Pulmonary Nocardiosis Developed in a Hematopoietic Stem Cell Transplant Recipient with Bronchiolitis Obliterans

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Abstract

The chronic graft-versus-host disease often requires unceasing immunosuppressive therapy (IST), which increases a risk of infectious complications in hematopoietic stem cell transplantation (HSCT) recipients. We report an adult T-cell leukemia/lymphoma case who developed pulmonary nocardiosis, a rare pulmonary complication, after allogeneic HSCT despite administration of the prophylactic trimethoprim-sulfamethoxazole (TMP/STX). The inhaled corticosteroid in addition to systemic IST had been started for bronchiolitis obliterans 4 months prior to nocardiosis development. The patient was successfully treated with an increased dose of TMP/STX combined with meropenem. Transplantation physicians should keep this rare pulmonary complication in mind during sustained IST.

Key words: pulmonary nocardiosis, allogeneic stem cell transplantation, bronchiolitis obliterans, adult T-cell leukemia/lymphoma

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Introduction

Although advances in supportive care have brought about a significant improvement in the outcome of hematopoietic stem cell transplantation (HSCT), chronic graft-versus-host disease (cGVHD) is one of the most common and potentially life-threatening late complications of HSCT. The multiple organ dysfunction associated with cGVHD leads to severe morbidity, however the major cause of death in these patients is infectious diseases based on serious immune dysfunction, which is due to cGVHD itself as well as therapeutic immunosuppressive agents (1).

Nocardia species are gram-positive aerobic actinomycetes ordinarily found in soil, which infect immunocompromised humans predominantly through the respiratory tract disseminating in circulation potentially to the brain and the skin (2-5). The underlying conditions in patients with nocardiosis include corticosteroid medication, antineoplastic chemotherapy, solid-organ transplantation, AIDS, and chronic obstructive pulmonary disease (COPD) (6-9). HSCT has recently been described as a risk factor for nocardiosis, especially when the systemic immunosuppressive therapy (IST) is prolonged to control GVHD (5, 10-13).

We describe herein a case of adult T-cell leukemia/lymphoma (ATL) complicated with pulmonary nocardiosis during IST for bronchiolitis obliterans (BO) following allogeneic peripheral blood stem cell transplantation (PBSCT). According to our experience, nocardiosis should be kept in mind as a late pulmonary complication, even if a prophylactic dose of trimethoprim-sulfamethoxazole (TMP/STX) is given. To our best knowledge, this is the first case report of pulmonary nocardiosis which developed in an ATL patient following PBSCT.

Case Report

A 48-year-old male patient was referred to our hospital...
Figure 1. CT scan showed bilateral bronchial wall thickening mainly in the lower lobes, and air trapping was detected on expiratory CT. These findings were compatible to BO.

because of systemic lymphadenopathy. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) imaging demonstrated multiple nodal lesions as well as the involvement of lung and spleen. Although he possessed antibodies against human T-cell lymphotropic virus type 1 (HTLV-1), a clonal integration of HTLV-1 proviral DNA was not detected by the southern blot analysis of his supraclavicular lymph node biopsy sample. Thus, he was diagnosed pathologically as Hodgkin’s lymphoma (nodular sclerosis type, clinical stage IV) in October 2007. After 8 courses of standard ABVD chemotherapy he achieved a complete remission with some tolerable complications including a reactivation of varicella-zoster virus. Thereafter, “flower cells”, which possessed a CD4+CD25+ phenotype, increased in the blood concurring with the persistent cytomegalovirus (CMV) gastritis. At that time of this writing, a monoclonal integration of HTLV-1 proviral DNA was documented in his blood sample, thus he was diagnosed as ATL, acute type, in November 2008. After two courses of conventional CHOP chemotherapy, he achieved a partial remission and subsequently underwent allogeneic PBSCT from an HLA-matched sibling donor, who was also an HTLV-1 carrier, in February 2009. The preparative regimen for transplantation consisted of total body irradiation (12 Gy total in 6 fractions on day -7 to -5) and cyclophosphamide (60 mg/kg/day on day -3 to -2). The GVHD prophylaxis was performed by intravenous cyclosporine (CsA) (3 mg/kg/day) starting on day -1 and short term methotrexate on days 1 (10 mg/sqm), 3 (7 mg/sqm), 6 (7 mg/sqm), and 11 (7 mg/sqm). On day 14, 2.65×10^6/kgCD34+ cells were successfully infused achieving a prompt neutrophil engraftment. Although he developed CMV antigenemia on day 19, a preemptive gancyclovir therapy effectively inhibited the recurrence of CMV gastritis. The short tandem repeat analysis of his bone marrow revealed a complete chimerism on day 28, and CT scan performed on day 34 confirmed that his ATL was in a complete remission. He was discharged from our hospital on day 42 without any sign of acute GVHD.

Approximately 5 months after PBSCT, he developed sicca syndrome concurring with mild shortness of breath. CT scan showed wall thickness of peripheral bronchi and air trapping, both of which are features of bronchiolitis obliterans (BO) (Fig. 1). The diagnosis of extensive cGVHD was made, and low-dose (0.5 mg/kg) prednisolone was started in addition to CsA. The simultaneous use of inhaled steroid and clarithromycin (200 mg/day, orally) improved his respiratory symptoms. Itraconazole (200 mg/day, orally) and trimethoprim-sulfamethoxazole (TMP/STX, 80/400 mg, orally) were given as preventive measure against fungous infection and Pneumocystis jiroveci pneumonia (PJP), respectively.

Four months later he complained of chest discomfort, productive cough, and dyspnea on effort. Physical examination was unremarkable, however CT scan revealed a dense nodular lesion in the right upper lobe of his lung (Fig. 2A). The broncho-alveolar lavage fluid (BALF) examination documented branching gram-positive bacilli, which was suspicious of Nocardia species (Fig. 2B), as well as Pseudomonas aeruginosa. The culture of BALF and sputum samples determined the growth of Nocardia asteroides. No disseminated lesion was detected in the brain, the skin, or other organs. He was treated with the increased dose of TMP/STX (320/1,600 mg daily) combined with meropenem (0.5 g every 8 hours), which was known to be effective against both N. asteroides and P. aeruginosa. The further increment of TMP/STX was intolerable because of the renal dysfunction (serum creatinine; 1.42 mg/dL). At the occurrence of pulmonary nocardiosis, BO was continuously treated with prednisolone (0.5 mg/kg; same as initial dose), CsA (trough level; ~150 ng/mL), and inhaled steroid. These immunosuppressive agents were carefully reduced as follows; systemic prednisolone was tapered to 0.3 mg/kg, and the trough level of CsA was aimed at ~100 ng/mL, while the same dose of inhaled steroid was continued. He made a rapid recovery after starting the combination therapy, and meropenem was discontinued on day 14. The follow-up CT scan performed 2
months after the initiation of therapy showed that the primary lung lesion had almost disappeared. He will continue having the same dose of TMP/STX (320/1,600 mg daily) for 9–12 months.

**Discussion**

*Nocardia* species are gram-positive, non-sporing rods that cause opportunistic infection in immunocompromised hosts. The present case is considered to be a high-risk for nocardiosis based on the following: 1) diagnosis of Hodgkin’s lymphoma and ATL, both of which relate to impaired cellular immunity (14), 2) inadequate immune reconstitution after allogeneic PBSCT, and 3) concurrence of BO with cGVHD, which require local inhaled corticosteroid therapy in addition to systemic IST.

Deem (15) et al reported the specific T cell-mediated killing of *Nocardia*, suggesting that T cell immunity is key to eradicating *Nocardia*. The occurrence of persistent CMV gastritis in the present case seemed to reflect defective T cell immunity, which might lead to inadequate clearance of *Nocardia*. Patients with incomplete immune reconstitution following allogeneic HSCT are believed to have a significantly increased risk of nocardiosis.Reportedly, the overall incidence of nocardiosis in allogeneic HSCT recipients is 0.3 to 1.7% (16, 17). In fact, among cancer patients who contracted nocardiosis, 31% of them were HSCT recipients (18). COPD was also recognized as a risk of nocardiosis (9). Several cases who developed nocardiosis in concurrence with BO have been reported (11, 13). In the present case, additional inhaled corticosteroid therapy against BO might further weaken local cellular immunity, leading to a failure in eradicating *Nocardia*.

The prophylactic dose of TMP/STX is given routinely after HSCT. Because TMP/STX possesses antimicrobial activities against PJP as well as *Nocardia*, it is recognized that HSCT recipients develop nocardiosis less frequently than other organ transplantation recipients. Reportedly, low-dose TMP/STX seemed to be superior to inhaled pentamidine as a preventive measure against nocardiosis (10), whereas the other report described that a prophylaxis with 4 tablets (320/1600 mg) of TMP/STX weekly was insufficient (17). In our experience, despite the fact that 80/400 mg of TMP/STX had been administered daily, the patient developed nocardiosis, indicating that even this dose might be insufficient to completely prevent this rare complication, especially in patients receiving multiple immunosuppressive drugs to control cGVHD.

TMP/STX is a standard therapy for nocardiosis based on in vitro synergistic anti-*Nocardia* activities of two agents, as well as due to an excellent pharmacokinetics/pharmacodynamics with oral administration (19). Most of the reported cases were treated with 640/3,200 mg daily dose of TMP/STX (5, 11, 12), although this medication often caused myelosuppression and renal dysfunction especially in patients receiving calcineurin-inhibitors after allogeneic HSCT. In recent years, carbapenem has been shown to possess anti-*Nocardia* activities both in vivo (20, 21) and in vitro (22). This alternative treatment is less toxic and exhibits a significant effect on TMP/STX resistant species such as *N. farcinica* and *N. otitidiscaviarum*. Thus, it can be applied to patients in whom TMP/STX treatment has failed or is poorly tolerated (23). In the present case, it was necessary to reduce the TMP/STX dose (320/1,600 mg daily) due to impaired renal function. Furthermore, the detailed specification of *Nocardia* species required a long-term culture of BALF sample. Therefore, we added meropenem (0.5 g every 8 hours) for the first 14 days, resulting in a good clinical response without deterioration of renal function. The simultaneous use of meropenem had the further benefit for stabilizing concomitant infection of *Pseudomonas aeruginosa*. Tu et al analyzed 21 cases of pulmonary nocardiosis and re-
vealed that 4 patients had concomitant infection of Pseudomonas aeruginosa (24). In their report, the authors recommended a combination antimicrobial regimen (TMP/STX plus carbapenem) to control nocardiosis complicated with other bacterial pathogens (24). In conclusion, in the present case a rapid diagnosis using BALF and an appropriate intervention including TMP/STX and carbapenem contributed greatly to the improvement of his condition. Transplantation physicians should keep this rare pulmonary complication in mind during sustained IST, even if the prophylactic TMP/STX is given. There may be room for discussion about more intensive prophylaxis with TMP/STX, if tolerable, in “high-risk” patients like the present case.

References