Clinical Study
Clinical Characteristics of Nocardia Infection in Patients with Rheumatic Diseases

Mieko Yamagata, Koichi Hirose, Kei Ikeda, and Hiroshi Nakajima

Department of Allergy and Clinical Immunology, Chiba University Hospital, 1-8-1 Inohana, Chiba, Chiba City 260-8677, Japan

Correspondence should be addressed to Koichi Hirose; hirose-kh@faculty.chiba-u.jp

Received 4 July 2013; Accepted 26 August 2013

Abstract

Although Nocardiosis has considerable recurrence and mortality rates, characteristics and risk factors of Nocardia infection have not been assessed in patients with rheumatic diseases. Here, we examined the characteristics and risk factors of Nocardia infection in rheumatic disease patients in our hospital. Ten rheumatic disease patients who developed Nocardia infection were identified by retrospectively reviewing the medical records. Possible predisposing factors for Nocardia infection were high-dose glucocorticoid treatment, concomitant use of immunosuppressants, preexisting pulmonary diseases, and diabetes mellitus. All patients had pulmonary Nocardiosis, and six of them had disseminated Nocardiosis when their pulmonary lesions were identified.

1. Introduction

Nocardia species are ubiquitous environmental microorganisms which belong to a diverse group of bacteria known as aerobic actinomycetes [1]. More than 50 species of Nocardia have been identified, and at least 30 species of them have been reported to possess clinical significance [1]. The majority of Nocardia infections are caused by inhalation, which develops lung lesions called pulmonary Nocardiosis, while some infections are caused by traumatic percutaneous inoculation [2]. Nocardia species can spread from these primary infection sites to various organs hematogenously and develop a pathogenic condition called disseminated Nocardiosis.

Nocardia infection mainly occurs in immunocompromised hosts, including patients with Human Immunodeficiency Virus (HIV) infection, those who underwent organ transplantation, and those who received long-term corticosteroid therapy [3]. Although the incidence of Nocardia infection is low, its early detection and treatment in patients at high risk are clinically important due to its high mortality rate [4, 5]. Therefore, it is desired to identify the risk factors and clinical characteristics of Nocardia infection in each clinical cohort of immunocompromised hosts. In patients who are organ transplantation recipients or are infected with HIV, administration of high-dose corticosteroids, a history of Cytomegalovirus (CMV) infection, and low CD4+ T-cell counts in peripheral blood have been reported as risk factors for Nocardia infection [6, 7]. Although case reports of Nocardia infection in patients with rheumatic diseases underscore its importance [8–10], the risk factors for Nocardia infection in patients with rheumatic diseases have not been assessed yet. In this study, we retrospectively reviewed the medical records of our hospital and assessed the risk factors, clinical features, and microbial characteristics of Nocardia infection in patients with rheumatic diseases.

2. Methods

2.1. Patients. Rheumatic disease patients who developed culture-proven Nocardia infection from January 1995 to July 2012 were retrospectively identified by reviewing medical records in the Department of Allergy and Clinical Immunology, Chiba University Hospital, and clinical information was collected from the records. Disseminated Nocardia infection was defined as involvement of 2 or more organs.

2.2. Microbiology. Nocardia species were identified based on colonial and microscopic morphology and on the demonstration of partial acid-fast staining at the Microbiology Department in Chiba University Hospital.
3. Results

3.1. Clinical Features of Rheumatic Disease Patients Who Were Diagnosed with Nocardia Infection. The demographics and characteristics of 10 rheumatic disease patients who were diagnosed with Nocardia infection are shown in Table 1. The underlying rheumatic diseases of the patients were as follows: microscopic polyangiitis (n = 3), systemic lupus erythematosus (SLE) (n = 2), Behçet’s disease (n = 1), Sjögren’s syndrome (n = 1), granulomatosis with polyangiitis (n = 1), adult-onset Still’s disease (n = 1), and rheumatoid arthritis (RA) with vasculitis (n = 1). The mean time to develop Nocardia infection after the diagnosis of rheumatic diseases was more than 7 years, and 4 patients developed Nocardia infection more than 10 years after the onset of rheumatic diseases (Table 1).

The mean glucocorticoid dose at the onset of Nocardia infection was 19.7 mg (prednisolone equivalent)/day. Five patients were also receiving other immunosuppressants: azathioprine (n = 3), cyclosporine (n = 1), and intravenous administration of cyclophosphamide (n = 1) (Table 1). Although the association of anti-TNF therapy with Nocardia infection has been suggested [11, 12], none of our patients with Nocardia infection were receiving anti-TNF therapy. One patient developed Nocardia infection even though the patient was taking Trimethoprim-sulfamethoxazole (TMP-SMZ), the most commonly used antibiotics against Nocardia, for prophylaxis against pneumocystis jiroveci (Table 1).

Eight out of the 10 patients had diabetes mellitus, and 4 patients were poorly controlled (glycated hemoglobin [HbA1c] < 7.0%) (Table 2). Seven out of the 10 patients had pulmonary diseases including pulmonary lesions induced by underlying rheumatic diseases, a history of pulmonary tuberculosis, and pulmonary aspergillosis (Table 2). In contrast to the previous reports suggesting the association between Nocardia infection and lymphocytopenia [13, 14], white blood cell (WBC) counts and lymphocyte counts in peripheral blood in our patients were within normal limits (Table 2). In addition, no patients had severe hypogammaglobulinemia or hypoalbuminemia. These results suggest that treatment with high-dose glucocorticoid, concurrent use of immunosuppressants, and preexisting pulmonary diseases are associated with the development of Nocardia infection in patients with rheumatic diseases, which is consistent with the previous report on the patients with organ transplantation [6], and that the presence of diabetes mellitus further increases
the risk of *Nocardia* infection in patients with rheumatic diseases.

3.2. Characteristics of Nocardia Infection in Patients with Rheumatic Diseases. The strains of *Nocardia* species isolated from the patients with rheumatic diseases are shown in Table 3. *N. farcinica* was the most common species in our patients (*n* = 5). All patients were diagnosed in outpatient settings and had pulmonary Nocardiosis. Importantly, intensive examination revealed that 6 out of the 10 patients had disseminated diseases (brain abscess (*n* = 3), multiple muscle abscess (*n* = 1), mediastinum abscess (*n* = 1), and subcutaneous abscess (*n* = 1)) when their lung lesions were detected (Table 3).

<table>
<thead>
<tr>
<th>Case no.</th>
<th><em>Nocardia</em> spp</th>
<th>Pulmonary nocardiosis</th>
<th>Extrapulmonary lesion</th>
<th>Initial therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>N. asteroides</em></td>
<td>Yes</td>
<td>Mediastinal abscess</td>
<td>IMP/CS + MINO + TMP-SMZ</td>
<td>Remission</td>
</tr>
<tr>
<td>2</td>
<td>N.D.</td>
<td>Yes</td>
<td>Brain abscess</td>
<td>PAPM/BP + CLDM + TMP-SMZ</td>
<td>Remission</td>
</tr>
<tr>
<td>3</td>
<td><em>N. farcinica</em></td>
<td>Yes</td>
<td>Iliopsoas abscess</td>
<td>MEPM</td>
<td>Remission</td>
</tr>
<tr>
<td>4</td>
<td><em>N. nova</em></td>
<td>Yes</td>
<td>Brain abscess</td>
<td>MEPM + TMP-SMZ</td>
<td>Remission</td>
</tr>
<tr>
<td>5</td>
<td><em>N. farcinica</em></td>
<td>Yes</td>
<td>No</td>
<td>MEPM + ABK</td>
<td>Remission</td>
</tr>
<tr>
<td>6</td>
<td><em>N. farcinica</em></td>
<td>Yes</td>
<td>No</td>
<td>MEPM</td>
<td>Recurrence</td>
</tr>
<tr>
<td>7</td>
<td>N.D.</td>
<td>Yes</td>
<td>Brain abscess</td>
<td>IMP/CS</td>
<td>Remission</td>
</tr>
<tr>
<td>8</td>
<td>N.D.</td>
<td>Yes</td>
<td>No</td>
<td>TMP-SMZ</td>
<td>Remission</td>
</tr>
<tr>
<td>9</td>
<td><em>N. farcinica</em></td>
<td>Yes</td>
<td>No</td>
<td>MEPM</td>
<td>Remission</td>
</tr>
<tr>
<td>10</td>
<td><em>N. farcinica</em></td>
<td>Yes</td>
<td>Subcutaneous abscess</td>
<td>TMP-SMZ</td>
<td>Remission</td>
</tr>
</tbody>
</table>


In this study, we showed that the administration of high-dose glucocorticoid and concurrent use of immunosuppressants seem to be risk factors for *Nocardia* infection in patients with rheumatic diseases (Table 1) in consistency with the previous studies focusing on patients with organ transplantation or neoplastic diseases [6, 17]. In contrast to the previous reports which suggest the association of anti-TNF-α therapy with *Nocardiosis* [11, 12], we did not find any rheumatic disease patients who developed *Nocardia* infection under treatment with anti-TNF-α biologics in our small number of cases.

In addition to these drugs used for the treatment of underlying rheumatic diseases, our data suggest that diabetes mellitus and preexisting pulmonary diseases are risk factors for *Nocardia* infection in rheumatic disease patients. On the other hand, lymphocytopenia and CMV infection, which have been suggested to be associated with *Nocardia* infection in patients with organ transplantation or neoplastic diseases [6, 13, 14], were not identified in our patients with rheumatic diseases who developed *Nocardia* infection under treatment with anti-TNF-α biologics in our small number of cases.

In addition to these drugs used for the treatment of underlying rheumatic diseases, our data suggest that diabetes mellitus and preexisting pulmonary diseases are risk factors for *Nocardia* infection in rheumatic disease patients. On the other hand, lymphocytopenia and CMV infection, which have been suggested to be associated with *Nocardia* infection in patients with organ transplantation or neoplastic diseases [6, 13, 14], were not identified in our patients with rheumatic diseases who developed *Nocardia* infection under treatment with anti-TNF-α biologics in our small number of cases. Taken together, these results suggest that the risk factors for development of *Nocardia* infection can be different in patients with rheumatic diseases compared to those with organ transplantation or neoplastic diseases presumably because of the differences in the preexisting immunological abnormalities and/or the therapy for underlying diseases. Further studies with larger sample size are needed to assess the detailed risk factors for *Nocardiosis* in patients with rheumatic diseases.
Our results suggest that extrapulmonary lesions of \textit{Nocardia} infection are frequently observed in patients with rheumatic diseases. We found that 6 out of the 10 patients had extrapulmonary abscesses when their pulmonary lesions were diagnosed (Table 3). Although it is well known that \textit{Nocardia} species readily spread hematogenously, the proportion of disseminated \textit{Nocardia} infection in our patients is higher than that in previous reports \cite{6, 20}. At present, the reason for the high frequency of disseminated \textit{Nocardia} infection in patients with rheumatic diseases is unknown. However, these results underscore the importance of the intensive examination for extrapulmonary lesions when the diagnosis of pulmonary \textit{Nocardia} infection is made in patients with rheumatic diseases.

5. Conclusion

Our results suggest that the predisposing factors for \textit{Nocardiosis} in rheumatic disease patients are high-dose glucocorticoid therapy, concomitant use of immunosuppressants, preexisting pulmonary diseases, and diabetes mellitus. Our results also suggest that the intensive examination for extrapulmonary lesions is needed when the diagnosis of pulmonary \textit{Nocardia} infection is made in patients with rheumatic diseases.

Acknowledgments

This work was supported in part by grants-in-a-ids for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, the Japanese Government and by Global COE Program (Global Center for Education and Research in Immune System Regulation and Treatment), MEXT, Japan. The authors thank Drs. S. Tanaka, D. Nakagomi, J. Hosokawa, S. Makita, A. Matsuki, and K. Meguro for taking care of patients.

References

\begin{thebibliography}{99}
\end{thebibliography}