Testicular Nocardiosis Accompanied by Cutaneous Lesions in an Immunocompetent Man

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Abstract

We herein report the case of a 77-year-old man admitted for an acute cutaneous infection and persistent fever. A physical examination revealed systemic small blisters and scrotal swelling. He was suspected of having complications from chickenpox or bullous impetigo as the initial diagnosis. Nocardia was detected on aspiration biopsy of the small blisters and the surgically removed testis at a later date. Testicular nocardiosis is a rare condition; however, we should consider nocardiosis in the differential diagnosis because delay in providing treatment may worsen a patient’s general condition.

Key words: testicular nocardiosis, cutaneous nocardiosis, methicillin-resistant \textit{Staphylococcus aureus} (MRSA), chickenpox, small blisters, immunocompetent patient


Introduction

Nocardiosis is an uncommon bacterial infection that presents with a wide variety of clinical manifestations in both immunocompetent and immunocompromised patients (1). During the past three decades, 30-85\% of 	extit{Nocardia} infections were detected in immunocompromised patients (2). A diagnosis of nocardiosis can easily be missed because there are no characteristic symptoms. Cutaneous nocardiosis presents as either a part of a disseminated infection or a primary infection resulting from inoculation (1). Primary cutaneous nocardiosis is relatively rare. Furthermore, the testis is an extremely rare location for 	extit{Nocardia} infection, and accurate morbidity and mortality rates are as yet unclear (3). Nocardiosis includes a broad range of clinical presentations and can present with manifestations similar to those of several other infections. We herein report a case of testicular nocardiosis accompanied by cutaneous lesions similar to the blisters of chickenpox or bullous impetigo in an immunocompe-

Case Report

A 77-year-old Japanese man was admitted to our hospital with a fever and arthralgia in his extremities. He was a retired factory worker. His activities of daily living had been independent 15 days before admission. He did not have a remarkable past medical history. No obvious wounds or history of animal contact were evident. Although his symptoms had progressed for 14 days and his dietary intake was remarkably reduced, he had not obtained medical help. He was in an indistinct consciousness state and poorly nourished due to the fever lasting for two weeks. On admission, his vital signs were as follows: body temperature, 37.6°C; heart rate, 120 beats/min; SpO2, 95\% (on room air); respiratory rate, 21 breaths/min; and blood pressure, 163/83 mmHg. A physical examination revealed one-week worsening systemic small blisters with pus (Fig. 1A-C), a two-week persistent fever, cellulitis in the right medial malleolus

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Figure 1. Small blisters were seen on the patient’s face (A), inferior limbs (B) and buttocks (C). The patient’s scrotum was significantly enlarged (C). D: A Gram stain of pus aspirated from a small blister. The *Nocardia* bacteria appeared as delicate, filamentous, branching Gram-positive rods.

and scrotal swelling with mild tenderness (Fig. 1C). No wounds were observed on the surface of the scrotal skin. A laboratory examination revealed leukocytosis (white blood cell count: $28.3 \times 10^9/L$), elevation of the C-reactive protein level ($19.3 \text{ mg/dL}$) and mild renal (BUN: $30.5 \text{ mg/dL}$, Cr: $1.23 \text{ mg/dL}$) and liver dysfunction (AST: $74 \text{ IU/L}$, ALT: $49 \text{ IU/L}$) (Table). A urinalysis showed no abnormalities. The white cell counts in the urinary sediment were slightly elevated (10 to 19 per high-power field); however, no bacteria were detected on a urinary smear test or a urine culture. Chest radiograph showed no abnormalities. A systemic examination with computed tomography (CT) showed no lesions in the lungs, brain or other visceral organs. The findings of the cerebrospinal fluid (CSF) were normal, and a CSF culture for bacteria was negative. A Tzanck smear test of a blister on the right inferior limb revealed no evidence of herpetic balloon cells; however, the presence of giant cells characteristic of a viral infection was suspected in part of the specimen. Therefore, the patient was initially suspected of having chickenpox complicated by a bacterial infection. He was treated with intravenous acyclovir at a dose of 250 mg every 12 hours for 14 days for chickenpox, taking into account the decline in the renal function, and intravenous cefepime at a dose of 1 g every 12 hours for cellulitis after obtaining the results of two sets of blood cultures. Although the high fever persisted after hospitalization, no bacteria were detected in the blood cultures obtained on admission. Later, the results of a serological test revealed that the patient was negative for IgM antibodies for VZV, HSV and CMV. On the 6th day, methicillin-resistant *Staphylococcus aureus* (MRSA) was detected in the second blood culture obtained on the 4th day. As a result, the antimicrobials were changed from cefepime to vancomycin (0.75 g every 12 hours) on the 10th day (Fig. 3). As the multiple blisters did not improve, an aspiration biopsy of the skin was performed on the 7th day by a dermatologist in our hospital. White-yellowish pus without an odor that appeared to be similar to sulfur granules was aspirated. A Gram-stain of the aspirated pus showed filamentous Gram-positive rods with many leukocytes. No Gram-positive cocci were detected in the cultures of the small blisters. Consequently, the microorganism was diagnosed as the *Nocardia* species on the 16th day. Based on the results of antibiotic susceptibility testing for the species, an intravenous infusion of meropenem (0.5 g every 12 hours) was added to VCM. The systemic blisters disappeared and the cellulitis improved on the 20th day.
patient’s surgery was planned on a normal schedule because the testicular swelling had gradually reduced and the indicators of inflammatory responses on blood tests such as the leukocyte counts and CRP values had gradually improved. On the 22nd day, the scrotal contents were surgically removed. Macroscopically, multiple abscesses were found in the removed testis (Fig. 2A). Actinomycetes were observed in the abscess on microscopic examination (Fig. 2B). The patient was pathologically diagnosed with pyogenic orchitis. He became afebrile on the 29th day. The intravenous antimicrobial therapy was replaced with oral trimethoprim/sulfamethoxazole (TMP-SMX) (160/800 mg twice a day). However, the drug caused a drug eruption with oral minocycline (100 mg twice a day). As minocycline was less sensitive to the days from the start of internal use. As minocycline was therefore replaced with oral minocycline after four months at a nearby hospital. On the 22nd day, the scrotal contents were surgically removed. Macroscopically, multiple abscesses were found in the removed testis (Fig. 2A). Actinomycetes were observed in the abscess on microscopic examination (Fig. 2B). The patient was pathologically diagnosed with pyogenic orchitis. He became afebrile on the 29th day. The intravenous antimicrobial therapy was replaced with oral trimethoprim/sulfamethoxazole (TMP-SMX) (160/800 mg twice a day). However, the drug caused a drug eruption and was therefore replaced with oral minocycline after four days from the start of internal use. As minocycline was found to be less sensitive to the Nocardia species than TMP/SMX in antibiotic susceptibility testing, treatment with TMP/SMX (0.8/4 mg/daily) was restarted at an extremely low dose after drug eruption improved on the 50th day. Thereafter, the patient experienced recurrent bouts of low grade fever at intervals of approximately one week; an intravenous drip of IPM/CS was administered each time (Fig. 3). The patient’s temperature fell to below 37°C and his serum CRP level improved to 0.3 mg/dL on the 54th day. He was transferred to a nearby hospital on the 56th day. Treatment with oral minocycline was continued for two months, and TMP/SMX therapy, which was gradually increased to 120/600 mg twice a day on the 30th day after being restarted, was continued for four months at a nearby hospital. After the patient was discharged from the hospital, 16S-rRNA sequencing identified Nocardia brasiliensis in a sample extracted from the paraffin sections of the testicular lesions.

**Discussion**

Nocardiosis is an uncommon Gram-positive bacterial infection that is typically regarded as being an opportunistic infection. However, approximately one-third of infected patients are immunocompetent (1). Hadak et al. previously reported an overall mortality rate of 25% in a study that included 53 patients with Nocardial infection, 43 (81%) of whom had an underlying immunodeficiency (4). Our patient did not have any previous complications and was regarded as having an approximately normal immune function, except that he was elderly.

Disseminated nocardiosis is defined as the involvement of two or more noncontiguous foci. The most commonly involved sites of nocardiosis are the lungs, central nervous system and skin. In the present case, infection of the skin and testis was evident on cultures. Although nocardiosis is generally considered to be hematogenously disseminated, identifying Nocardia species in blood cultures is uncommon (5). Disseminated nocardiosis presents with cutaneous lesions in approximately 2% of cases (6). Cutaneous disease usually occurs via direct inoculation of the organism. Cutaneous lesions, which occur secondary to hematogenous dissemination, are typically multiple and widespread. In this case, skin and testicular lesions were simultaneously observed on admission. The site of onset of nocardiosis was unclear. No wounds considered to be the site of entry were observed on the surface of the patient’s scrotum. Therefore, a portion of his cutaneous lesions were thought to have spread hematogenously to the systemic skin and testicular lesions. Although CT, blood cultures and CSF findings revealed no lesions in the lungs, brain or other visceral organs, except for the skin and testicular lesions, it was difficult to exclude the possible existence of small foci in the lungs, a site commonly involved in nocardiosis.

Epididymo-orchitis is usually caused by Gram-negative urinary pathogens; Nocardia infection as a cause is rare (7). Several case reports of testicular nocardiosis have been reported and all involved immunocompromised patients such as transplant recipients or patients treated with immunosuppressants or anticancer agents (3, 7-11). In previous reports, patients with testicular nocardiosis treated with immunosup-

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*[Figure 2. A: A macroscopic examination revealed several abscesses in the testes. B: A microscopic examination of the testicular abscesses showed a doughnut-shaped sulfur granule with inflammatory infiltration and filamentous, branching rods. (Hematoxylin and Eosin staining, x200).*]
pressants have been reported to exhibit a 50% mortality rate (3). Patients who survive seem to benefit from aggressive surgical debridement and long-term sulfonamide therapy. Therefore, nocardiosis should be considered in the diagnosis of epididymo-orchitis in immunocompetent as well as immunocompromised patients. Nocardiosis has a broad range of clinical presentations and can present with manifestations similar to those of several other infections. This patient showed a unique clinical appearance with cutaneous manifestations presenting as chickenpox-like blisters distributed systemically. It is difficult to identify nocardiosis by inspection only because the disease is an uncommon cause of skin infections and its lesions are clinically indistinguishable from those produced by common pyogenic bacteria such as *Staphylococcus aureus* and group A *Streptococcus*. In this case, treatment with an intravenous drip of acyclovir for two weeks was prescribed until the results of the cultures of the small blisters revealed *Nocardia* on the 16th day. In hindsight, the white-yellowish pus without odor, which appeared similar to sulfur granules, was a typical skin finding of cutaneous nocardiosis. Therefore, cutaneous nocardiosis should have been considered as a differential diagnosis at the time of admission.

Antimicrobial susceptibility patterns vary among different studies, countries and *Nocardia* species (5). The optimal duration of antimicrobial treatment for nocardiosis has not yet been determined. In general, isolated cutaneous infections in immunocompetent patients are treated for three to six months and those occurring in immunocompromised patients are treated for six to 12 months (5, 12). On the other hand, all immunocompromised patients, except those with isolated cutaneous infections, are treated for more than 12 months. In the present case, treatment for nocardiosis was initiated according to the results of antibiotic susceptibility testing for the species. As the patients was considered to be immunocompetent before hospitalization, oral minocycline therapy was changed after he was transferred to a nearby hospital to TMP/SMX, which was increased to 120/600 mg twice a day on the 30th day after being restarted and then continued for four months.

With regard to prophylaxis against *Pneumocystis carinii* infection in HIV-infected patients who discontinue TMP-SMX due to adverse reactions that are not life-threatening, it is recommended to attempt to reintroduce TMP-SMX therapy. The efficacy of a regimen of gradual dose escalation used to desensitize patients has been evidenced by the results of a randomized trial (13). Although carbapenem antibiotics show good antimicrobial susceptibility to *Nocardia*, we intended to avoid long-term administration of those antibiotics because the patient had MRSA sepsis complications concurrently with *Nocardia* infection and exhibited a slight decline in his renal function. Therefore, as it was possible to administer TMP-SMX orally over a long period and the drug had good antimicrobial susceptibility to *Nocardia*, desensitization was performed and TMP-SMX was selected for therapy. Thereafter, the patient experienced no recurrence during more than six months of follow-up.
More than 70 species of the genus *Nocardia* are known, of which 33 have been shown to cause disease in humans (14-16). Making a detailed classification of the *Nocardia* species is difficult in the microbiology laboratory of our hospital because complicated biochemical methods are required. It is difficult to identify the *Nocardia* species using only phenotypic methods. Therefore, we sent specimens to the most advanced facilities to obtain a detailed classification of the *Nocardia* species.

At a later date, DNA was extracted from paraffin sections of the testicular lesions. Subsequently, a sequence analyses of 16S-rRNA revealed that the strain in this case was *Nocardia brasiliensis* (14). In the present case, MRSA was detected in the abscess on the surface of the scrotum, but not in the skin vesicles, on the second blood culture. As no skin disorders such as ulcers or wounds were observed on the surface of the scrotum, the portal of entry and the timing of MRSA infection were unclear. Assessing an initial clinical diagnosis of nocardiosis may be difficult due to the presence of nonspecific clinical symptoms that may cause a delay in making a diagnosis. Furthermore, epididymo-orchitis caused by nocardiosis is extremely rare, and the mortality rate of the disease is high. As long as a diagnosis of nocardiosis is not suspected, making a quick and accurate diagnosis will be difficult. Therefore, nocardiosis should be considered as a differential diagnosis in immunocompetent as well as immunocompromised patients with small blisters or scrotal swelling.

### Table. Laboratory Findings on Admission

<table>
<thead>
<tr>
<th>Uric acid</th>
<th>Blood chemistry</th>
<th>ESR</th>
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</thead>
<tbody>
<tr>
<td>Protein</td>
<td>Alb 2.9 g/dL</td>
<td>69 mm (1 hr)</td>
</tr>
<tr>
<td>Glucose</td>
<td>T-bil 0.8 mg/dL</td>
<td>112 mm (2 hr)</td>
</tr>
<tr>
<td>Ketone body</td>
<td>AST 74 IU/L</td>
<td></td>
</tr>
<tr>
<td>Occult blood</td>
<td>ALT 49 IU/L</td>
<td>Serological test</td>
</tr>
<tr>
<td></td>
<td>ALP 379 IU/L</td>
<td>CRP 19.3 mg/dL</td>
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<tr>
<td></td>
<td>LDH 401 IU/L</td>
<td>IgG 1,508 mg/dL</td>
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<tr>
<td></td>
<td>CPK 477 IU/L</td>
<td>IgA 589 mg/dL</td>
</tr>
<tr>
<td></td>
<td>ChE 153 IU/L</td>
<td>IgM 97 mg/dL</td>
</tr>
</tbody>
</table>

| WBC | 28,300 /μL |
| Neu | 90.1 % |
| Eo | 0.0 % |
| Baso | 0.2 % |
| Mono | 4.4 % |
| Lym | 5.3 % |
| RBC | 411 × 10⁶ /μL |
| Hb | 13.4 g/dL |
| Plt | 24.5 × 10⁶ /μL |

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

### References


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