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Case Report

Widespread nocardiosis in a patient with refractory ANCA-associated vasculitides: relapse or mimics? A case report and literature review

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Abstract: Immunocompromised patients are at high risk of *Nocardia,* however infection in these patients can also mimic relapsed or refractory autoimmune disease and that make diagnosis difficult. Herein is described a 60-year-old male diagnosed with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) who presented with fever, short of breath, cough, headache, and a subcutaneous mass in his right forearm after 3 months therapy with full-dose oral corticosteroid and intravenous cyclophosphamide. Given that the currently available laboratory tests and associated imaging features are nonspecific, it was quite difficult to differentiate between a recurrence of the patient's AVV and infection as a complication. The patient was finally diagnosed with systemic nocardiosis base on a subcutaneous abscess puncture fluid culture after 3 weeks of hospitalization. Trimethoprim-sulfamethoxazole (TMP-SMX) was administered while the steroid was tapered, after which the patient's systemic manifestations gradually resolved. A literature review identified 24 cases of nocardiosis as a complication of systemic vasculitis was performed. Male patients with systemic vasculitis (especially AAV or Behcet's disease) aged ≥ 60 years who were treated with corticosteroid in conjunction with or without immunosuppressant therapy were at high risk of *Nocardia* infection. Although cases can simultaneously have multiple systems involved and elevated inflammation indexes, it might be helpful to take a detailed disease history and check for evidence of abscesses. Moreover, clinical suspicion combined with repeated tissue biopsy and bacteria culture should be encouraged because making the correct diagnosis as soon as possible will lead to better prognosis.

Keywords: *Nocardia*, nocardiosis, systemic vasculitis, anti-neutrophil cytoplasmic antibody-associated vasculitis, corticosteroid, immunosuppressant, inflammation, infection, diagnosis, trimethoprim-sulfamethoxazole

Introduction

The genus *Nocardia* is a ubiquitous group of environmental bacteria that usually induce an opportunistic infection in immunocompromised hosts [1]. Recent reports have shown an increase in the incidence of infections due to *Nocardia* spp., probably due to a higher degree of clinical suspicion and the use of more aggressive treatments for other conditions (e.g., corticosteroid, chemotherapeutic agents and immunosuppression for organ transplantations) [2, 3], as well as the appearance of acquired immunodeficiency syndrome [4]. Patients with systemic vasculitis are always treated with high-dose corticosteroid and immunosuppressants. During this period, some systemic vasculitis patients could be exposed to infections by a variety of pathogens, including *Nocardia*. Despite the similar clinical manifestations of both *Nocardia* infection and the active condition of systemic vasculitis, the management of these two diseases is very different. Determining the different features of these conditions such that the correct diagnosis can be made is very important for improving the prognoses of both. Here, a case of systemic nocardiosis with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is described with a presentation that mimicked the active stage of AAV. A review of all similar cases reported in English is also included.

Case report

A 60-year-old Chinese male was admitted to our hospital in July 2011 because of swelling

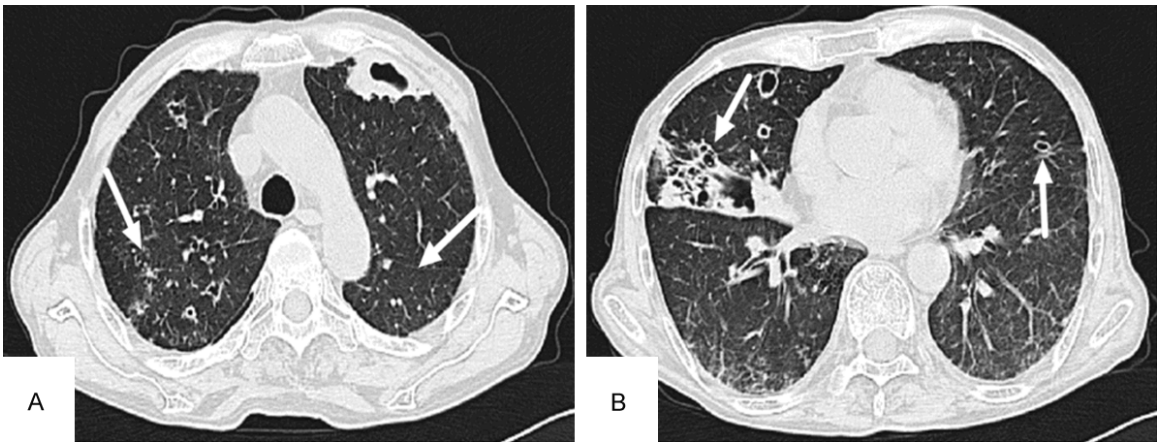

Figure 1. HRCT of the patient's chest on week after admission. Multiple lesions of cavitation lesions (B, arrows) and small nodules (A, arrows) are visible in both lungs.

and pain with both shins, headache, numbness in his toes, and a fever lasting for 2 weeks. Three months previously, he had been diagnosed with AAV based on muscle pain, fever, peripheral neuritis, interstial lung disease, proteinuria with markedly elevated perineuclear-type anti-neutrophil cytoplasmic antibodies (pANCA 1:40, IIF), and increased myeloperoxidase levels of 200 IU/mL (normal level: < 30 IU/ml as assessed by ELISA). At that time, methylprednisolone (mPSL) with an initial dose of 80 mg daily was then administered for 10 days, followed by 60 mg of oral prednisone daily along with intravenous cyclophosphamide (0.6 g per month for 2 months). The majority of his AVV symptoms were improved quickly, and the prednisone treatment was gradually tapered to 35 mg daily for 1 week.

Two weeks before the patient's admission, he had suffered from a relapse of fever, headache, short of breath, and he had many rashes along the neck area and shins as well as erythema on his right forearm. Upon admission, his body temperature was 37.9°C with a pulse rate of 99 bpm and blood pressure of 121/70 mmHg. Inspiratory and expiratory crackles were heard in both sides of lower lungs. The patient was slightly positive for signs of meningeal irritation but was negative for bilateral Babinski's signs. Laboratory tests revealed increased white blood cell count (12,400/μL), increased erythrocyte sedimentation rate (ESR) (37 mm/h), and increased level of C-reactive protein (CRP) (148.3 mg/L), compared with normal levels. Urine analysis results showed a slight proteinuria with 620 mg/24 h and hematuria with 30/Hp. His serum creatinine level and liver function were still normal. Blood bacterial and fungal cultures from both hands (performed 3 times each) were all negative, and pANCA showed 1:40 positive with myeloperoxidase (MPO) (220 IU/ul). A biopsy of the rashes on his lower extremities revealed nonspecific inflammatory changes. Antibiotic therapy, including moxifloxacin, azithromycin and ceftriaxone, were administrated for 1 week with no response.

Because of the multiple cavitation lesions and small nodules in both lungs detected by high-resolution computed tomography (HRCT) of the chest (**Figure 1A** and **1B**), a lung puncture was also performed, and the corresponding histologic examination showed something resembling *Aspergillus* hypha in the necrotic tissue. A lumbar puncture was also performed, which revealed a normal cerebrospinal fluid (CSF) pressure (120 mmH_2O) with a white blood cell count of 28×10^6 cells/L (neutrophilic granulocyte: 20%, lymphocyte: 80%). Another puncture of the subcutaneous mass in the patient's right forearm was performed, and the resulting smear showed only some inflammatory cells that were mostly neutrophils, without any microorganisms detected. The administered antibiotic was changed to caspofungin, but the patient did not respond to this drug either.

Because of the patient's severe headache and altered state of consciousness without any positive finding via brain MRI, a repeated lumbar puncture was performed, and it revealed that the white blood cells count had further increased to 290×10^6 cells/L (neutrophils:

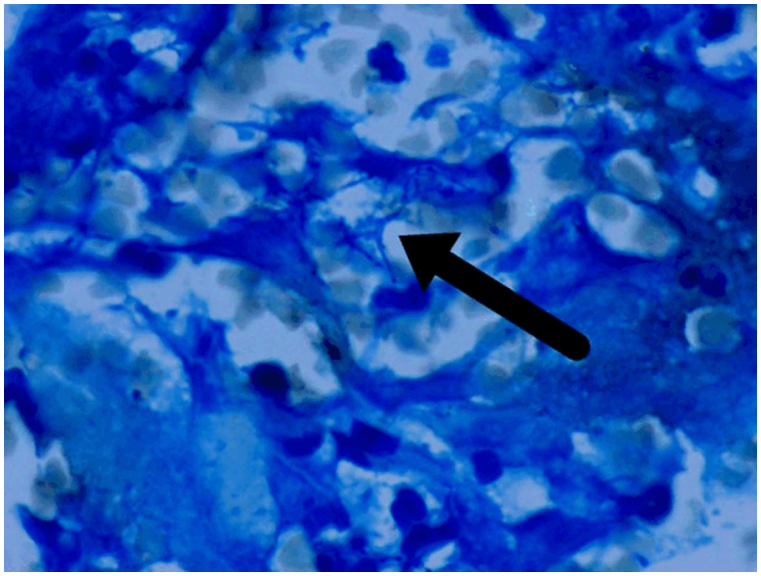

Figure 2. Histopathological findings of pus culture revealed filamentous branching rods, which was Nocardia brasiliensis (acid-fast stain, oil microscopy ×100) (arrow).

90%, lymphocytes: 10%). Thus, AAV with infectious disease including intracranial infection was considered to be the most likely diagnosis, and the patient was given 60 mg of methylprednisonelone intravenously. Finally, a repeated puncture of the subcutaneous mass in his right forearm was performed, and the culture of the puncture fluid was positive for *Nocardia brasiliensis* (**Figure 2**). Trimethoprim-sulfamethoxazole (TMP-SMX) (1280 mg + 6400 mg/d) was then added to the patient's drug regimen, and voriconazole was switched to ceftriaxone. His symptoms of fever, headache, subcutaneous mass in the right forearm, and cough were gradually alleviated 1 week later. A third lumbar puncture was performed, which revealed a white blood cell count with 20×10^6 cells/L (neutrophils: 10%, lymphocytes: 90%).

After a sufficient dose of TMP-SMX therapy for 21 days, a low dose maintenance treatment (160 mg + 800 mg/d) was used for one year to prevent the recurrence of nocardiosis due to the patient's long-term therapy with glucocorticoid. A repeated chest HRCT 6 months later showed that the patient's lung cavitation and small nodules had improved markedly (**Figure 3A** and **3B**). At his most recent follow-up in October 2018, the patient felt very well, and he had been off all drugs and had no relapses.

Literature review

A systematic literature search was performed in PubMed using the subject terms "nocardiosis" and "vasculitis" to identify relevant articles from December 1949 through November 2018. The publication language was restricted to English. Review articles, articles with important information missing, and articles for which the full text was not found were excluded.

In total, 52 articles were identified by the search criteria, of which eight non-English articles, 21 articles that did not describe cases of nocardiosis in patients with systemic vasculitis, and one article lacking the full text were excluded from this review. Twenty-two articles [5-26] with comprehensive clinical and laboratory data from 24 patients were analyzed in detail, including the age of onset, gender, primary disease, symptoms, laboratory tests results, MRI, or CT images, treatment, and prognosis (**Table 1**).

Statistical analysis

Date were analysis with Microsoft Excel 2010. The age range of disease onset was from 19 to 83 years old, and the median age was 58.3 ± 19.2 years old. There were 13 patients whose onset age was ≥ 60 (54.2%). The ratio of males to females was 19:5. Of the total 24 cases, 9 had been diagnosed with AAV (37.5%) and 6 had been diagnosed with Behcet's disease (25%). Glucocorticoids were used in all patients, and immunosuppressants were administrated to 15 of them (62.5%). The disease activity of vasculitis was stable in majority cases at the time when they were diagnosed with *Nocardia* infection. The most commonly involved organs included lung (66.7%), brain (45.8%), skin (33.3%) and eyes (12.5%). Other areas, like testis, heart, pancreas, peritoneum, kidneys, thyroid, paranasal sinuses, and mastoid, were also reported to be involved [14, 24].

The most common clinical manifestations were mainly respiratory symptoms; they included

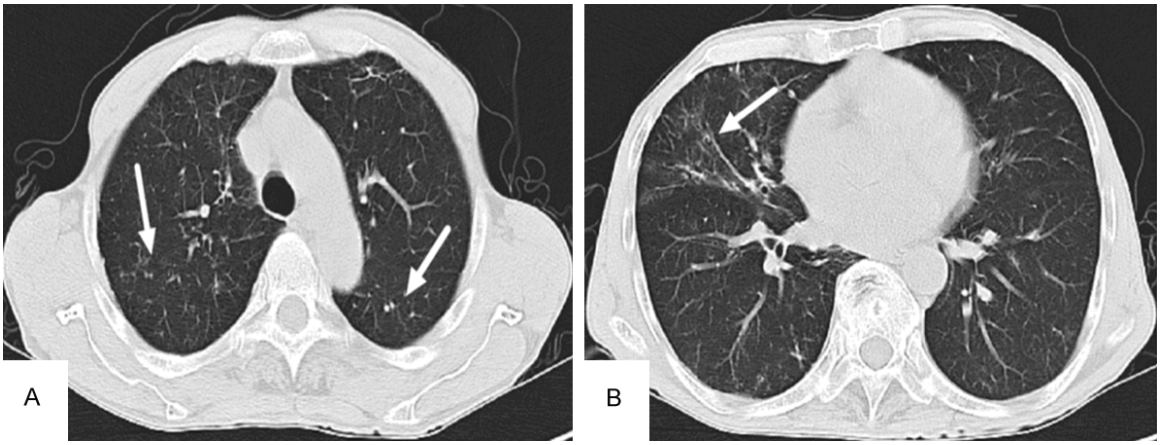

Figure 3. HRCT of the patient's chest six months after treatment with TMP-SMX. The cavitation lesions (B, arrow) and small nodules (A, arrows) had obviously lessened at this point.

Table 1. Summary of the clinical manifestations of norcardiosis in patient with systemic vasculitis

Clinical manifestations	No. of patients	Percentage (%)
Symptoms		
Fever	14	58.3
Cough	13	54.2
Short of breath	8	33.3
Subcutaneous mass/abscess	8	33.3
Sputum	7	29.2
Cchest pain	5	20.8
Fatigue	3	12.5
Night sweats	3	12.5
Neurological symptoms	3	12.5
Visual impairment	3	12.5
Hemoptysis	3	12.5
Weight loss	2	8.3
Nausea	2	8.3
Headache	2	8.3
Purulent drainage from ear and noses	1	4.2
Dysphagia and odynophagia	1	4.2
Buttock pain	1	4.2
Pelvic and scrotal pain	1	4.2
Altered states of consciousness	1	4.2
Orbital pain	1	4.2
Laboratory tests		
White blood cells (or neutrophil ratio) increased	14	58.3
C-reactive protein increased	11	45.8
Lymphocyte ratio decreased	8	33.3
Hemoglobin decreased	7	29.2
Erythrocyte sedimentation rate increased	6	25.0
Hematocrit decreased	4	16.7
Cd4 + t cell decreased	2	8.3
Affected areas		
Single	16	66.7

Multiple	8	33.3
Lung	16	66.7
Brain	11	45.8
Skin	8	33.3
Eye	3	12.5
Testis	1	4.2
Heart	1	4.2
Pancreas	1	4.2
Peritoneum	1	4.2
Kidney	1	4.2
Thyroid	1	4.2
Paranasal sinuses	1	4.2
Mastoid	1	4.2
Diagnostic methods		
Tissue culture by biopsy	20	83.3
Sputum culture/sputum smear	7	29.2
The universal 16s rrna gene pcr	3	12.5
Blood culture	1	4.2
MALDI-TOF MS	1	4.2
Species		
Nocardia asteroides	11	45.8
Nocardia farinica	5	20.8
Nocardia otitidiscaviarum	1	4.2
Nocardia pseudobrasiliensis	1	4.2
Nocardia concava	1	4.2
Unclassified	5	20.8
Therapy		
TMP-SMX	17	70.8
Minocyline	4	16.7
Imipenem	4	16.7
Ceftriaxone	4	16.7
Meropenem	3	12.5
Levofloxacin	3	12.5
Amikacin	2	8.3
Amoxicillin-clavulanic	2	8.3
Unknown	2	8.3
Prognosis		
Cure	19	79.2
Die	4	16.7
Unknown	1	4.2
Primary diseases		
ANCA associated systemic Vasculitis	9	37.5
Behcet's disease	6	25.0
Polymyalgia rheumatica/giant cell (temporal) arteritis	4	16.7
Leukocytoclastic vasculitis	2	8.3
Rheumatoid vasculitis	1	4.2
Unclassified vasculitis syndrome (polyarteritis nodosa was suspected)	1	4.2
Anaphylactoid purpura	1	4.2

fever (58.3%), cough (54.2%), shortness of breath (33.3%), sputum (29.2%) and chest pain (20.8%), and subcutaneous mass/abscess (33.3%). Laboratory tests of these patients always revealed that, compared with normal levels, the white blood cell count (or neutrophil ratio) was increased (58.3%), the lymphocyte ratio was decrease (33.3%), the hemoglobin level was decreased (29.2%), and the CRP (45.8%) and ESR levels were both increased (25%). Diagnosis was usually based on tissue culture of a biopsy (83.3%) and/or sputum culture (29.2%). Recently, 16s rRNA PCR [6, 16, 26] and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOFMS) [26] have been used to identify difficult cases. Of the 24 patients, there were 17 cases infected by members of *Nocardia asteroids* complex (70.8%), such as *N asteroides, Nocardia farcinica* and *Nocardia nova* complex. Two cases were diagnosed as being infected with *Nocardia otitidiscaviarum* [17] and *Nocardia pseudobrasiliensis* [6], respectively. Additionally, 70.8% of patients were treated with TMP-SMX; 18 of them (79.2%) were cured, but 4 patients (16.7%) died from various causes [14, 16, 21, 24].

Discussion

Nocardia is a well-known "opportunistic pathogen", with most infections occurring in patients who have immunosuppressive conditions. Patients with depressed cell-mediated immunity are at an especially high risk for infection with *Nocardia*, including those with lymphoma, other selected malignancies, human immunodeficiency virus infection, and solid-organ or hematopoietic stem cell transplant as well as those receiving long-term treatment with steroids or other medications that suppress cell-mediated immunity [28, 29]. As an autoimmune disease, systemic vasculitis is always treated aggressively with high-dose prednisone, and most patients also need combination therapy with immunosuppressants, such as cyclosphosphamide, azathioprine, cyclosporine, and methotrexate. Furthermore, it is quite difficult to differentiate a disease situation, such as *Nocardia* infection, from poor control of the underlying condition. Both conditions have the common symptoms of fever, rash, cough, shortness of breath, chest pain, abscess formation, and even headache. Abscess formation is a common clinical feature of nocardiosis, which includes pulmonary abscess, cerebral abscess, and subcutaneous abscess as the most common clinical manifestations. Although pulmonary nocardiosis is reported as the most common clinical presentation of *Nocardia* infection, concurrent cerebral and cutaneous nocardiosis have greater value for making the appropriate diagnosis. Kontoyiannis et al. [30] reported that 64% of patients had concurrent pulmonary nocardiosis, 28% had concurrent cutaneous disease, and 19% had concurrent CNS disease. More than one-third of the patients were found to have systemic vasculitis with multiple organs infected. For example, the patient whose case is reported above also had pulmonary, cerebral and cutaneous infection due to *Nocardia*.

Another issue requiring further research is whether certain species of *Nocardia* are more commonly associated with specific disease conditions. To date, more than 50 species of *Nocardia* have been described. Most of them belong to the *N. asteroides* complex group, which is responsible for most common clinical manifestations of nocardiosis [1]. Our patient was identified as being infected with *N. brasiliensis*, which has been reported as the most common *Nocardia* species in cutaneous disease (especially progressive and lymphocutaneous disease) [27]. To the best of our knowledge, this is the first case of *N. brasiliensis* infection in AAV.

Notably, it was challenging to diagnose nocardiosis in our case and doing so required repeated biopsies. Unlike other Gram-positive bacterium, *Nocardia* appears as a filamentous bacterium with hyphae-like branching on direct microscopy, which makes it easily confused with fungus [1]. Even though a lung biopsy and histopathology had been performed in this case, their results initially showed something resembling *Aspergillus* hypha in the necrotic tissue. Because patient with immunosuppressive conditions are also at high risk of contracting *Aspergillus* infection, caspofungin was administered initially. The lack of response to caspofungin helped in the determination that the observed hyphae belonged to *Nocardia*, rather than to *Aspergillus*. Thus hypha-like changes should also be differentiated from nocardiosis, especially in immunosuppressed patients. According to literature review, the majority of

nacadiosis cases were diagnosed with tissue culture of a biopsy; this indicates that performing more tissue cultures may be helpful in obtaining the appropriate diagnosis for refractory and difficult infectious patients. Therefore, pathologic evidence by biopsy should be obtained as much as possible and will usually need to be repeated several times.

This study showed that tissue culture of a biopsy was the most effective method for the diagnosis of nocardiosis. However, biopsies are invasive, and risk-effectiveness ratio should be evaluated before undertaking these procedures. Other methods, like sputum culture and blood culture, which are less risky and invasive, may be less likely to be positive but may be helpful to differentiating other diagnoses. Thus, in cases where the suspected diagnosis is nocardiosis, deciding how to test for it is the key point to making the correct diagnosis. Although pathogen examination is still the "gold standard" when bacterial infections are investigated, the technique is hampered by several factors, such as small volumes, antibiotic treatment, suboptimal incubation duration, and suboptimal growth medium. The universal 16S rRNA gene PCR and sequencing of the amplification has been used for identification of fast- and slow-growing and uncultured bacteria in different types of clinical samples [31-33]. There have been three reported cases that identified the infection-causing bacteria with this method; it was applied when the culture result was negative [16] or when there was difficulty regarding further clarification of pathogen [6, 26].

Nocardia displays variable *in vitro* and antimicrobial susceptibility patterns, and management of nocardial infections must be individualized [34]. *Nocardia* isolated from clinically significant infections should undergo antimicrobial susceptibility testing to assist in treatment decisions. Sulfonamides, including sulfadiazine and sulfisoxazole, have been the antimicrobials of choice to treat nocardiosis for the past 50 years despite having bacteriostatic rather than bactericidal activity [35]. TMP-SMX is the most commonly used sulfonamide preparation in the Uninted States, and it is active against most *Nocardia* species. Our patient as well as 69.6% of the patients we reviewed all took TMP-SMX. Alternative antimicrobial agents with activity against *Nocardia* include amikacin, imipenem, meropenem, ceftriaxone, cefotaxime, minocycline, moxifloxacin, levofloxacin, linezolid, tigecycline, and amoxicillin-clavulanic acid. For most forms of nocardiosis, initial combination drug therapy is recommended. Combination therapy with imipenem and cefotaxime, amikacin and TMP-SMX, imipenem and TMP-SMX, amikacin and cefotaxime, or amikacin and imipenem may provide enhanced activity [36]. In patients with CNS disease, therapy should include drugs with favorable CNS penetration (eg, TMP-SMX and ceftriaxone). Combination therapy should continue until clinical improvement occurs and *Nocardia* species identification and antimicrobial drug susceptibility information can be confirmed; single-drug therapy may suffice thereafter. The treatment duration is generally prolonged to minimize the risk of disease relapse. Immunocompetent patients with pulmonary or multifocal (non-CNS) nocardiosis may be successfully treated with 6-12 months of antimicrobial therapy, whereas immunosuppressed patients and those with CNS disease should receive at least 12 months of antimicrobial therapy with the appropriate clinical monitoring. This patient was an immunosuppressed patient with CNS involvement, so he received antimicrobial therapy of daily TMP-SMX for one year, and, as of the time of writing, had not presented with a relapse. Thus, therapy with TMP-SMX, initial combination drug therapy, and long treatment duration are the principles of successful nocardiosis treatment.

Among the nocardiosis patients in this study, there were four patients who eventually died, with one dying from acute myocardial infarction [16], and the other three from overwhelming infections [14, 21, 24]. Two of them died before diagnosis [14, 16], and three of them had multiple organ nocardiosis [14, 21, 24]. All of them had CNS disease. These findings suggest that multiple organ involvement and especially CNS disease predict the poor prognosis for nocardiosis but that earlier diagnosis and timely treatment may improve the prognosis.

Conclusion

A combination of respiratory symptoms, abscess formation, multiple organs involvement, and increased inflammation indexes in a patient with systemic vasculitis indicate a likely infection with *Nocardia*. However, these symptoms are similar to the original disease activity

and can be difficult to distinguish from a relapse. Repeated tissue biopsy and bacteria culture should be performed and this may allow an earlier correct diagnosis and lead to a positive outcome for these patients.

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Disclosure of conflict of interest

None.

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References

[1] John W. Wilson. Nocardiosis: updates and clinical overview. Mayo Clinic Proc 2012; 87: 403-407.

[2] Arduino RC, Johnson PC, Miranda AG. Nocardiosis in renal transplant recipients undergoing immunosuppression with cyclosporine. Clin Infect Dis 1993; 16: 505-512.

[3] Van Burik JA, Hackman RC, Nadeem SQ, Hiemenz JW, White MH, Flowers ME, Bowden RA. Nocardiosis after bone marrow transplantation: a retrospective study. Clin Infect Dis 1997; 24: 1154-1160.

[4] Bach MC, Sabath LD, Finland M. Susceptibility of Nocardia asteroids to 45 antimicrobial agents in vitro. Antimicrob Agents Chemother 1973; 3: 1-8.

[5] Sirisena D, Al Swedan L, Jayne D, Chakravarty K. A case of systemic nocardiosis in systemic vasculitis and a review of the literature. Singapore Med J 2013; 54: 127-130.

[6] Seol CA, Sung H, Kim DH, Ji M, Chong YP, Kim MN. The first Korean case of disseminated mycetoma caused by Nocardia pseudobrasiliensis in a patient on long-term corticosteroid therapy for the treatment of microscopic polyangiitis. Ann Lab Med 2013; 33: 203-207.

[7] Iwazu K, Iwazu Y, Takeda S, Akimoto T, Yumura W, Takahashi H, Ito C, Kanai K, Taniguchi N, Hirai Y, Kusano E. Successful treatment of serial opportunistic infections including disseminated nocardiosis and cryptococcal meningitis in a patient with ANCA-associated vasculitis. Intern Med 2012; 51: 3051-3056.

[8] Ilyas N, Fountzilas C. A cerebral mass in a patient with Churg Strauss syndrome. N Z Med J 2011; 124: 94-97.

[9] Kumar R, Chhina DK, Kaushal V, Mahajan R, Kaur H. Cytological diagnosis of pulmonary nocardiosis in an immunocompromised patient. Indian J Med Microbiol 2008; 26: 380-382.

[10] Tada Y, Fukuoka M, Mitamura M, Koarada S, Suematsu R, Inoue H, Ohta A, Nagasawa K. Nocardiosis in adult-onset Still's disease and vasculitis syndrome. Am J Med Sci 2008; 336: 77-80.

[11] Kusaka S, Ikuno Y, Ohguro N, Hori Y, Tano Y. Orbital infection following posterior subtenon triamcinolone injection. Acta Ophthalmol Scand 2007; 85: 692-693.

[12] Safdar N, Kaul DR, Saint S. Clinical problem-solving. Into the woods. N Engl J Med 2007; 356: 943-947.

[13] Sherber NS, Olivere JW, Martins CR. An 80-year-old man with a nonhealing glabellar lesion. Primary cutaneous nocardiosis. Arch Pathol Lab Med 2006; 130: 100-101.

[14] Héron E, Augustin P, Cervera P, Girmens JF, Généreau T, Lortholary O, Cabane J. Systemic nocardiosis mimicking an ocular relapse of giant-cell arteritis. Rheumatology (Oxford) 2006; 45: 641-643.

[15] Routh JC, Lischer GH, Leibovich BC. Epididymo-orchitis and testicular abscess due to Nocardia asteroides complex. Urology 2005; 65: 591.

[16] Sonesson A, Oqvist B, Hagstam P, Björkman-Burtscher IM, Miörner H, Petersson AC. An immunosuppressed patient with systemic vasculitis suffering from cerebral abscesses due to Nocardia farcinica identified by 16S rRNA gene universal PCR. Nephrol Dial Transplant 2004; 19: 2896-2900.

[17] Yoshida K, Bandoh S, Fujita J, Tokuda M, Negayama K, Ishida T. Pyothorax caused by Nocardia otitidiscaviarum in a patient with rheumatoid vasculitis. Intern Med 2004; 43: 615-619.

[18] Warnatz K, Peter HH, Schumacher M, Wiese L, Prasse A, Petschner F, Vaith P, Volk B, Weiner SM. Infectious CNS disease as a differential diagnosis in systemic rheumatic diseases: three case reports and a review of the literature. Ann Rheum Dis 2003; 62: 50-57.

[19] Auzary C, Du Boutin LT, Wechsler B, Chollet P, Piette JC. Disseminated nocardiosis present-

ing as a flare of Behçet's disease. Rheumatology (Oxford) 2001; 40: 949-952.
[20] Korkmaz C, Aydinli A, Erol N, Yildirim N, Akgtün Y, Inci R, Boiron P. Widespread nocardiosis in two patients with Behçet's disease. Clin Exp Rheumatol 2001; 19: 459-462.
[21] Pamuk GE, Pamuk ON, Tabak F, Mert A, Oztürk R, Aktuğlu Y. Systemic Nocardia infection in a patient with Behçet's disease. Rheumatology (Oxford) 2001; 40: 597-599.
[22] Shafiq M, Schoch PE, Cunha BA, Iliescu MD. Nocardia asteroides and Cryptococcus neoformans lung abscess. Am J Med 2000; 109: 70-71.
[23] Knox CM, Whitcher JP, Cevellos V, Margolis TP, Irvine AR. Nocardia scleritis. Am J Ophthalmol 1997; 123: 713-714.
[24] Venzor J, Hua Q, Bressler RB, Miranda CH, Huston DP. Behçet's-like syndrome associated with idiopathic CD4+ T-lymphocytopenia, opportunistic infections, and a large population of TCR alpha beta+ CD4- CD8- T cells. Am J Med Sci 1997; 313: 236-238.
[25] Holt RI, Kwan JT, Sefton AM, Cunningham J. Successful treatment of concomitant pulmonary nocardiosis and aspergillosis in an immunocompromised renal patient. Eur J Clin Microbiol Infect Dis 1993; 12: 110-112.
[26] Hirayama T, Takazono T, Horai Y, Tashiro M, Saijo T, Kosai K, Morinaga Y, Kurihara S, Nakamura S, Imamura Y, Miyazaki T, Tsukamoto M, Izumikawa K, Yanaqihara K, Kawakami A, Kohno S. Pulmonary nocardiosis caused by nocardia concave with a literature review. Intern Med 2016; 55: 1213-1217.
[27] Lerner PI. Nocardiosis. Clin Infect Dis 1996; 22: 891-903; quiz 904-905.
[28] Young LS, Rubin RH. Mycobacterial and nocardial disease in the compromised host. A Clinical Approach to Infection in the Compromised Host, 4th edition. In: Rubin RH and Young LS, editors. New York: Kluwer Academic; 2002. pp. 257-261.
[29] Long PF. A retrospective study of Nocardia infections associated with the acquired immune deficiency syndrome (AIDS). Infection 1994; 22: 362-364.
[30] Kontoyiannis DP, Ruoff K, Hooper DC. Nocardia bacteremia: report of 4 cases and review of the literature. Medicine (Baltimore) 1998; 77: 255-267.
[31] Goldenberger D, Künzli A, Vogt P, Zbinden R, Altwegg M. Molecular diagnosis of bacterial endocarditis by broad-range PCR amplification and direct sequencing. J Clin Microbiol 1997; 35: 2733-2739.
[32] Relman DA, Schmidt TM, MacDermott RP, Falkow S. Identification of the uncultured bacillus of Whipple's disease. N Engl J Med 1992; 327: 293-301.
[33] Rantakokko-Jalava K, Nikkari S, Jalava J, Eerola E, Skurnik M, Meurman O, Ruuskanen O, Alanen A, Kotilainen E, Toivanen P, Kotilainen P. Direct amplification of rRNA genes in diagnosis of bacterial infections. J Clin Microbiol 2000; 38: 32-39.
[34] Muñoz J, Mirelis B, Aragón LM, Gutiérrez N, Sánchez F, Español M, Esparcia O, Gurguí M, Domingo P, Coll P. Clinical and microbiological features of nocardiosis 1997-2003. J Med Microbiol 2007; 56: 545-550.
[35] McNeil MM, Brown JM, Hutwagner LC, Schiff TA. Evaluation of therapy for Nocardia asteroides complex infection: CDN/NCID report. Infect Dis Clin Pract 1995; 4: 287-292.
[36] Gombert ME, Aulicino TM. Synergism of imipenem and amikacin in combination with other antibiotics against Nocardia asteroides. Antimicrob Agents Chemother 1983; 24: 810-811.