

DISSEMINATED NOCARDIOSIS MIMICKING EXACERBATION OF PULMONARY SARCOIDOSIS

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ABSTRACT. Nocardiosis is a rare, mixed suppurative and granulomatous, bacterial infection that can affect various organs, but most commonly lungs. Clinical manifestation is usually uncharacteristic; can mimic fungal, parasitic and mycobacterial infections or malignancy. Presentation can be also similar to that of the other granulomatous diseases, among them sarcoidosis. We present an unusual case of disseminated nocardiosis in a patient diagnosed before with sarcoidosis and treated with glucocorticoids. Clinical symptoms initially mimicked exacerbation of pulmonary sarcoidosis. The course of disease was severe. (*Sarcoidosis Vasc Diffuse Lung Dis* 2013; 30: 65-69)

KEY WORDS: nocardiosis, pulmonary sarcoidosis, immunosuppression

INTRODUCTION

Nocardia species belongs to the group of aerobic Gram-positive actinomycetes that can multiply intracellularly (1). These bacteria can cause localized or systemic, mixed suppurative and granulomatous disease. More than 30 species pathogenic for humans have been described (2). The exact frequency of nocardiosis is unknown, but about 1000 cases in

the United States and about 150-200 in France are reported each year (3); incidence is estimated to be about 0,4 cases per 10⁵ persons-year. However, in immunocompromised patients the frequency of these infections can reach even 1122 cases per 10⁵ persons (4). Cell-mediated immunity is crucial for the infection control. Therefore at least 60 percent of nocardiosis is diagnosed in immunocompromised hosts. Well documented risk factors for *Nocardia* infection include: transplantation, AIDS, glucocorticoids treatment or underlying malignancy (5). Diabetes, alcohol abuse, chronic lung diseases are other predisposing conditions. However, sometimes, no evident underlying immune abnormality is detected (6, 7).

For nocardiosis typical is dissemination to many internal organs as well as resistance to antimicrobial therapy and tendency to escape from immune re-

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sponse (1). The most common and primary site of infection are the lungs. Clinical and radiological symptoms in every case may vary.

Nocardia has a particular tendency to locate in skin and skin-associated lymphatic tissue and in the nervous system (8). Disseminated disease occurs in 32% of cases (7) and may have a poor prognosis with mortality depending on the underlying condition (40%-50% in immunocompromised patients) (6-9). Such high mortality is likely a consequence of both active intracellular growth (1) as well as reactivation of a latent infection (6).

Nocardiosis is difficult to diagnose on the basis of clinical, radiological or histological findings. Final diagnosis requires microbiological identification by culture and/or molecular methods. Bacteria can grow on standard media, but only after 5-21 days (9), therefore the prolonged culture incubation should be performed. Properly handled tissue specimens can often show *Nocardia* as Gram-positive bacteria. Nocardiosis requires a long-lasting antibiotic therapy, the duration of which is based on the organ involvement. Infection of central nervous system requires antibiotic treatment for at least 12 months. Sometimes surgery is needed.

Sarcoidosis is a systemic granulomatous disease of unknown etiology that also can affect multiple organs with the main location in the lungs. It is characterized by several immune abnormalities, including a depletion of CD4+ blood T lymphocytes. In addition, cell-mediated immunity can be depressed due to steroid treatment of sarcoidosis. Under such conditions patients with sarcoidosis are predisposed to opportunistic infections. Such infections are rare, but could be fatal (10).

CASE REPORT

A 37-year old man, diagnosed 2 years earlier with pulmonary sarcoidosis (on the basis of clinical symptoms, typical radiological findings and histologic confirmation) and treated continuously with methylprednisolone (16-24 mg per day), was admitted to our hospital because of a 3-month history of mild fever, general weakness and cough. His physician suspected exacerbation of pulmonary sarcoidosis and increased the dose of glucocorticoids, without improvement. On admission, physical examination

revealed multiple, hard, subcutaneous nodules in the lumbar, inguinal and gluteal regions, and on the lower part of abdomen. On physical examination crackles over the bottom of the right lung were heard. Laboratory tests showed slight normocytic anemia (10,4 g/dl Hb), increased neutrophilic count ($12 \cdot 10^3/\text{mm}^3$) and high serum CRP level (82 mg/L). Large consolidation in the right lower lobe (segments VIII, IX, X), a few small nodules - also in right lung - and enlarged mediastinal lymph nodes, were seen on a chest CT scan. X-Ray picture is shown on figure 2, panel C. All blood, urine, sputum and broncho-alveolar lavage fluid cultures were negative for pathogenic bacteria and fungi (the cultures were held according to our laboratory standard procedures - 48 hours for urine, 72 for BAL and sputum, 7 days for blood samples).

Subcutaneous nodules were hyperechogenic on ultrasonography. Within a few days they became erythematous, evocative of abscesses and required incision and drainage. All microbiological cultures of the abscess aspirates taken by surgeons were negative. The histopathological findings (nonspecific granulomatous inflammation) - Figure 1 were inconclusive. Despite broad spectrum antibiotic therapy (vancomycin and amikacin) the patient's state constantly deteriorated. Due to severe abdominal pain, CT scan of the abdomen was performed showing multiple retro- and preperitoneal abscesses (figure 2, panel B), and one abscess located in medi-

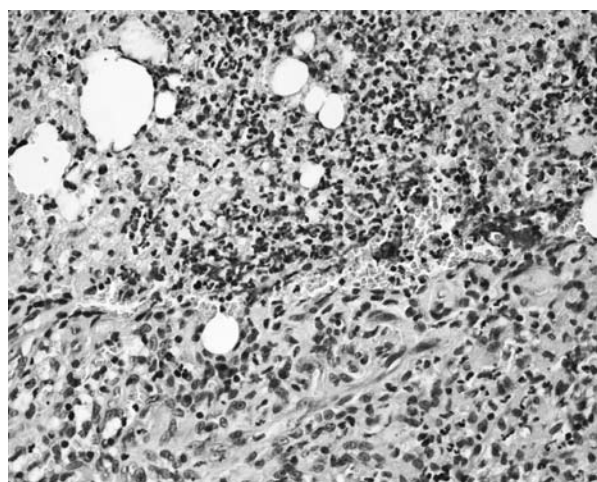


Fig. 1. Histopathologic findings. Nonspecific granulomatous inflammation, accompanied by suppurative infiltration with neutrophils (magnification 30x)

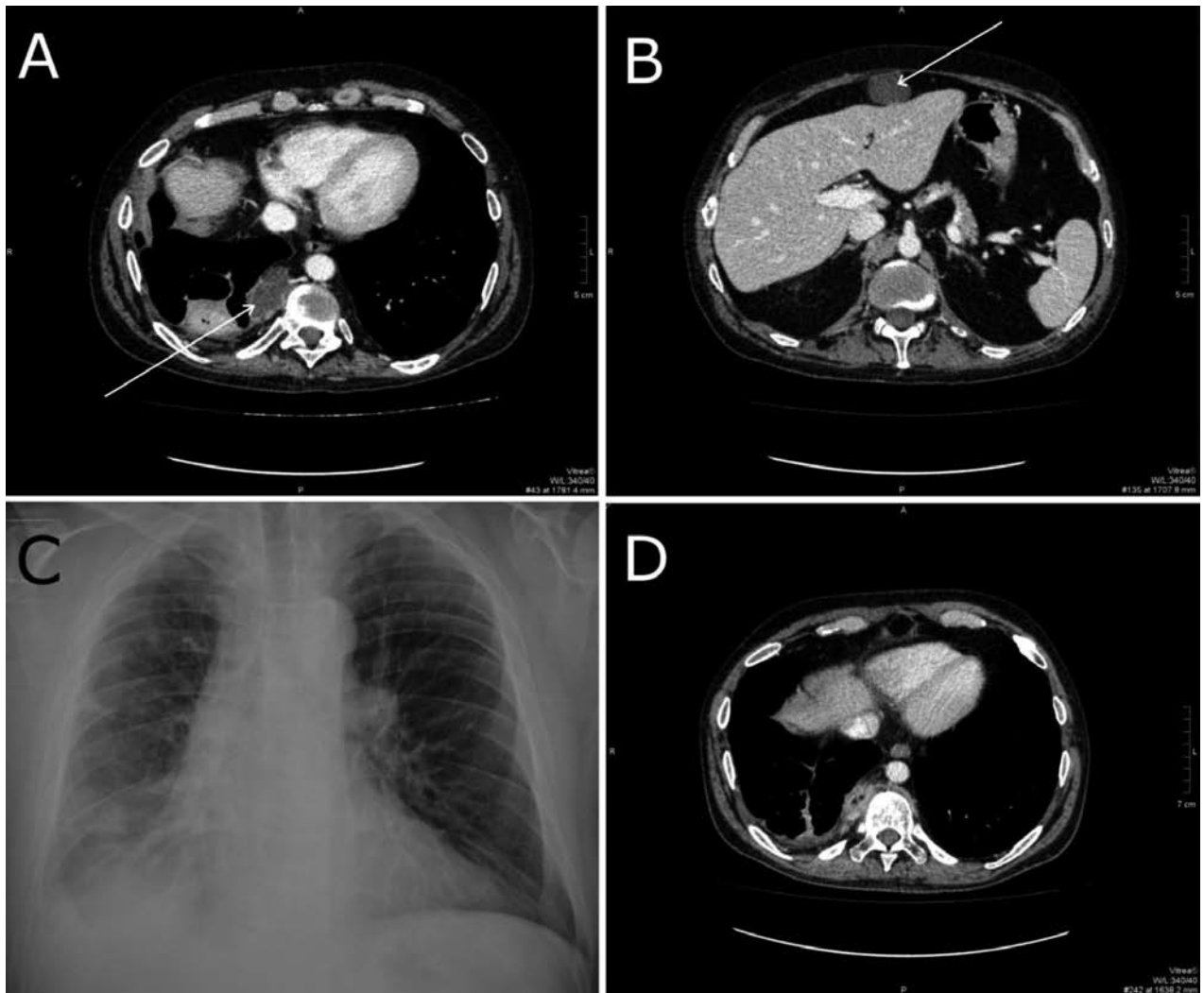


Fig. 2. The CT scans showing mediastinal abscess (arrows) at the onset (A), and after 3 months of treatment (D). Panel B shows a preperitoneal abscess, of which a fine needle biopsy was performed. Additionally, in panel C, a lobar consolidation in the right lung can be seen on chest-radiograph.

astinum (figure 2, panel A). A fine needle aspiration of an abscess situated in preperitoneal fat (panel B, shown by arrow) was performed. Gram stains of the pus revealed positive bacillus. After bacteria growth our laboratory identified *Listeria grayi* using API Coryne strip (bioMérieux, Marcy l'Etoile, France). Because of the fact, that clinical presentation was not typical for listeriosis, the sample was sent for final confirmation to the WHO collaborating center for *Listeria* (Institut Pasteur, Paris). This laboratory excluded the presence of *Listeria grayi*. Complete sequence of the bacteria 16S rRNA gene from the obtained specimen was carried out as described previ-

ously (12). A total of 1,480 continuous nucleotides were determined. The complete 16S rRNA gene sequence of the isolate was compared to all bacterial sequences available from the GenBank database by using the BLAST program. Finally, the type strain *Nocardia farcinica* was found to 0.1% of divergence. This isolate thus belongs to the species *Nocardia farcinica*. Percent *rrs* sequence divergence between our isolate and the nearest species were 1.2 (*N. asiatica*, *N. higoensis*, *N. shimofusensis*), 1.5 (*N. thailandica*), 1.7 (*N. abscessus*), 1.8 (*N. arthritis*). A phylogenetic tree was generated by using the neighbour-joining algorithm (11).

Because *Nocardia* have a special tropism to the central nervous system (6) with uncharacteristic and frequently clinically silent manifestation of a neural infection, a magnetic resonance imaging of brain should be performed in all confirmed cases of nocardiosis. In our patient this imaging showed no abnormalities.

Finally, cotrimoxazole was introduced at a dose of 960 mg twice a day and was maintained (in a reduced dose) for one year (treatment according to the guidelines published by Center for Disease Control and Prevention). At 12 months of follow-up, almost complete regression of abdominal, mediastinal and pulmonary lesions was observed (regression of mediastinal abscess is shown in *picture 2, panel D*). The dose of glucocorticoids was also tapered gradually to 4 mg every second day. The patient is currently in good clinical conditions and normal physical activity.

DISCUSSION

Nocardiosis has an insidious course and can also be evocative of other opportunistic infections of fungal, parasitic, and bacterial origins or malignancies. Typical radiologic findings in nocardiosis and sarcoidosis are different. However, sometimes, both may have similar picture. Hui et al (13) analyzed radiological findings in 35 patients with pulmonary nocardiosis and confirmed a large spectrum of non-specific abnormalities. Among the most common were pulmonary nodules (64%) – solitary or multiple – often with cavities, larger than usually in sarcoidosis, and non-segmental consolidations (55%). A few patients had pleural effusion. Lobar consolidations or ground-glass opacities were also observed. However, the most typical for sarcoidosis symmetric hilar adenopathy, is a rare manifestation of nocardiosis. Nocardiosis can present with hilar adenopathy, but asymmetric - in the region draining a peripheral lung lesion.

Nocardiosis can follow or merge insidiously with the underlying sarcoidosis particularly in the context of difficult pathogen identification. However, despite of CD 4+ T-lymphocytopenia, and chronic steroid treatment, opportunistic infections are relatively rare in patients with sarcoidosis. In 2004 Girard et al (10) reviewed the literature for reports on opportunistic infections in sarcoidosis. They identified 65 such cases, and in 6 of them nocardiosis was

diagnosed. The other important infections occurring in the patients treated for sarcoidosis were: cryptococcosis, aspergillosis, histoplasmosis, mycobacteriosis and pneumocytosis. The mean time interval from the beginning of steroid treatment till the first symptoms of the opportunistic infection was 7 months. The authors concluded that sarcoidosis by itself was not a risk factor for opportunistic infections (except for cryptococcosis), and proposed that opportunistic infections were mainly associated with corticosteroid treatment (10).

The precise pathophysiology of sarcoidosis remains unclear. Different putative causative infectious agents have been implicated (14-16). Some authors have also suggested that infectious complications in sarcoidosis may represent the emergence of a so far an undiagnosed indolent granulomatous infection (not factual sarcoidosis) which can be initially masked by the systemic corticosteroid therapy (17). When sarcoidosis and granulomatous infection coincide the question whether one condition preceded and/or predisposed to the other is pending.

When sarcoidosis, or its exacerbation is suspected, a thorough microbiologic and serologic evaluation for possible infectious agents causing granulomatous diseases should be always considered, as sometimes their outcome can be fatal. Nocardiosis ought to be considered especially in the case of pulmonary and cutaneous involvement or systemic non-specific symptoms in patients with impaired cell-mediated immunity. When it is suspected, the prolonged incubation of the cultures should be performed. In our case recognition of the causative agent appeared to be difficult. The diagnosis could have been done earlier, but microbiological cultures were held only for 72 hours – not enough to determine *Nocardia* species.

Molecular methods should be used when phenotypic study does not lead to a conclusive identification. Moreover, molecular methods based on 16S rDNA amplification and sequencing should also be used on clinical samples which cultures remain sterile.

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