Pulmonary Nocardiosis Associated with Idiopathic Thrombocytopenic Purpura

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Abstract

A 69-year-old woman with idiopathic thrombocytopenic purpura, who was regularly followed and treated with prednisolone and danazol, was admitted to our hospital because of shortness of breath. Chest roentgenogram showed a large amount of left-sided pleural effusion. Gram-positive branching rods, subsequently identified as Nocardia farcinica, were isolated from the fluid. Antibiotic treatment together with pleural drainage with an intercostal catheter resulted in complete remission of pyothorax. Pulmonary nocardiosis is a rare disease, but recognition of the disease in immunocompromised patients and the prompt initiation of appropriate treatments based on isolation of the pathogen can lead to a successful outcome.

(Key words: prednisolone, immunocompromised host, thrombocytosis, thrombopoietin, interleukin 6)

Introduction

Nocardia species are aerobic actinomycetes commonly found in the soil. Previous studies (1) have shown that nocardiosis occurs predominantly in immunocompromised patients such as those with hematological malignancies, those with collagen vascular diseases, and recipients of organ transplant, and that it sometimes causes a lethal outcome in these patients. The common site of the infection is the lung, although clinical manifestations are quite variable in each patient ranging from an insidious onset to an acute one resembling pulmonary infarction (2). Here, we report a patient with pulmonary nocardiosis, which was manifested by pyothorax during the follow-up period of idiopathic thrombocytopenic purpura (ITP) and successfully treated with imipenem/cilastacin (IPM/CS).

Case Report

A 69-year-old woman was diagnosed to have ITP based on purpuric spots, thrombocytopenia, increased megakaryocyte in her bone marrow, and positivity for platelet associated immunoglobulin in 1987. Prednisolone, azathioprine, anabolic steroids, high dose of intravenous gamma-immunoglobulin, and splenectomy had failed to improve her thrombocytopenia and the platelet count remained at about 10 to 30x10^9/μl. In June 1999, she complained of increased leg purpuric spots. Her platelet count dropped to 8x10^9/μl in spite of 10 mg/day of oral prednisolone and 200 mg/day of danazol. Then the dose of steroids was doubled. Thereafter her platelet count increased to around 20x10^9/μl.

On her visit at the end of September 1999, her platelet count rose to 126x10^9/μl, but we could not find any cause for this increase on physical examination or with her normal white blood cell (WBC) count. Two weeks later, she presented with shortness of breath and loss of appetite. The results of her physical examination were unremarkable except for a few rales at the left lung base. Her WBC count was 18.4x10^9/μl with marked neutrophilia (91%) and platelet count 160x10^9/μl. Biochemical analysis was unremarkable. C-reactive protein was 24.7 mg/dl. Fasting plasma glucose and hemoglobin A1c were 146 mg/dl and 6.8%, respectively. Chest roentgenogram revealed consolidate-like shadow in the left mid-lower lung field and massive left-sided pleural effusion (Fig. 1A). Chest CT showed the presence of the fluid encapsulated by irregularly thickened pleural membrane (Fig. 1B). Because of the prolonged use of steroids without prophylaxis, we suspected tuberculous pleuritis at the time of admission. She was treated with antituberculous agents and intravenous imipenem/cilastacin (IPM/CS) for concomitant bacterial infections. A therapeutic thoracentesis was performed, and Gram-positive branching rods, subsequently identified as Nocardia farcinica with biochemical methods, were found in the pleural fluid (Fig. 2). No mycobacterium was found and the result of polymerase chain reaction of M. tuberculosis was negative in the fluid; the antituberculous agents were then discontinued except for prophylactic dose of iso-
Pulmonary Nocardiosis and ITP

Figure 1. A) Chest roentgenogram at admission. Left-sided pleural effusion was found (black arrowheads). B) Chest CT at admission. Irregularly thickened pleural membrane was found to encapsulate the fluid (white arrowheads).

Figure 2. Gram stain of pleural fluid smear. Characteristic Gram-positive branching rods, subsequently identified as *Nocardiia farcinica*, were found (×1,000).

Table 1. Surface Markers and Function of Peripheral Blood Mononuclear Cells in This Case

<table>
<thead>
<tr>
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<th>Reference range</th>
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<tbody>
<tr>
<td>CD3</td>
<td>92.9% (60–75)</td>
</tr>
<tr>
<td>CD4</td>
<td>36.1% (30–45)</td>
</tr>
<tr>
<td>CD8</td>
<td>43.5% (25–35)</td>
</tr>
<tr>
<td>Con A</td>
<td>26.2 (74–508)</td>
</tr>
<tr>
<td>PHA</td>
<td>39.3 (52–458)</td>
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</tbody>
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Table: Con A: concanavalin A, PHA: phytohemagglutin. The results of Con A and PHA were expressed by proliferating activity induced by each lectin divided by spontaneous proliferating activity.

nizid. Her hyperglycemia was effectively treated with insulin therapy.

Breathing became easy and her appetite gradually recovered. Abnormal chest X-ray findings disappeared almost completely after two weeks of the therapy and the increased platelet count also gradually returned to the previous levels, between 20 and 30×10^3/μl. As subsequent maintenance therapy, 100 mg/day of minocycline followed IPM/CS due to severe skin rash from trimethoprim-sulfamethoxazole (TMP-SMX). To avoid relapse or recurrence of nocardiosis, she was advised to continue oral minocycline for at least one year.

As it was reasonable to consider that long-term corticosteroid therapy had made this patient susceptible to nocardiosis, we evaluated whether her T-lymphocytes were competent, as glucocorticoids are known to impair T cell responses. Although the number of each T-lymphocyte subset was not decreased according to surface markers, the response to concanavalin A and phytohemagglutinin was moderately attenuated (Table 1).

Relative thrombocytosis, seen before and shortly after her symptoms and signs developed, was thought reactive to nocardial infection. It is known thrombopoietic cytokines contribute at least partially to this phenomenon (3, 4). To evaluate if this was the case, we measured the serum level of two potent thrombopoietic cytokines, thrombopoietin (TPO) and interleukin 6 (IL-6), at admission and near recovery. As shown in Table 2, both cytokines were elevated in association with thrombocytosis.
**Discussion**

*Nocardia* species are aerobic actinomycetes and common inhabitants of soil. Nocardiosis usually occurs as an opportunistic infection in immunocompromised patients. The most common site of infection is the lung, acquired via inhalation. The presentation is quite variable ranging from an insidious onset to an acute presentation similar to that of pulmonary infarction (5). The diagnosis should be based on isolation of *Nocardia* spp., but it is often difficult to identify in sputum cultures. If nocardiosis is suspected clinically, invasive diagnostic techniques, such as transbronchial biopsy, percutaneous lung aspiration, needle biopsy and open lung biopsy, must be performed (6, 7) if possible. The mainstay of therapy has been sulfonamides, and TMP-SMX has been clinically effective as well. Amikacin, imipenem, ceftriaxone, cefotaxime, and fluoroquinolones are drugs of choice as well (1).

The most common pathogen of pulmonary nocardiosis is *N. asteroides*, which has been shown to be a heterogeneous group of organisms, which are subdivided into several subtypes based on biochemical properties and antibiotic susceptibility patterns. *N. asteroides sensu stricto, N. farcinica, N. nova,* and others (1, 8). *N. farcinica* is less frequently seen, but is known to be more resistant to antibiotics (9) and virulent than *N. asteroides* (10). Catalase activity against oxygen burst of phagocytic cells, secreted superoxide dismutase, and cell wall contents are believed to be associated with virulence (8), but what determines the difference of virulence among those subtypes is not fully understood.

In this case report, we illustrated pulmonary nocardiosis associated with idiopathic thrombocytopenic purpura (ITP). It is difficult to isolate the pathogen since only less than 30% of pulmonary nocardiosis is diagnosed with the result of sputum cultures (11). In the present case we could successfully isolate the pathogen in the pleural fluid. As mentioned above, we emphasize the importance of invasive maneuvers to reach the correct diagnosis in pulmonary nocardiosis. It is widely accepted that the first line of antimicrobial agents against *Nocardia* spp. is sulfonamide or TMP-SMX. But we continued the therapy unchanged after isolation of *Nocardia* because not only had her clinical course indicated effectiveness of IPM/CS but also it has been reported that IPM/CS is effective for *Nocardia in vivo* (12–15). Although some antimicrobial agents including IPM/CS have shown in vitro inhibition of greater than 80% for *N. asteroides* (15), as far as we know, only Lo and Rolston (12) have reported a case of pulmonary nocardiosis that was successfully treated with IPM/CS alone. And some reports (6, 16) have shown fatal outcomes with empirical antibiotic regimens including imipenem. The factors that determine the difference between in vitro and in vivo susceptibilities of antibiotics are not clear. As in the case presented here, sulfonamide and TMP-SMX are known to have common adverse effects of bone marrow toxicity and skin rash, and thus the use of minocycline is recommended instead (14). We also chose minocycline following IPM/CS and achieved successful treatment. It is noteworthy that delayed diagnosis and inappropriate therapy can result in lethal outcomes. Therefore, it is important to recognize the disease itself, especially in immunocompromised patients and prompt initiation of the appropriate treatment based on isolation of the pathogen is critical.

Suppression of cell-mediated immune response, particularly macrophages and T cells, plays an important role to establish the nocardiosis (8). Glucocorticoid is well recognized and widely used for immune suppression, and one of the great risk factors for invasive nocardiosis. In the present case, both prolonged corticosteroid administration and the hyperglycemic state, which is occasionally seen as an adverse effect of steroids, were considered to be the major contributors to her impaired immunity (Table 1). Reactive thrombocytosis, defined as a platelet level of greater than 440×10^3/μl (4), is occasionally seen in infectious diseases, collagen vascular diseases, and malignancies. It seems to be caused at least in part by augmented thrombopoiesis under the influence of several cytokines (3, 4) as a result of an inflammatory process. Also it has been reported in nocardiosis (5, 17–19), but no possible reason for thrombocytosis has been shown. Although the relative thrombocytosis seen here did not meet the criteria, it was easy to consider that it was quite similar to the reactive one since she was suffering from ITP, which is characterized by augmented consumption of the platelet. As expected, the serum levels of TPO and IL-6, potent thrombopoietic cytokines, were elevated as shown in Table 2. Therefore, we concluded that these cytokines were major contributing factors in the thrombocytosis in this patient.

**Conclusion**

We described a case of pulmonary nocardiosis associated with ITP. Although it is rare, nocardiosis must be recognized, especially in immunocompromised patients. Prompt initiation of appropriate treatments based on isolation of the pathogen is important.

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References