenia.[22–24] As much of the focus on invasive fungal infections in patients with MM remains on invasive aspergillosis, limited data are available about cryptococcosis in MM.

A PubMed literature search performed on 21 December 2021 using 'cryptococcus' or 'cryptococcosis' and 'multiple myeloma' revealed 37 results (Figure 2).[25] Of those providing patient level details, 12 reports accounting for 13 patients were included (Table 1).[9–20] Median age was 63 years (range, 26–76 years) and 69% ($n=9$) were men. Medical history was reported for few patients, but included one patient with HIV;[9] one with renal dysfunction;[17] one with diabetes mellitus, hypertension, and diabetic nephropathy;[18] and one with hepatic cirrhosis,[20] in addition to our case with atrial fibrillation, heart failure with reduced EF, and renal dysfunction. Two patients with no reported medical history underwent HIV testing which was non-reactive.[16,10]

Duration of MM was reported in few cases, but was diagnosed a median of 8 years (range, 1.33–12 years) prior to diagnosis of cryptococcosis.[9,12,14,15] Thirty-six percent (*n* = 5) of patients had previously undergone transplantation for MM prior to diagnosis of cryptococcosis.[10,11–13,18] While 86% (*n* = 12) of patients were receiving anti-MM therapies, 43% (*n* = 6) had received more than one previous treatment line with one patient receiving their fourth-line treatment,[16] our patient receiving his fifth-line treatment, and another receiving their sixth-line treatment[16] at the time of cryptococcosis was diagnosed. The most common anti-MM therapies included corticosteroids (67%, *n* = 8/12), lenalidomide (33%, *n* = 4/12), pomalidomide (33%, *n* = 4/12), cyclophosphamide (25%, *n* = 3/12), and bortezomib (17%, *n* = 2/12). Notably, 75% (*n* = 6/8) of patients receiving lenalidomide or pomalidomide were receiving concomitant corticosteroids, while our patient being treated with pomalidomide and one other receiving lenalidomide[19] were not receiving concomitant corticosteroids.

Disseminated cryptococcosis was present in 93% (*n* = 13) of patients, of which *Cryptococcus* spp. was detected in the CSF of 69% (*n* = 9/13) of patients *via* microbiologic identification in 89% (*n* = 8/9). Notably, one patient was found to have a cerebellar lesion with mass effect on the fourth ventricle causing hydrocephalus presumed to be a parenchymal cryptococcoma.[11] In addition, two patients presented with cutaneous cryptococcosis involving the nasal dorsum,[12,13] one patient had osseous cryptococcosis of the right femur,[19] while one patient had cryptococcal sinusitis involving the left sphenoid sinus.[15] *C. neoformans* was identified as the causative organism in all cases, except for one where the diagnosis of cryptococcosis was established based on detection of cryptococcal antigenemia.[16]

Amphotericin B and flucytosine were most commonly used in the initial management of cryptococcosis [86% (*n* = 12) and 71% (*n* = 10), respectively]. Fluconazole monotherapy was administered to one patient with cutaneous cryptococcosis as CSF and blood cultures were sterile.[12] Clinical improvement was observed in 79% (*n* = 11) of patients following initiation of antifungal therapy. However, 43% (*n* = 6) of patients expired,[9,14,16,17] which was most often attributed to progression of MM.[9,16] Our patient had been

previously started on micafungin due to administration of dexamethasone for COVID-19, but *C. neoformans* was not identified until after he expired.

While invasive fungal infections have previously been associated with a prolonged duration of MM and receipt of concomitant corticosteroids resulting in a cumulative immunodeficiency, this might not be generalizable to cryptococcosis. In two of the excluded case reports,[26,27] diagnosis of cryptococcosis prompted searches for an underlying cause of immunodeficiency leading to subsequent diagnosis of MM, which suggests that cryptococcosis might not be restricted to late-stage MM. Furthermore, 43% (*n* = 6/14) of all patients included in this review were not receiving concomitant corticosteroids for MM prior to diagnosis of cryptococcosis. While our patient was receiving dexamethasone as part of the medical management of COVID-19, he had only received 5 days of therapy prior to growth of *C. neoformans*. Although unclear, even short courses of corticosteroids could have triggered an opportunistic fungal reactivation.

Notably, cases of *C. neoformans* in patients with COVID-19 have been reported.[28] The precise mechanism remains unknown, but likely involves SARS-CoV-2 infection, immunomodulatory therapy, or a combination of both. We suspect our patient had disseminated cryptococcosis due to MM-associated immunodeficiency prior to diagnosis of COVID-19 or receipt of dexamethasone. Whether the immunomodulatory activity of pomalidomide contributed to our patient's risk for cryptococcosis is unknown.

Pomalidomide, a derivative of thalidomide, inhibits tumor necrosis factor (TNF)-α and is associated with increased anti-MM activity compared with thalidomide.[29,30] In a mouse model study of *C. neoformans*, administration of neutralizing TNF-α antiserum decreased recruitment of CD4 cells, neutrophils, and macrophages by 65%, 84%, and greater than 98%, respectively.[31] Furthermore, mice treated with neutralizing TNF-α antiserum were unable to eradicate *C. neoformans* from their lungs or prevent cerebral or splenic dissemination. Eliminating TNF-α leads to impaired activation of CD4 cells, which are largely responsible for the cell-mediated immune response against *C. neoformans*.[32,33] Alternatively,

thalidomide and thalidomide analogues promote T-cell proliferation, primarily the CD8+ subset, and increase production of interleukin (IL)-2 and interferon (INF)-γ.[34,35] Previous data suggest no increased risk of infection with thalidomide and thalidomide analogues unless combined with corticosteroids.[35–37] However, downregulation of host immune response due to receipt of corticosteroids and COVID-19-associated lymphopenia may have also contributed to reactivation of previously latent cryptococcosis.[38,39]

Although an optimal antifungal treatment regimen has yet to be identified in MM with cryptococcosis, most patients should receive combination therapy with amphotericin B and flucytosine until the extent of disease is determined (e.g. meningoencephalitis, disseminated, or severe pulmonary disease), based on efficacy data derived from persons living with HIV and solid organ transplant recipients.[40,41] In resource-limited settings, high-dose fluconazole with or without amphotericin B might be most efficacious due to lack of availability and prohibitive costs associated with flucytosine. Induction therapy should be continued for 4 weeks or longer depending on the extent of disease. Patients should then be transitioned to higher doses of fluconazole for a minimum of 8 weeks as consolidation therapy followed by a lower dose for at least 1 year or perhaps lifelong as the underlying immunodeficiency in patients with MM is unlikely to resolve.

Conclusion

Most cases of cryptococcosis are reported in patients with late-stage MM, as well as those receiving novel anti-myeloma agents, such as pomalidomide, in combination with corticosteroids or following transplantation. However, it is likely cryptococcosis may be underdiagnosed in this population. Due to the cumulative immunodeficiency present in patients with MM, clinicians must be suspicious of cryptococcosis at any stage of MM.

Declarations

Ethics approval and consent to participate
Our report did not require ethical board approval as it described the treatment of a single patient which does not meet the federal definition of human subjects research. This anonymized case was documented in the context of routine care and the information presented was anonymized in accordance with the Declaration of Helsinki.

Consent for publication
Consent was unable to be obtained as the patient is deceased and relatives were not contactable as contact information was no longer available at the time this case report was developed. As such, patient details have been anonymized as much as possible.

Author contributions
Daniel B. Chastain: Conceptualization; Data curation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests
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Availability of data and materials
All data are available as part of this article.

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