Case report

Nocardia intracranial mycotic aneurysm associated with proteasome inhibitor

Siriththin Chansirikarnjana\textsuperscript{a}, Anucha Apisarnthanarak\textsuperscript{a,b}, Nuntra Suwantarat\textsuperscript{a,c}, Pansachee Damronglerd\textsuperscript{a,b}, Sasinuch Rutjanawech\textsuperscript{a,b}, Suttichai Visuttichaikit\textsuperscript{a}, Thana Khawcharoenporn\textsuperscript{a,b,*}

\textsuperscript{a}Thammasat University Hospital, Pathumthani, 12120, Thailand
\textsuperscript{b}Division of Infectious Diseases, Faculty of Medicine, Thammasat University, Pathumthani, 12120, Thailand
\textsuperscript{c}Chulabhorn International College of Medicine, Thammasat University, Pathumthani, 12120, Thailand

\textbf{A R T I C L E  I N F O}

Article history:
Received 13 June 2019
Received in revised form 16 July 2019
Accepted 16 July 2019

\textbf{Keywords:}
Nocardia
Nocardia farcinica
Mycotic aneurysm
Multiple myeloma
Proteasome inhibitor

\textbf{A B S T R A C T}

We report a case of \textit{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.

© 2019 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

\section*{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 \textit{Nocardia farcinica} manifesting as a ruptured intracranial mycotic aneurysm associated with bortezomib and corticosteroid treatment in a multiple myeloma patient.

\section*{Case report}

A 69-year-old Thai patient with multiple myeloma had been on a chemotherapy regimen including bortezomib (1.3 mg/m\textsuperscript{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) \textit{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
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 16S 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 μg/mL), moxifloxacin (MIC ≤ 0.25 μg/mL), and resistance to ceftriaxone (MIC > 64 μg/mL). The treatment regimen was changed to TMP-SMX (15 mg/kg/day) and moxifloxacin (400 mg/day). The patient

| 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) | *N. cyriacigeorgica* | Meropenem then oral amoxicillin-clavulanic acid Imipenem/cilastatin then TMP-SMX | Survived | | Pamukçuğoğlu et al. [8] |
| 2        | 60/F MM | Cyclophosphamide, bortezomib, dexamethasone | Dysarthria, and gait disturbance | CNS (abscesses) | *N. cyriacigeorgica* | Meropenem then oral amoxicillin-clavulanic acid Imipenem/cilastatin then TMP-SMX | Survived | | Pamukçuğoğlu et al. [8] |
| 3        | 71/M MM | Lenalidomide, carfilzomib, dexamethasone | Fever, tachypnea, decreased breath sound right mid-lower lung zones | Pulmonary | *N. abscessus* | TMP-SMX and meropenem then TMP-SMX and minocycline | Recurrent | | Mendonça et al. [9] |
| 4        | 69/M MM | Lenalidomide, bortezomib, dexamethasone | Fever, dyspnea, alteration of consciousness, right side weakness | Pulmonary, CNS (abscesses, mycotic aneurysm) | *N. 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) myotic 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] have 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 definitive 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 myotic 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.

Funding

No funding received.

Ethical approval

Ethical approval was not required.

Author contribution

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

Dr. Anucha Apisarnthanarak contributed to writing the manuscript and reading and approving the final version of the manuscript.

Dr. Nuntra Suwantaarat contributed to writing the manuscript and reading and approving the final version of the manuscript.

Dr. Pansachee Damronglerd contributed to writing the manuscript and reading and approving the final version of the manuscript.

Dr. Suttichai Visutticaikit contributed to writing the manuscript and reading and approving the final version of the manuscript.

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

Dr. Sasinuch Rutjanaewech contributed to writing manuscript and reading and approving the final version of the manuscript.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

References

[1] Kandi V. Human nocardiosis infections: a review of pulmonary nocardiosis. Cureus 2015;7. doi: http://dx.doi.org/10.7759/cureus.304.e304.
[2] Nucci M, Anaisse E. Infections in patients with multiple myeloma in the era of high-dose therapy and novel agents. Clin Infect Dis 2009;49:1211–25. doi: http://dx.doi.org/10.1086/605564.
[3] Pellom ST, Dudimah DF, Thounaojaim MC, Sayers TJ, Shanker A. Modulatory effects of bortezomib on host immune cell functions. Immunotherapy 2015;7:1011–22. doi: http://dx.doi.org/10.2217/imm.15.66.
[4] Laubach JP, Mitsiades CS, Hideshima T, Schlossman R, Chauhan D, Munshi N, et al. Bortezomib in the management of multiple myeloma. Cancer Manag Res 2009;1:107–17.
[5] Valkovic T, Gaćć V, Ivandic J, Petrov B, Dobrila-Dintinjana R, Dadić-Hero E, et al. Infections in hospitalised patients with multiple myeloma: main characteristics and risk factors. Turk J Haematol 2015;32:234–42. doi: http:// dx.doi.org/10.4274/tjh.2013.0173.
[6] Anagnostou T, Arvanitis M, Pourkoumpetis TK, Desalernos A, Carneiro HA, Mylonakis E. Nocardiosis of the central nervous system: experience from a general hospital and review of 84 cases from the literature. Medicine (Baltimore) 2014;93:19–32. doi: http://dx.doi.org/10.1097/ MD.0000000000000012.
[7] Farran Y, Antony S. Nocardia abscessus-related intracranial aneurysm of the internal carotid artery with associated brain abscess: a case report and review of the literature. J Infect Public Health 2016;9:358–61. doi: http://dx.doi.org/10.1016/j.jiph.2015.11.009.
[8] Pamukçuoglu M, Emmez H, Tunçan OG, Oner AY, Carik MY, Senol E, et al. Brain abscess caused by Nocardia cyriacigeorgica in two patients with multiple myeloma: novel agents, new spectrum of infections. Hematology 2014;19:158–62. doi: http://dx.doi.org/10.1179/1007845413Y.00000000000108.
[9] Mendonca NP, Kadayakakka DK, Forde IC, Rudkovskaia A, Saul ZK, Lobo DJ. Pulmonary nocardiosis in a multiple myeloma patient treated with proteasome inhibitors. Am J Case Rep 2016;17:76–9.
[10] Briizi K, Hines EM, McGowan KL, Shah SS. Diagnostic accuracy of cerebrospinal fluid gram stain in children with suspected bacterial meningitis. Pediatr Infect Dis J 2012;31:195–7. doi: http://dx.doi.org/10.1097/ INF.0b013e31823ad7be.
[11] Martínez Tomás R, Menéndez Villanueva R, Reyes Calzada S, Santos Durantez M, Vallés Tarazona JM, Modesto Alapont M, et al. Pulmonary nocardiosis: risk factors and outcomes. Respirology 2007;12:394–400, doi:http://dx.doi.org/10.1111/j.1440-1843.2007.01078.x.

[12] Shariff M, Gunasekaran J. Pulmonary nocardiosis: review of cases and an update. Can Respir J 2016;2016:4, doi:http://dx.doi.org/10.1155/2016/7494202.

[13] Brown-Elliott BA, Brown JM, Conville PS, Wallace Jr. RJ. Clinical and laboratory features of the Nocardia spp. based on current molecular taxonomy. Clin Microbiol Rev 2006;19:259–82, doi:http://dx.doi.org/10.1128/CMR.19.2.259-282.2006.

[14] Hasegawa T, Gono T, Ito J, Kogure T, Yazawa K, Mikami Y. Identification of Nocardia farcinica by a PCR primer amplifying a specific DNA band for the bacterium. Nihon Ishinkin Gakkai Zasshi 2007;48:173–5.

[15] Clinical Laboratory Standards Institute. Susceptibility testing of mycobacteria, Nocardia spp., and other aerobic actinomycetes. CLSI standard M24. 3rd edition Wayne, PA: Clin Lab Stand Inst; 2018.

[16] Wilson JW. Nocardiosis: updates and clinical overview. Mayo Clin Proc 2012;87:403–7, doi:http://dx.doi.org/10.1016/j.mayocp.2011.11.016.