Successful Treatment of Serial Opportunistic Infections Including Disseminated Nocardiosis and Cryptococcal Meningitis in a Patient with ANCA-associated Vasculitis

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Abstract

We herein present a case of serial opportunistic infections that included disseminated nocardiosis and cryptococcal meningitis in a 67-year-old man who was diagnosed with ANCA-associated vasculitis and treated with corticosteroids. Upon admission, the initial manifestations of the disease included subcutaneous tumors and multiple lesions in the brain and lungs. Nocardia farcinica was identified in a culture of the aspirated pus. The patient was successfully treated for disseminated nocardiosis with antibiotics. However, three months after discharge, he was hospitalized with complaints of nuchal pain. Cryptococcus neoformans was identified on a culture of the cerebrospinal fluid. Anti-fungal treatment resulted in the remission of cryptococcal meningitis.

Key words: MPO-ANCA, ANCA associated vasculitis, disseminated nocardiosis, cryptococcal meningitis, immunosuppression, renal failure

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Introduction

Small vessel vasculitic syndromes (e.g., Wegener’s granulomatosis and microscopic polyangiitis) are frequently grouped together under anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV) (1, 2). The use of immunosuppressive therapy with a combination of cyclophosphamide and glucocorticoids has markedly improves the outcomes of patients with AAV (3, 4). Unfortunately, this therapy is often associated with major side effects (4). Among the most serious adverse effects are opportunistic infections that result from an immunosuppressed state (4, 5). Nocardiosis and Cryptococcus sp. are usually considered to be opportunistic pathogens, and both organisms cause infection in immunosuppressed hosts during treatment with high-dose corticosteroids (6).

We herein describe a rare case of sequential infection with Nocardia farcinica followed by Cryptococcus neoformans in a man who underwent long-term corticosteroid therapy and report the successful treatment of both organisms without the recurrence of AAV or any exacerbation of the patient’s renal function.

Case Report

A 67-year-old Japanese man was admitted to our hospital in June 2006 due to progressive deterioration of his renal function [serum creatinine (sCr): 5.46 mg/dL, creatinine clearance (CCr): 16 mL/min]. Based on a positive test for anti-myeloperoxidase anti-neutrophil cytoplasmic antibodies (MPO-ANCA) and the histological findings of a percutane-

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ous renal biopsy (pauci-immune crescentic glomerulonephritis), the patient was diagnosed with AAV and was treated with intravenous methylprednisolone (mPSL) at a dose of 500 mg daily for three days followed by oral prednisolone (PSL) at a dose of 40 mg/day (0.7 mg/kg) according to the Japanese guidelines for the treatment of rapidly progressive glomerulonephritis (7). The patient worked as a plasterer, and he had never smoked. A computed tomography (CT) scan of the chest revealed no obvious pulmonary lesion. Treatment with oral sulfamethoxazole-trimethoprim (SMX-TMP: 160 mg of trimethoprim and 800 mg of sulfamethoxazole/week) and gargling with a 20x dilution of amphotericin B (100 mg/mL) was initiated for antimicrobial prophylaxis. The dose of PSL was initially tapered by 10 mg every two weeks, and thereafter by 2.5 mg per month. Because the level of MPO-ANCA became negative with improvement of the patient’s renal function (sCr: 2.39 mg/dL) after 7 months, the dose of PSL was gradually tapered to 3 mg/day and the antimicrobial prophylaxis was discontinued (Fig. 1). After the AAV relapsed in April 2008, intravenous pulse therapy with 500 mg of mPSL was administered for three days followed by 40 mg/day of oral PSL (0.8 mg/kg) with the same antimicrobial prophylaxis. After the patient’s renal function recovered, the dose of PSL was tapered to 30 mg/day (Fig. 1). Treatment with PSL was continued for eight weeks due to a high titer of MPO-ANCA and elevated levels of C-reactive protein. The patient was subsequently admitted to our unit in June 2008 with the complaints of a productive cough, fever and subcutaneous tumors in the right forearm, the left scapular region of the back (Fig. 2A), lumbar region, and left femur. His blood pressure was 104/62 mmHg, his pulse was 64 beats/min and his temperature was 36.6°C. Laboratory tests revealed a hemoglobin level of 8.1 g/dL, a hematocrit level of 24.5%, a white blood cell count of 17,500/μL (lymphocyte count: 600/μL, CD4-CD8: 3052

Figure 1. Changes in the counts of CD4-positive lymphocytes and lymphocytes, in response to different doses and cumulative doses of prednisolone. When the CD4-positive lymphocyte count was less than 250/μL, disseminated nocardiosis and cryptococcal meningitis were diagnosed. After proper prophylaxis was administered, no opportunistic infections occurred, even when the CD4-positive lymphocyte count was less than 250/μL. AMT-Gr: gargling with a 20x dilution of amphotericin B, MINO: minomycin, CVA/AMPC: amoxicillin/clavulanic, LVFX: levofoxacin, SMT-TMP: sulfamethoxazole-trimethoprim
Figure 2. A subcutaneous tumor (black arrow head) in the left scapular region of the back (A). A CT scan of the chest showing a subcutaneous mass (white arrowhead) in the left scapular region of the back (B) and multiple well-defined lesions located in the entire lung fields bilaterally (C). A brain CT scan showing a low-density lesion in the right periventricular white-matter (D). Nocardia with branching, beaded gram-positive and acid-fast filamentous rods on a Gram-stained (E) and modified Ziehl-Neelsen stained (F) smear of the aspirated pus obtained from the subcutaneous abscess (×400). Nocardia spp. was identified in sputum in Ogawa medium (G). India ink stain of the CSF showing encapsulated yeast (H). An expanded image is inserted in Fig. 2H.

scopic evaluation of the aspirated pus obtained from the subcutaneous abscess showed Gram-positive acid-fast filament-like bacteria (Fig. 2E, F) identified on culture as Nocardia farcinica. In vitro susceptibility testing of this isolate revealed sensitivity to imipenem and ciprofloxacin and resistance to tobramycin and kanamycin. Nocardia spp. was not identified on sputum or bronchoalveolar lavage fluid cultures at first. Subsequently, Nocardia spp. was identified in the sputum after long-term culture in Ogawa medium (Fig. 2G). Cryptococcus spp. was not cultured in any of the specimens. The patient was treated with intravenous imipenem/cilastatin at a dose of 500 mg daily and oral minomycin at a dose of 200 mg daily. Based on the sensitivity testing, imipenem was switched to 300 mg of oral levofloxacin (LVFX) every other day after five weeks. The patient’s skin and subcutaneous lesions immediately improved after treatment including drainage. However, the antibiotics were insufficient to treat the patient’s brain abscess and lung nodules. Therefore, we restarted treatment with SMX-TMP (160 mg of trimethoprim and 800 mg of sulfamethoxazole twice a daily), which had been discontinued after the exacerbation of the patient’s renal function on admission. Subsequently, the brain abscess and lung nodules were found to be markedly reduced on follow-up brain and chest CT. Minomycin was then exchanged for amoxicillin/clavulanic (CVA/AMPC) due to a product recall.
was 84 beats/min and his temperature was 37.2°C. The patient’s blood pressure was 134/98 mmHg, his pulse was 84 beats/min and his temperature was 37.2°C. The results of laboratory tests revealed a hemoglobin level of 11.7 g/dL, a hematocrit level of 35.3%, a white blood cell count of 9,700/μL, CD4-positive lymphocyte count: 900/μL, a blood urea nitrogen level of 55 mg/dL, an sCr level of 3.42 mg/dL and a Ccr level of 16 mL/min. A urinalysis showed mild hematuria without active sediments (10 red blood cells per high power field). No MPO-ANCA activity was detected. The serum cryptococcal antigen ratio was 1:2,048. A lumbar puncture yielded clear cerebrospinal fluid (CSF) under a normal opening pressure with a glucose concentration of 14 mg/dL, a protein level of 128 mg/dL, pleocytosis of 108 cells/mL, a cryptococcal antigen ratio of 1:256 and encapsulated yeasts on India ink staining (Fig. 2H). The CSF remained sterile and was cultured under conditions appropriate to allow for the isolation of Cryptococcus neoformans. We suspected an infection with aerobic bacteria because a CT scan of the chest demonstrated a new pulmonary lesion (with a slightly thickened cyst wall) despite improvement of the pulmonary nodules, and the patient lived next-door to a pigeon house. The patient was treated with intravenous amphotericin B at a dose of 180 mg daily (this was switched to intravenous fluconazole at a dose of 100 mg daily due to the development of liver dysfunction as an adverse effect) and oral 5-flucytosine (5-FC) at a dose of 1,500 mg daily. The course of the cryptococcal meningitis infection was uncomplicated; cerebrospinal fluid samples obtained at regular intervals up to four weeks after the initiation of therapy were all sterile, and a gradual reduction observed in the antigen titer (1:64) with normalization of the protein and glucose levels. After two months of treatment with intravenous amphotericin B or fluconazole and oral 5-FC, the therapy was changed to oral fluconazole at a dose of 100 mg daily and 5-FC. Although these drugs were discontinued due to impairment of the patient’s renal function and a negative result for serum cryptococcal antigens shortly after the initiation of treatment, there has since been no recurrence. Following discharge, the patient’s renal function has been well preserved and no relapse of AAV has occurred (Fig. 3).

Three months after discharge and after the dose of PSL was tapered to 7.5 mg/day, the patient was hospitalized for investigation after complaining of appetite loss and nuchal pain. A physical examination revealed mild disorientation. The patient’s blood pressure was 134/98 mmHg, his pulse was 84 beats/min and his temperature was 37.2°C. The results of laboratory tests revealed a hemoglobin level of 11.7 g/dL, a hematocrit level of 35.3%, a white blood cell count of 9,700/μL, CD4-positive lymphocyte count: 900/μL, a blood urea nitrogen level of 55 mg/dL, an sCr level of 3.42 mg/dL and a Ccr level of 16 mL/min. A urinalysis showed mild hematuria without active sediments (10 red blood cells per high power field). No MPO-ANCA activity was detected. The serum cryptococcal antigen ratio was 1:2,048. A lumbar puncture yielded clear cerebrospinal fluid (CSF) under a normal opening pressure with a glucose concentration of 14 mg/dL, a protein level of 128 mg/dL, pleocytosis of 108 cells/mL, a cryptococcal antigen ratio of 1:256 and encapsulated yeasts on India ink staining (Fig. 2H). The CSF remained sterile and was cultured under conditions appropriate to allow for the isolation of Cryptococcus neoformans. We suspected an infection with aerobic bacteria because a CT scan of the chest demonstrated a new pulmonary lesion (with a slightly thickened cyst wall) despite improvement of the pulmonary nodules, and the patient lived next-door to a pigeon house. The patient was treated with intravenous amphotericin B at a dose of 180 mg daily (this was switched to intravenous fluconazole at a dose of 100 mg daily due to the development of liver dysfunction as an adverse effect) and oral 5-flucytosine (5-FC) at a dose of 1,500 mg daily. The course of the cryptococcal meningitis infection was uncomplicated; cerebrospinal fluid samples obtained at regular intervals up to four weeks after the initiation of therapy were all sterile, and a gradual reduction observed in the antigen titer (1:64) with normalization of the protein and glucose levels. After two months of treatment with intravenous amphotericin B or fluconazole and oral 5-FC, the therapy was changed to oral fluconazole at a dose of 100 mg daily and 5-FC. Although these drugs were discontinued due to impairment of the patient’s renal function and a negative result for serum cryptococcal antigens shortly after the initiation of treatment, there has since been no recurrence. Following discharge, the patient’s renal function has been well preserved and no relapse of AAV has occurred (Fig. 3).

Discussion

To our knowledge, this is the first reported case of the successful treatment of dual infection of Nocardia farcinica and Cryptococcus neoformans in an immunosuppressed host. While two cases of dual infection have been reported in an immunocompetent host (8, 9), these cases involved dual infection with Nocardia transvalensis (8) or N. farcinica (9) and Cryptococcus neoformans (8, 9). Two reports have described concurrent infection in patients receiving corticosteroids (10, 11); including cases of dual infection with Nocardia brasiliensis (10) or asteroides (11) and Cryptococcus neoformans (10, 11).

Only one case has documented a fatality due to disseminated nocardiosis in a patient with AAV (12). The overall incidence of nocardiosis in different types of immunosuppressed populations has been estimated to range from 0.4% to 3.6% with a related mortality up to 77% (13-15). The presence of lesions in two or more organs in the body defines systemic or disseminated disease. Primary pulmonary infection is the most common clinical pattern and can easily result in disseminated nocardia infection if treatment is not adequate at the outset. Disseminated disease results from either hematogenous or lymphatic spread, and extrapolummonary infections consist primarily of skin and soft tissue infections and brain abscesses (16). Skin infections include ulcerative lesions, a sporotrichoidal presentation and subcutaneous abscesses (6). Our patient exhibited disseminated disease involving skin and soft tissue infections, brain abscesses, and a pulmonary infection.

Sulphonamides, primarily SMX-TMP, continue to be the mainstay of treatment. Some authorities recommend a combination of drugs, including carbapenem derivatives, for induction therapy (6). Minocycline can be used alone or in combination when necessary (6). Immunosuppressed patients should be treated for at least one year, or longer if there are intermittent increases in immunosuppression (6).

Prophylaxis with SMX-TMP is recommended in patients receiving prolonged high-dose corticosteroid therapy (6) because therapy with corticosteroids is the most important risk factor for infectious diseases, including nocardiosis. However, SMX-TMP prophylaxis should not be considered a guarantee of absolute protection against nocardiosis because two previous studies have reported high rates (21.6-60%) of nocardiosis among patients undergoing SMX-TMP prophylaxis (6, 17). Our patient also exhibited nocardiosis under SMX-TMP prophylaxis while receiving steroid therapy, and the patient’s pulmonary lesions worsened during the temporarily discontinuation (10 days) of LVFX while being treated with SMX-TMP and minomycin. Therefore, the clinicians

![Figure 3. Changes in the MPO-ANCA titers and serum creatinine levels. After the diagnosis of disseminated nocardiosis was made, the patient’s renal function was preserved and no relapse of AAV occurred.](image-url)
should be aware of the possibility for nocardiosis infection during the corticosteroid therapy, even when the patients are on SMX-TMP prophylaxis. Since no relapse of the nocardiosis had occurred in our case, triple therapy with SMX-TMP, LVFX and CVA/AMPC under low CD4-positive lymphocyte counts and prophylaxis with multi-antimicrobial drugs may therefore be useful in the prevention of nocardiosis. However, it may be difficult to implement such a strategy in developed countries because of the low incidence of nocardiosis and cryptococcal infections relative to concerns about developing resistance to microbial drugs.

Only one fatal case of disseminated cryptococcosis, including cryptococcal meningitis, has been reported among patients with AAV (18). Meningitis is observed in 1.4-1.6% of the patients with SLE, and Cryptococcus neoformans has been isolated in only 20% of these cases (19, 20). The mortality rate of cryptococcal infection has been reported to be between 10% and 48% in various studies (21, 22). Poor prognostic factors in non-HIV patients are: female gender, age greater than 60 years, severe underlying illness, high Cryptococcal antigen titers, large numbers of cryptococci in the CSF and severe sepsis (21).

Amphotericin B is the mainstay of treatment for all forms of cryptococcosis. Treatment with amphotericin B for at least 10 weeks is warranted and all previously positive cultures generally become negative. Normalization of CSF glucose and a decrease in the antigen titer indicates successful treatment. Following amphotericin administration, fluconazole may be administered for six months (23). A liposomal preparation of amphotericin B (liposomal amphotericin B) allows for the delivery of much larger doses of amphotericin B with considerably less nephrotoxicity (23). Liposomal amphotericin B has been shown to provide an equally efficacious alternative to amphotericin B deoxycholate in patients with acquired immunodeficiency syndrome (AIDS) with acute cryptococcal meningitis (24). Therefore, in cryptococcal meningitis patients with preexisting renal disease or intolerable infusion-related toxicity, as in this case, liposomal amphotericin B should be considered the drug of choice.

It likely makes common sense for high-risk patients to avoid exposure to high concentrations of C. neoformans, that may be found, as in the present case, in places heavily contaminated with pigeon excreta (23). Nevertheless, avoidance of exposure may not be a realistic strategy in most cases (23). Primary antifungal prophylaxis with fluconazole markedly reduces cryptococcal meningitis in AIDS patients with low CD4 counts (25), and antifungal prophylaxis should be considered for immunosuppressive patients with AAV (26). In this case, we recognized that the patient lived next to a pigeon house at the time of the onset of cryptococcal meningitis. After we instructed the patient to stay away from the pigeon house, he did not exhibit any relapses of the cryptococcal infection despite the low CD4-positive lymphocyte counts. If we had suggested the avoidance of exposure and initiated antifungal prophylaxis from the outset, then the occurrence of cryptococcal meningitis could likely have been prevented. Therefore, clinicians should pay attention to the home environment and take preventive measures against infectious diseases, including antifungal prophylaxis.

It is important to establish an appropriate microbial diagnosis, among the broad list of potential microbial invaders in immunosuppressed patients (11). A diagnostic work-up should include active diagnostic investigations for uncommon pathogens, including bronchoscopy in combination with bronchoalveolar lavage, biopsy and histological examination, culturing for bacteria, fungi and viral agents in body fluids, serological tests and microscopy with acid-fast staining for opportunistic pathogens (11). In our case, the pathogens were immediately identified in the aspirated pus obtained from the subcutaneous abscess and CSF, and this early diagnosis resulted in the remission of the disseminated nocardiosis and cryptococcal meningitis.

In conclusion, both infections are rare and contribute to a high mortality rate in immunosuppressed populations. However, our patient was successfully treated for dual infection and an exacerbation of the renal function without recurrence of AAV. Our case demonstrates that the possibility of nocardia and cryptococcal infection should be considered and that early diagnosis based upon specimens obtained with aggressive approaches such as fine-needle aspiration of an abscess, bronchoscopic lavage or lumbar puncture are valuable in assisting with the prompt diagnosis and treatment of such infections in AAV patients.

The authors state that they have no Conflict of Interest (COI).

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References


