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Case report

Long-term treatment of persistent disseminated *Nocardia cyriacigeorgica* infection

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ABSTRACT

In this paper a disseminated persistent *Nocardia cyriacigeorgica* infection in an immunocompetent patient is described. The patient's long-term treatment, as well as its implications for managing similar cases in the future, is emphasized. Presenting with high fever, multiple nodules, and ulcerative cutaneous lesions of body sites, the patient was treated with various antimicrobials. Under combined therapy, empyema and arthritis, leading to disseminated nocardiosis, were seen. The overall treatment course was 28 months. It can be concluded that the choice of the antibiotics and optimal duration of treatment are uncertain; therefore the treatment of nocardiosis requires expertise.

Introduction

Herein we describe a case of disseminated *Nocardia cyriacigeorgica* infection, a recently identified species, in an immunocompetent patient. The infection was most likely acquired from direct inoculation of body surfaces as a result of occupational exposure. Different factors that may have contributed to the long-term treatment of the disease and the subsequent relapse in this patient in spite of *in vitro* susceptibility of the isolate to all drugs administered are discussed.

Case report

Patient clinical status

A 45-year-old woman, who has been working as a farmer was hospitalized with symptoms of high fever, multiple nodules, and ulcerative lesions of various body sites. She had no underlying diseases and only had scratches on her hand as a probable indicator of occupational trauma. Previously she had been treated for cellulitis and lymphedema in the ward

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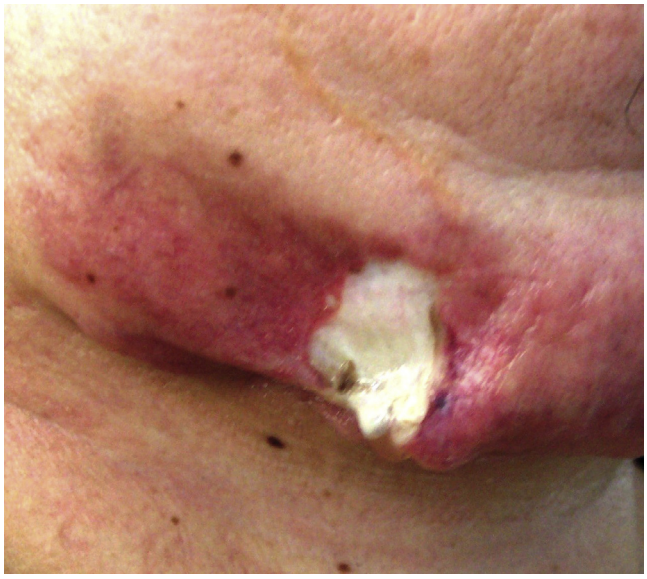

Fig. 1 – The ulcerative lesion on the patient's chin.

of internal medicine for two weeks and then moved to the infectious diseases clinic. She presented with fever (38.5° C), multiple cutaneous, erythematous, edematous nodules, and abscesses over the left breast and on the left upper and lower extremities. Similar edematous or ulcerative lesions were later seen under the chin (Fig. 1), on dorso-thorocal, and lombar regions. The lower extremities were edematous. Under therapy some partial resolution of cutaneous lesions were observed. Also, painful new nodules appeared in the following two weeks and some existing nodules continued to expand in size. The nodules and ulcerative lesions varied in size from 2 to 12 cm and were tender and erythematous. Remarkable resolution of some cutaneous and subcutaneous lesions (Fig. 2) was seen. Some of the pre-existing nodules have ulcerated and that underwent surgical debridement. Despite *in vitro* susceptibility of the isolate to all drugs administered, new pyogenic abscesses, empyema of the thorax, and respiratory distress have ensued. The chest radiograph showed left-sided pleural collection. Thoracocentesis and surgical drainage were

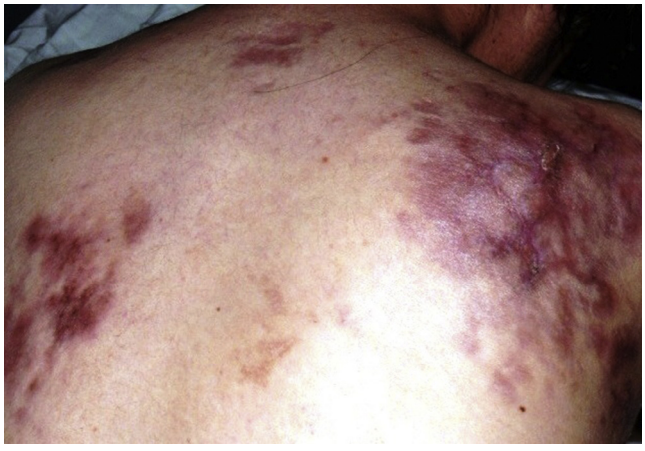

Fig. 2 – The scars of the healed lesions on the dorso-thorocal region of the body.

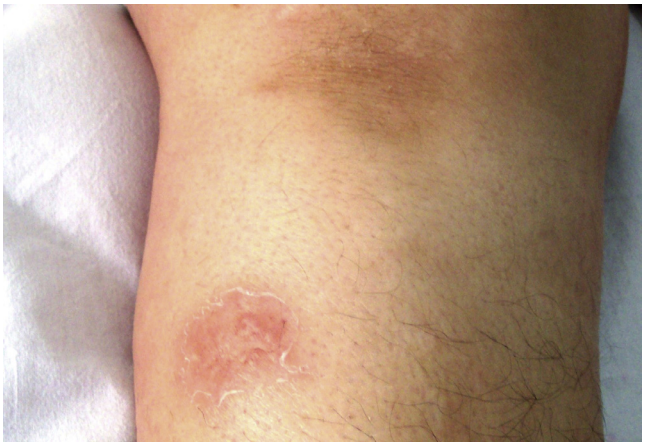

Fig. 3 – The cutaneous nodule on the lower extremity.

performed; pleural fluid was obtained for culture. Pleural empyema also occurred on the right side of the lung within two weeks; again surgical drainage was performed. Three months after admission, empyema and skin nodules had fully resolved with scarring. Under suppression maintenance therapy, relapsing fever and cutaneous nodules (Fig. 3) have ensued which were later cleared by an additional two months of treatment. Six months later with combined antimicrobial therapy, the patient was discharged from the hospital on doxycycline maintenance monotherapy. Arthritis of the right knee and ankle, high fever, and new cutaneous lesions developed within a month of hospital discharge and the patient was again hospitalized. The patient presented with high fever and new nodules. A new drug (linezolid) which was not on the market at that time was initiated. After clinical and laboratory response to therapy at the end of one year, some fluctuating cutaneous symptoms had appeared for a period of ten more months. The patient then remained healthy in the following three years of follow-up (Table 1).

Laboratory methods for diagnosis

Erythrocyte sedimentation rate (EST) was 10 mm/h, blood count was as follows: leukocyte 7070 mm^{-3}, Hb 9.1 g/L, Ht 32.5, platelet 419,000 mm^{-3}. CRP was 9.7 mg/dL. All biochemical tests except moderate hypoproteinemia (albumin 3 mg/dL, globulin 1.9 mg/dL) were within normal ranges. Chest radiograph and urinalysis were also normal. Gram-stained preparations of pus from ulcerative lesions showed mostly Gram-positive small rods and coccoid fragments within leukocytes. Ziehl–Nielsen stained preparations were negative. Bacteriological culture showed no growth. Later, abscesses material and pleural fluid cultured on Myco/F-Lytic BACTEC liquid medium (brain–heart and 7H9 Middlebrook) and Loewenstein–Jenseen medium grew presumptive *Nocardia* species in a pure culture within one week. Branching rods were seen in Ziehl–Nielsen with 1% sulfuric acid (modified Kinyoun technique) stained preparations, a typical feature of nocardiae.[1–4] The microorganism was confirmed as *N. cyriacigeorgica* at the reference laboratory in France. The strain was reported as sensitive to amikacin, gentamicin,

Table 1 – Features of disseminated *Nocardia cyriacigeorgica* infection.

Symptoms	Laboratory findings	Treatment	Duration of therapy	Clinical outcome
High fever, new nodules	ESR 10 mm/h, WBC 7070 mm^{-3}, Hb 13.8 g/L, CRP 9.7 mg/dL	Ceftizoxime 6 g/d + clindamycin 1800 mg/d	1st ⇒ 14th days	Partial resolution, new lesion (chin)
Ulcerative lesion under chin	Gram stain: small rods and coccus	TMP/SXT 10 mg/kg/day + Imipenem 2 g/day	14th ⇒ 45th days	New lesions (dorso-thorocal region) bone marrow suppression (WBC 7240 mm^{-3}, Hb 6.7 g/dL, Ht 22.1, PLT 118,000 mm^{-3}) "Breakthrough"
Disseminated skin lesions + respiratory distress	Chest radiogram: Pleural empyema Pleural fluid: "Aerobic nocardiform actinomycetes ESR 63 mm/h, CRP 21.6 mg/dL	Imipenem 2 g/day + amikacin 1 g/day + doxycycline 200 mg/day Surgical: drainage and debridement	45th ⇒ 90th days	Resolution of cutaneous lesions and empyema
Scarred cutaneous lesions	ESR 38 mm/h, CRP 0.65 mg/dL	Amikacin 1 g/day + doxycycline 200 mg/day	3rd ⇒ 4th months	Relapse
High fever, new nodules	ESR 85 mm/h, CRP 5.2 mg/dL	Imipenem 2 g/day + amikacin 1 g/day + vancomycine 2 g/day	4th ⇒ 6th months	Suppression or cure Discharge from hospital
None	ESR 45 mm/h, CRP 0.66 mg/dL	Doxycycline 200 mg/day	6th ⇒ 7th months	Re-activation
Arthritis (right knee and ankle)	ESR 95 mm/h, CRP 21 mg/dL	Ceftriaxone 2 g/day + amikacin 1 g/day + doxycycline 200 mg/day	7th ⇒ 9th months	Hospitalization No response, new symptoms
New nodules formation (subclavian catheter region)	ESR 104 mm/h, WBC 8800 mm^{-3}, Hb 12.7 g/L, CRP 14.7 mg/dL	Linezolid 1200 mg/day + doxycycline 200 mg/day	9th ⇒ 12th months	Suppression or cure + adverse effects due to linezolid
Peripheric neuropathy, severe malaise	ESR 42 mm/h, CRP 1.06 mg/dL	TMP/SXT 5 mg/kg/day + doxycycline 200 mg/day + B6 vitamin	12th ⇒ 15th months	Resolution discharge from hospital (13th month)
Fluctuating mild cutaneous symptoms	ESR 26 mm/h, Hb g/L, Ht 39.8, CRP 0.73 mg/dL	TMP/SXT 5 mg/kg/day + doxycycline 200 mg/day	15th ⇒ 22nd months	Resolution and cure
None	ESR 10 mm/h, WBC 8080 mm^{-3}, Hb 14.2 g/L, Ht 43.1 CRP 0.3 mg/dL	TMP/SXT 5 mg/kg/day + doxycycline 200 mg/day	22nd ⇒ 28th months	Well-being

cefotaxime, ceftriaxone, cefepime, imipenem, vancomycin, trimethoprim/sulphamethoxazole (TMP/SXT), minocycline, doxycycline, and linezolid. Disk susceptibility test was performed according to Boiron and Provost.[5] Empyema of the thorax was diagnosed by chest radiograph and chest computed tomography (CT). Further tests did not reveal any evidence of an underlying immunocompromised state.

Treatment and clinical outcome

Ceftizoxime and clindamycin combination (two weeks) were switched to TMP/SXT plus imipenem (one month) for treating one of those fastidious microorganisms including *Rhodococcus*, *Nocardia*, *Actinomyces*, *Peptococcus*, etc., which was suspected as a causative agent based on the Gram smear. Surgical debridement of the dorso-thorocal lesions and surgical drainage of the left-sided and then the right-sided empyema fluid were also implemented in addition to medical therapy. Bone marrow suppression due to TMP/SXT with a 10 mg/kg/day trimethoprim dose had developed. The targeted antibiotic therapy to the isolated *Nocardia* was then a combination of imipenem, amikacin, and doxycycline for 45 days. The response to this regimen was good. As maintenance therapy amikacin plus doxycycline (one month) was given but this regimen had failed and the disease symptoms reactivated with high fever and new nodules' formation. Therapy was discontinued after six months and the patient discharged from the hospital. Maintenance therapy with doxycycline monotherapy was prescribed. Approximately a month later the disease recurred with symptoms of arthritis and followed by high fever and cutaneous nodules. Neither resolution nor progression of symptoms was observed by combining ceftriaxone, amikacin, and doxycycline for two additional months. After nine months from initiation of disease symptoms linezolid, a drug not on the market at that time, in combination with doxycycine was started. Clinical cure of the disease was obtained after linezolid therapy for three months but eradication of the organism could not be achieved due to cessation of linezolid, because of significant adverse effects (ESR and CRP levels decreased to 26 mm/h from 104 mm/h and to 0.73 mg/dL from 14.7 mg/dL, respectively). Mild relapsing episodes of cutaneous lesions were treated with TMP/SXT (5 mg/kg/day) and doxycycline for ten more months till no remission and the same antimicrobial combination was further lengthened for six more months after resolution of all disease symptoms with no side effects. The overall treatment course was 28-month long. The patient remained healthy and had no signs of relapse after being followed-up for additional three years without therapy.

Definitions

Disseminated nocardiosis was defined as nocardia infection in two or more non-contiguous sites. Breakthrough nocardiosis was deemed when a recurrent nocardial infection occurred in a patient receiving systemic antibacterials with known *in vitro* activity against *Nocardia* spp. Relapse or reactivation of the disease was noted when an initial improvement was followed by reappearance of clinical symptoms and laboratory findings.[6]

Discussion

The literature survey of post-treatment follow-up of *Nocardia* infections is often too brief or unknown, making the ultimate success of therapy uncertain.[7] Members of the *N. asteroides* complex are more frequently involved in pulmonary infections. Recently, several new species have been described in this complex. The present report is a case of disseminated persistent infection in an immunocompetent patient with primary cutaneous involvement, empyema, and arthritis due to *N. cyriacigeorgica*, which was formerly part of the *N. asteroides* complex. Previous cases of *N. cyriacigeorgica* infections have been reported in immunocompromised patients.[8,9]

The experience with nocardiosis suggests that when the infection is disseminated, the clinical response is slow.[10] Therefore successful therapy requires combination of antimicrobial drugs and appropriate surgical drainage. The optimal antimicrobial therapy depends on the severity and localization of the infection, the species of *Nocardia*, host immune status, potential drug interactions, toxicity associated with antibiotic usage, and duration of illness prior to diagnosis.[1,2,11]

Imipenem and amikacin seemed to be the most effective agents, and *in vitro* synergism has been demonstrated between imipenem and TMP/SXT, imipenem and cefotaxime, amikacin and TMP/SXT.[1,2,12,13] Although synergy has been reported in the literature, Kanemitsu et al.[14] described that synergy was present in 83% of 23 *N. asteroides* strains treated with amikacin and TMP/SXT, in 26% of 15 strains treated with amikacin plus ceftriaxone, and in 5% of 26 tests conducted with amikacin and imipenem, thus showing that synergic effect of antimicrobial combinations were not observed in all cases. In the present case, combination therapy with imipenem, amikacin, and doxycycline did not improve disease outcome unless vancomycin was added.

New antimicrobial agents are needed. The relatively high incidence of adverse events, such as diffuse rash and myelosuppression occurrence during sulfonamide therapy, has been reported. Besides, there is lack of alternative highly active oral agents.[1,2,14] Linezolid is the first antimicrobial to be active against all clinically significant species of the genus *Nocardia*.[14,15] It has been reported to be effective in treatment, especially in disseminated disease. Because of its activity and availability as an oral agent and the current limitations of the sulfonamides, linezolid has the potential to be the primary drug of choice for treating *Nocardia* disease.[16] Treatment related anemia and peripheral neuropathy have been reported,[16] which resolved when linezolid therapy is discontinued, as observed in the present case.

Remissions and exacerbations lasting for days or weeks are characteristic of the disease.[11,17,18] The disease may spread hematogenously leading to long-term persistent nocardiosis.[18] In the absence of consensus on the length of therapy, investigators mostly recommend to prolong medication between 6 and 24 months because of the relapsing nature of the infection.[6,19] Further progression of cutaneous disease to empyema and arthritis, "breakthrough nocardiosis" under combined therapy was seen in the present case. Therefore, treatment duration of 28 months was the longest reported period in the literature.

The sequence of different combined antibiotics used, for so long in this patient might have implications for managing similar cases in the future. Antibiotics with intracellular activity may be beneficial in long-term treatment of the disease. As there are no unanimous guidelines on the therapy of nocardia infections, at the moment the optimal duration of treatment is uncertain and requires expertise.

Conflicts of interest

The authors declare no conflicts of interest.

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