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【 CASE REPORT 】

Disseminated Cryptococcosis in a Patient with Multiple Myeloma Treated with Daratumumab, Lenalidomide, and Dexamethasone

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Abstract:
We report a case of disseminated cryptococcosis in a patient with multiple myeloma (MM) during treatment with daratumumab, lenalidomide, and dexamethasone (DRd). A 62-year-old woman, who was diagnosed with IgGλ type MM, was treated with three cycles of bortezomib and dexamethasone and subsequently treated with three cycles of DRd before admission. She reached a stringent complete response and presented with lethargy and seizure. Laboratory findings revealed severe CD4 lymphopenia, and *Cryptococcus neoformans* was detected in her cerebrospinal fluid and blood culture. The risk of developing an opportunistic infection should be considered in patients treated with daratumumab.

Key words: daratumumab, disseminated cryptococcosis, lymphopenia

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Introduction

Cryptococcosis is a life-threatening, opportunistic fungal infection that predominantly affects immunocompromised hosts (1). Although the disease may occur in apparently normal, healthy hosts, most patients with symptomatic disseminated cryptococcosis have an underlying immunocompromised condition, such as human immunodeficiency virus (HIV) infection or especially CD4 lymphocytopenia; they may also have had prolonged treatment with corticosteroids, cirrhosis, organ transplantation, advanced malignancy, and diabetes (1-4). CNS involvement is the most common manifestation of disseminated cryptococcosis (3).

In patients with multiple myeloma (MM), cell-mediated immunity is suppressed with primary disease and treatments, such as steroids, proteasome inhibitors (PIs), and other immunosuppressive drugs. Daratumumab, a human IgGκ monoclonal antibody that targets CD38, in combination with lenalidomide and dexamethasone (DRd) significantly lengthened the progression-free survival of patients with relapsed or refractory MM, but it is known that daratumumab suppresses a patient's immunity to some degree (5). The National Comprehensive Cancer Network guidelines recommend the use of antifungal and antiviral agents as prophylaxis against *Pneumocystis jiroveci* pneumonia and herpes infection in MM patients treated with high-dose dexamethasone, PIs, or Daratumumab (6). There are several reports of cases of multiple myeloma (MM), in which fungal infections, including cryptococcosis, developed during autologous hematopoietic stem cell transplantation (7). Furthermore, there are also reports of cases of relapsed and refractory MM, treated with novel immunosuppressive therapies and high doses of corticosteroids (8, 9).

We herein report a case of disseminated cryptococcosis in a patient with MM during DRd treatment. To date, no cases of disseminated cryptococcosis during DRd treatment have been reported as adverse events of daratumumab. Given that there are unclear points, particular attention is needed to identify the effects of the immunosuppressive action of daratumumab on lymphocytes.

Case Report

The patient was a 62-year-old woman who had been diagnosed with IgGλ type MM (Internal Staging System: ISS=

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Table. Laboratory Data on Admission.

Hematology		Biochemistry		Immunology	
WBC	3,700 /μL	T-Bil	1 U/L	IgG	292 mg/dL
Neut	84.6 %	TP	5.6 mg/dL	IgA	4 mg/dL
Lym	7.7 %	Alb	3.5 mg/dL	IgM	11 mg/dL
Mono	2 %	AST	16 U/L	CD4	78.9 %
Eosino	0 %	ALT	60 U/L	CD8	16.0 %
Baso	0 %	LDH	242 U/L	CD4/8	4.93
RBC	330×10^4 /μL	γGTP	59 U/L		
Hb	10.7 g/dL	ALP	246 U/L	Cerebrospinal fluid	
MCV	93.6 fl	BUN	22.2 mg/dL	Cell count	66 /μL
Plt	10.9×10^4 /μL	Cre	2.0 mg/dL	Monocyte	48 /μL
Coagulation		eGFR	20.5	Polynuclear	18 /μL
PT-INR	1.01	Na	139 mEq/L	TP	93.3 mg/dL
APTT	23.6 sec	K	3.8 mEq/L	Cl	111 mEq/L
		Cl	102 mEq/L	Glu	9.7 mg/dL
		GLU	143 mg/dL		
		CRP	0.15 mg/dL		
		HbA1c	5.7 %		

WBC: white blood cell, Neu: neutrophil, Lym; lymphocyte, Mono; monocyte, Eosino; Eosinophil, Baso; Basophil, RBC: red blood cell, Hb: hemoglobin, Plt: platelet, PT: prothrombin time activity, PT-INR: prothrombin time activity-international normalized ratio, APTT: activated partial thromboplastin time, T-Bil: total bilirubin, TP: total protein, Alb: albumin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, BUN: blood urea nitrogen, Cre: creatinine, eGFR: estimate glomerular filtration rate, Glu: glucose, CRP: C-reactive protein, HbA1c: hemoglobin A1c

III, Revised ISS=III) with renal dysfunction. She was treated with three cycles of bortezomib (1.3 mg/m^2 days 1, 4, 8, 11) and dexamethasone (20 mg on the day of and the day after bortezomib on a 21-day cycle) (BD). She showed a partial response to treatment; however, after she experienced grade 3 diarrhea in association with bortezomib therapy, we decided to discontinue BD. Thereafter, stem cells were harvested using granulocyte colony stimulating factor (G-CSF) alone. She was subsequently treated with three cycles of DRd (daratumumab, 16 mg/kg, every week; lenalidomide, 10 mg/day, for 21 days, and dexamethasone, 40 mg/week), after which she showed a stringent complete response (sCR).

She was referred to the emergency room of our hospital again after presenting lethargy, rolling of the eyes and loss of consciousness for 3 minutes. Her past medical history included hemorrhagic cerebral infarction and symptomatic epilepsy one month before she was diagnosed MM-after which she was treated with levetiracetam (1,000 mg, once daily) to prevent epilepsy. On admission, she was afebrile but slightly somnolent. A physical examination revealed the absence of meningeal irritation and abnormal neurological symptoms. The laboratory data revealed lymphopenia [white blood cell count, 3,700/μL (lymphocytes, 7.7%; 284.9/μL), and CD4+ count, 224/μL], a normal C-reactive protein level (0.158 mg/dL), and severely low immunoglobulin levels (IgA, 4 mg/dL; IgG, 292 mg/dL; and IgM, 11 mg/dL) (Table). A chest X-ray and brain and chest computed tomography scan showed normal findings. Brain magnetic resonance imaging revealed previous hemorrhagic cerebral infarction (Fig. 1A and B). The patient's clinical course is shown in Fig. 2.

On the day of admission, partial seizure only affecting the patient's right arm was observed. She was then treated with diazepam (5 mg, intravenously), and the epilepsy stopped. Because she remained drowsy 3 days after admission, a cerebrospinal fluid (CSF) analysis was performed, which revealed the following findings: white blood cell count, 66/μL (mononucleosis, 48/μL); glucose, 9.7 mg/dL; and CSF pressure, 85 mmHg. Based on the suspicion of meningitis, treatment with broad-spectrum antibiotics, dexamethasone and an anti-herpes virus drug was initiated. However, on the evening of the same day, the patient suddenly suffered respiratory arrest. She was given emergency medical care and her vital signs stabilized. However, she remained unconscious with no spontaneous breathing. The India ink method detected the presence of *Cryptococcus* in the patient's CSF (Fig. 1C). CSF and serum cryptococcal antigen tests were also positive, and *Cryptococcus neoformans* was detected in the patient's blood and CSF cultures. The patient was treated with liposomal amphotericin-B (250 mg/day) and flucytosine (1,500 mg/day), and CSF drainage was performed to reduce the CSF pressure. However, despite these treatments, the patient remained unconscious and died 17 days after admission.

Discussion

The presentation of cryptococcosis was nonspecific and mimicked that of other common entities, both infectious and

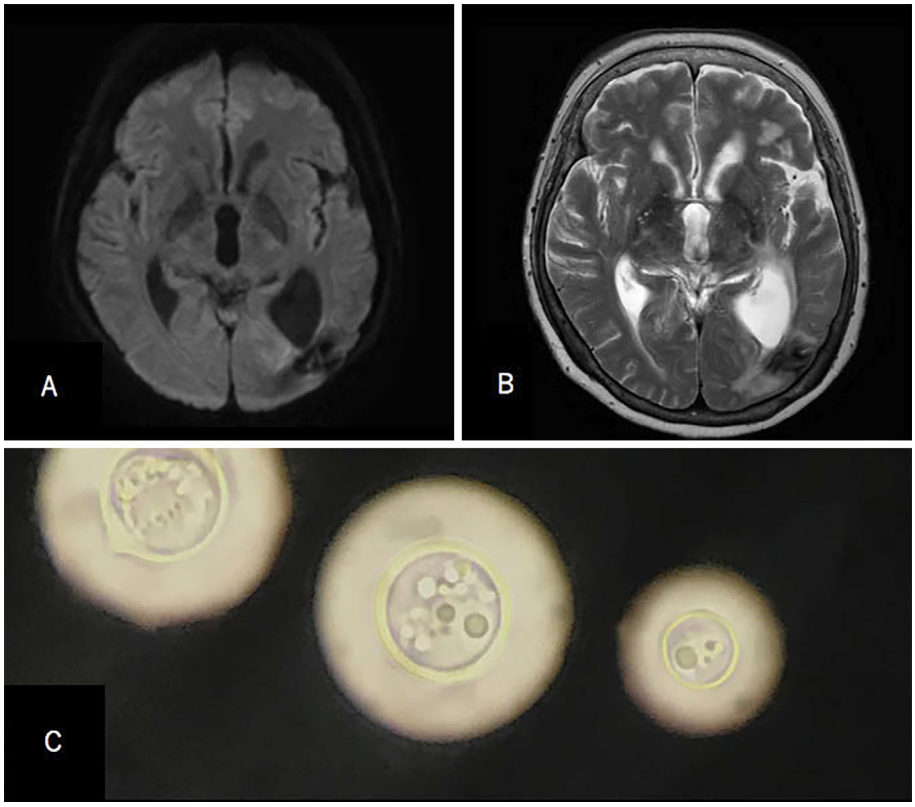
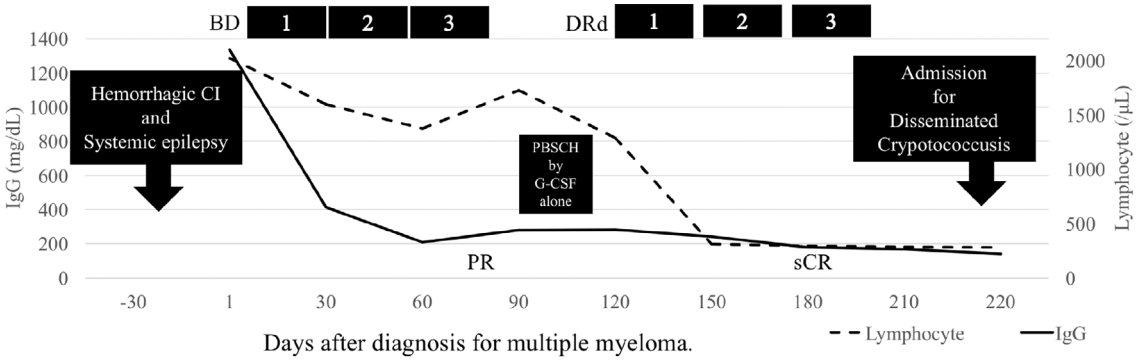


Figure 1. **A) B) Brain magnetic resonance imaging revealed previous hemorrhagic cerebral infarction. C) India ink method of cerebrospinal fluid was positive.**



BD: Bortezomib and Dexamethazone, DRd: Daratumumab, lenalidomide and dexamethazone,
CI: Cerebral infarction, PR: partial response, sCR: stringent complete response.
PBSCH: peripheral blood stem cell hervest, G-CSF: granulocyte-colony stimulating factor

Figure 2. **Transitive graph of IgG and lymphocyte count during treatment with BD and a DRd regimen.**

noninfectious (10). Typical symptoms of cryptococcal meningitis include headache, fever, and neck stiffness. Although these symptoms do not occur in many cases, atypical symptoms, such as disturbance of consciousness, personality disorder, and changes in character, may occur (10). This patient had a past medical history of hemorrhagic cerebral infarction and symptomatic epilepsy; she was suspected to have recurrent symptomatic epilepsy, as she was lethargic and experienced seizure attacks. She had no fever, and laboratory studies showed no signs of inflammation. Since she remained in a somnolent state, we decided to perform a lumbar puncture. Based on the results, the patient was diagnosed with cryptococcal meningitis. In this patient, an immunosuppressive state, MM, DRd treatment, hypogammaglobinemia and severe lymphopenia might have contributed to cryptococcal infection. The international standard induction treatment for cryptococcal meningitis prescribes 2 weeks of liposomal amphotericin B (3-4 mg/kg/day, intravenously) plus flucytosine (100 mg/kg/day); if the CSF pressure is ≥25 cm of CSF and there are symptoms of increased

intracranial pressure during induction therapy, CSF drainage should be performed to reduce the pressure by 50% or to a normal pressure of ≤20 cm of CSF (11, 12). She was treated according to this protocol.

Daratumumab is a human immunoglobulin monoclonal antibody that targets CD38 and which causes myeloma cell death through multiple mechanisms (13). CD38 is ubiquitously expressed on myeloma cells (14, 15) and other immune cells, including normal plasma cells, myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and regulatory B cells (Bregs) (16, 17). It is also expressed at relatively low levels on normal lymphoid and myeloid cells (18). Krejcik et al. reported that treatment with daratumumab caused a reduction in the immunosuppressive function of MDSCs, Tregs, and Bregs. Thus, in both peripheral blood and bone marrow, daratumumab induced significant increases of T cells and increased CD8:CD4 and CD8:Treg ratios (19). Van de Donk et al. also reported that the proportion of T cells preferentially increased in deep treatment responders, which is correlated with a higher CD8/CD4 T cell ratio (20). However, these results were different from our case. In the phase 3 trial of DRd treatment and the daratumumab plus bortezomib and dexamethasone (DBd) regimen, the rates of lymphopenia were reported to be 6.0% and 13.2%, respectively; lymphopenia also occurred in patients who were treated with daratumumab (5, 21). Until now, the mechanism through which lymphopenia occurs in patients treated daratumumab was not known. The CD38 expression in Tregs, Bregs, and another lymphocytes may be diverse in each MM patient. We would be interested to learn whether it does not increase the lymphocyte count in all cases, especially in deep responders. Immunomodulatory drugs (IMiDs) led to the upregulation of CD38 on myeloma cells (22) and Tregs (23); the expression rate of CD38 may change according to the previous lines of therapy. In this case, we hypothesized that the CD38 expression in T cells was upregulated by lenalidomide, and that it was more susceptible to daratumumab. As a result, lymphopenia may have occurred as a serious adverse event.

Although our patient had an sCR after three cycles of DRd treatment, severe lymphopenia occurred from the beginning of daratumumab treatment, and the lymphopenia did not resolve; furthermore, the number of CD8 (+) T cells decreased. Additional studies must be conducted to examine the effects of daratumumab on lymphocytes.

In our case, severe hypogammaglobinemia was also noted. CD38 is expressed by normal plasma cells because daratumumab directly targets normal plasmacytic CD38; daratumumab may cause a reduction in the production of immunoglobulins. Intravenous immunoglobulin therapy may be considered for hypogammaglobinemia, which occurred in our patient, to prevent infection.

As in our case, cryptococcal infection in MM patients with a small number of previous lines of therapy is rare. Disseminated cryptococcosis should be considered in patients with MM treated with daratumumab who have psychological symptoms, such as lethargy and seizure, especially if lymphocytopenia, a decreased CD4 cell count, or severe hypogammaglobinemia are observed. Regular monitoring of the CD4 cell counts and the gammaglobulin level is warranted in patients treated with daratumumab. Hematologists and general practitioners should be aware of the risk of opportunistic cryptococcal infection when encountering patients treated with daratumumab.

The authors state that they have no Conflict of Interest (COI).

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