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Case report

Nocardia intracranial mycotic aneurysm associated with proteasome inhibitor

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ABSTRACT

We report a case of *Nocardia farcinica* ruptured intracranial mycotic aneurysm associated with bortezomib and corticosteroid treatment in a multiple myeloma patient. The patient was treated with trimethoprim-sulfamethoxazole and moxifloxacin together with surgical repairment of intracranial mycotic aneurysm.

Introduction

Invasive nocardiosis is common among patients with cellular immune defect (e.g., diabetes, acquired immune deficiency syndrome [AIDS]). Delays in diagnosis may be responsible for treatment failure and poor prognosis, while mortality rate can be estimated up to 60% [1]. In the past decade, treatment with proteasome inhibitors has shown a favorable impact on mortality among multiple myeloma patients [2]. The medications inhibit the ubiquitin-proteasome pathway affecting both cellular and humoral immunity [3]. Bortezomib, a proteasome inhibitor in combination regimens, has been reported to be associated with reactivation of herpetic group viruses as well as a variety of bacterial pathogens [4,5]. Nocardiosis associated with proteasome inhibitor has been rarely reported. We report the first case of *Nocardia farcinica* manifesting as a ruptured intracranial mycotic aneurysm associated with bortezomib and corticosteroid treatment in a multiple myeloma patient.

Case report

A 69-year-old Thai patient with multiple myeloma had been on a chemotherapy regimen including bortezomib (1.3 mg/m^2), lenalidomide (25 mg), and dexamethasone (40 mg) repeated every 3 weeks. He was admitted for treatment of community-acquired pneumonia complicated by a thoracic empyema due to extremely-drug resistant (XDR) *Acinetobacter baumannii* requiring intercostal drainage (ICD) replacement. Meropenem and colistin were empirically initiated. Gram's stain of the ICD discharge revealed no organisms. Eighteen hours after admission, he developed alteration of consciousness with grade 3/5 right upper and lower extremity weakness. Emergency computerized tomography (CT) scan of the brain showed subarachnoid hemorrhage and multiple scattered small rim-enhancing lesions (Fig. 1A). CT angiogram of the brain revealed lobulated saccular outpouching lesion at the left middle carotid artery, suggestive of a ruptured mycotic aneurysm (Fig. 1B).

The patient underwent emergency clipping of the aneurysm which revealed necrotic aneurysm and thrombus occlusion at the left middle cerebral artery. The modified acid-fast staining of the aneurysm and thrombus revealed beaded branching organisms (Fig. 1C). The patient was started on intravenous trimethoprim-sulfamethoxazole (TMP-SMX, 15 mg/kg/day) and ceftriaxone (4 g/day). All immunosuppressants including bortezomib and

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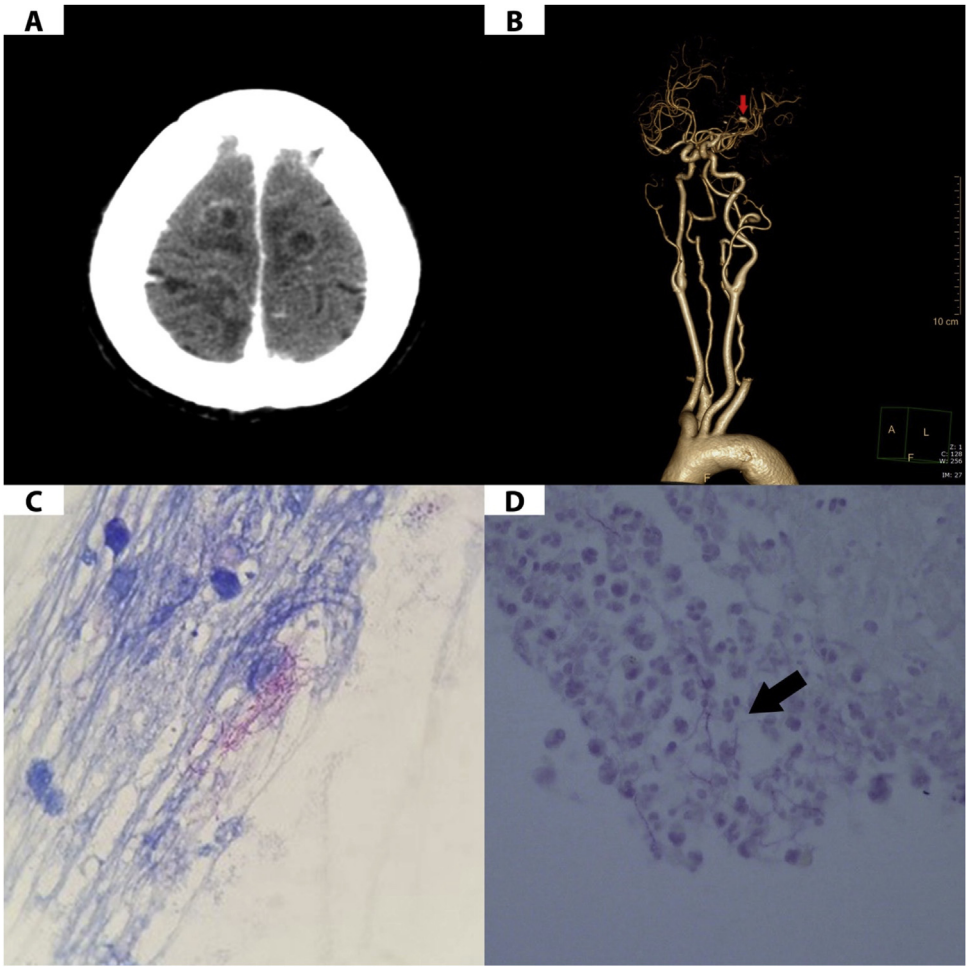

Fig. 1. (A) Computed tomography of the brain with contrast showed multiple small rim-enhancing lesions with marked perilesional vasogenic edema scattered at the gray and white junction of the bilateral cerebral hemisphere. (B) Computed tomography angiography of the brain showed a lobulated saccular outpouching lesion arising from the anterior branch at M2 segment of the left middle carotid artery (red arrow). (C) A modified acid-fast staining of the pus from the right chest wall showed beaded filamentous branching organisms with few white blood cells. (D) Gram's staining of thrombus inside the aneurysm showed few clusters of Gram-positive filamentous bacilli (arrow).

dexamethasone were discontinued. Histopathological findings revealed presence of thrombus and a few clusters of Gram-positive filamentous bacilli (Fig. 1D). On day 5 after incubation, the aerobic bacterial cultures from the aneurysm wall, thrombus and pus discharge grew chalky white colonies and changed to yellow colonies on sheep blood media (Oxoid Limited, France) and chocolate media (Oxoid Limited, France) consistent with *Nocardia* spp. The isolate was further identified by 16 s rRNA sequencing (BIONEER Corp., Korea) of the first 500 bp as *Nocardia farcinica*. The antimicrobial susceptibility test by broth microdilution method revealed susceptibility of the organism to TMP-SMX (MIC 2 ug/mL), moxifloxacin (MIC $\leq$ 0.25 ug/mL), and resistance to ceftriaxone (MIC > 64 ug/mL). The treatment regimen was changed to TMP-SMX (15 mg/kg/day) and moxifloxacin (400 mg/day). The patient

Table 1
Clinical features of previously published cases of Nocardia infection in MM patients received proteasome inhibitor and dexamethasone.

Case no.	Age/ sex	Underlying conditions	Chemotherapy regimen	Clinical presentation	Site of infection	*Nocardia* spp.	Treatment regimen	Outcomes	Reference
1	61/F	MM	Cyclophosphamide, bortezomib, dexamethasone	Seizure	CNS (abscesses)	*Nocardia cyriacigeorgica*	Meropenem then oral amoxicillin-clavulanic acid	Survived	Pamukçuoğlu et al. [8]
2	60/F	MM	Cyclophosphamide, bortezomib, dexamethasone	Dysarthria, and gait disturbance	CNS (abscesses)	*Nocardia cyriacigeorgica*	Imipenem/cilastatin then TMP-SMX	Survived	Pamukçuoğlu et al. [8]
3	71/ M	MM	Lenalidomide, carfilzomib, dexamethasone	Fever, tachypnea, decreased breath sound right mid-lower lung zones	Pulmonary	*Nocardia abscessus*	TMP-SMX and meropenem then TMP-SMX and minocycline	Recurrent /survived	Mendonca et al. [9]
4	69/ M	MM	Lenalidomide, bortezomib, dexamethasone	Fever, dyspnea, alteration of consciousness, right side weakness	Pulmonary, CNS (abscesses, mycotic aneurysm)	*Nocardia farcinica*	TMP/SMX and Moxifloxacin	Survived	Our case

CNS, central nervous system; MM, multiple myeloma; TMP-SMX, Trimethoprim-sulfamethoxazole.

recovered from infection and was discharged on hospital day 28 with oral TMP-SMX and moxifloxacin. At 12 months into treatment, the infection had been completely resolved without complications.

Discussion

Cerebral nocardiosis occur nearly 20% in pulmonary nocardiosis, usually manifests with signs and symptoms of increased intracranial pressure. The symptoms tend to be more indolent than bacterial brain abscesses. Thus, brain imaging should be considered in all patients with pulmonary nocardiosis [6]. Meningitis and central nervous system (CNS) mycotic aneurysm are far less common manifestations of CNS nocardiosis [7]. In a previous report [8,9], 3 patients with multiple myeloma who had received bortezomib and dexamethasone presented with CNS and/or pulmonary nocardiosis (Table 1). In all cases, the nocardiosis treatment was adjusted according to antimicrobial susceptibility test. The novel therapeutic agents for multiple myeloma, proteasome inhibitors such as bortezomib and carfilzomib have been reported to reduce the effects of T cells, B cells, NK cells and dendritic cells on host response system [10]. Bortezomib treatment was associated with an increased incidence of herpes zoster reactivation as compared to high-dose dexamethasone [4]. Furthermore, infections with a variety of bacterial pathogens including *Pseudomonas aeruginosa*, *Streptococcus* spp., Enterobacteriaceae [4] had been reported to be associated with bortezomib. In our case, corticosteroid use in the combination treatment for multiple myeloma might have increased the risk of nocardiosis [11].

The diagnosis of nocardiosis is based on the identification of *Nocardia* spp. from the infected sites. Gram staining and modified acid-fast staining are commonly used for initial identification of *Nocardia* spp. [12]. Cultures for *Nocardia* spp. can grow on most nonselective media and require a minimum of 48 to 72 h to several weeks before colonies are evident. The colonies morphology of *Nocardia* is variable [13]. In this case, the colony turned orange on day 6 and had a cotton ball representing abundant aerial filaments. These findings were consistent with *N. farcinica*. Although DNA sequencing is currently the best tool for species identification of *Nocardia.,* sequencing of first 500–606 base pairs of the 5′-end of the 16S rRNA gene is the recommended and feasible method [14]. The current recommended antimicrobial susceptibility testing to guide definite antimicrobial regimen is broth microdilution [15].

Most of *Nocardia* species that cause human infection are likely to be susceptible to TMP-SMX and linezolid. Thus, the recommended empirical antimicrobial is TMP-SMX based regimen while definite regimens are to be adjusted according to the susceptibility results. *N. farcinica* isolates have been reported commonly resistant to TMP-SMX and ceftriaxone. For definite treatment of pulmonary and CNS nocardiosis, recommended regimens should consist of an antimicrobial with good penetration to the lung tissues and blood-brain barrier. These antimicrobials include TMP-SMX, ceftriaxone, meropenem, and fluoroquinolone. Combination treatment with TMP-SMX-based regimen improves survival [16]. After identification of *N. farcinica*, the treatment with combined TMP-SMX and ceftriaxone was changed to TMP-SMX and moxifloxacin. The duration of treatment is generally prolonged for at least 12 months after the discontinuation of immunosuppressive agents to minimize risk of relapse [16]. Although the prognosis of disseminated nocardiosis is poor, combination treatment with TMP-SMX and moxifloxacin for 12 months have been used successfully in our patient.

In conclusion, we report a case of disseminated nocardiosis manifest with an intracranial mycotic aneurysm as an infectious complication of bortezomib and corticosteroid combination treatment. Early recognition for the pathogen and appropriate identification of *Nocardia* spp. are crucial to help guide for appropriate treatment to improve patient survival.

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Author contribution

Dr. Thana Khawcharoenporn contributed to collecting case data, writing the manuscript, and reading and approving the final version of the manuscript.

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Declaration of Competing Interest

The authors have no conflict of interest to declare.

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