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Disseminated *Nocardia farcinica*: Case report and review

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Case report

Disseminated nocardiosis is a well-described infection occurring in immunosuppressed individuals. Of the several species of *Nocardia*, *Nocardia farcinica* is being increasingly recognized as a pathogen capable of causing severe systemic disease. Described here is a case of disseminated nocardiosis with involvement of the brain, eyes, lymph nodes, and lung with biopsy-proven *N. farcinica*, with a discussion of the diagnosis and management of this particular patient. A review of disseminated nocardiosis in general, as well as of *N. farcinica* in particular, follows.

Diseminirana Nocardia farcinica: prikaz bolesnika i pregled literature

Prikaz bolesnika

Diseminirana nokardioza je infekcija koja se javlja kod imunosupresivnih osoba. Među nekoliko vrsta *Nocardia*, *Nocardia farcinica* se sve više prepoznaje kao uzročnikom teških sistemskih bolesti. U radu se opisuje slučaj biopsijom dokazane diseminirane nokardioze uzrokovane *N. farcinica*, koja je zahvatila mozak, oči, limfne čvorove, te pluća te se raspravlja o postavljanju dijagnoze i liječenju ovog bolesnika. Donosi se i opći pregled diseminirane nokardioze, a posebno one koju uzrokuje *N. farcinica*.

Case Report

A 53 year-old woman presented to the emergency department with a three-week history of generalized weakness, subjective fever, and new swollen mass below her left mandible. Four months earlier, she had been diagnosed with idiopathic Type I membranoproliferative glomerulonephritis and had been treated with a prednisone taper and chronic azathioprine. On examination, she was noted to have a fever to 39.5 °C, a swollen, indurated, tender cervical lymph node below the left mandible, and asymmetric weakness in the left leg compared to the right. The rest of her physical exam, including her pulmonary evaluation and neurological examination, were unremarkable.

Laboratory evaluation at admission revealed a total leukocyte count of 21,000/mm^3, of which 93 % were granulocytes. Her platelet count was 405,000/mm^3, more than double that from the previous month. She was also noted to have a new anemia, with a hemoglobin of 7.0 g/dL. A chest radiograph suggested posterior left lower lobe opacity, while a radiograph of the mandible did not demonstrate any bony abnormalities. A non-contrasted computed tomography scan of the chest revealed a large left-sided pulmonary consolidation with cavitation, as well as numerous scattered sub-centimeter pulmonary nodules throughout both lower lobes accompanied by shotty mediastinal lymphadenopathy. Due to the asymmetric lower extremity weakness noted on examination, magnetic resonance imaging of the brain was performed. This study revealed a 4.0 × 3.6 × 4.5 cm multilobulated cystic mass in the right frontal lobe with surrounding vasogenic edema. Numerous other smaller cystic lesions, the largest 1.4 cm in diameter, were noted diffusely throughout the brain and occurred at the gray-white matter junction. There was also a 5 mm rightward anterior midline shift without evidence of cerebellar herniation.

A sputum gram stain and culture was obtained, which revealed numerous polymorphonuclear neutrophils and beaded filamentous gram positive bacilli. Fine needle as-

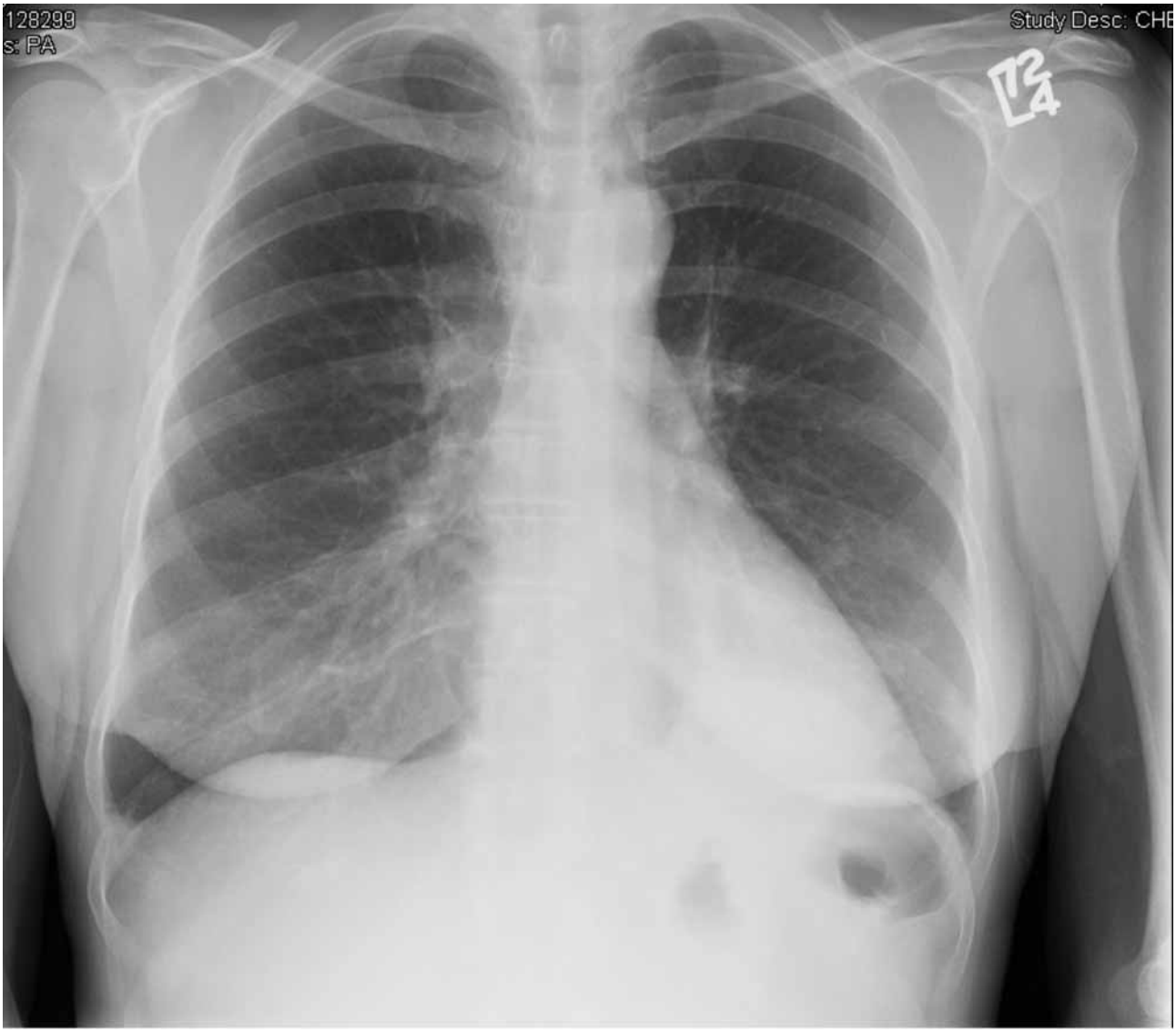


Figure 1.

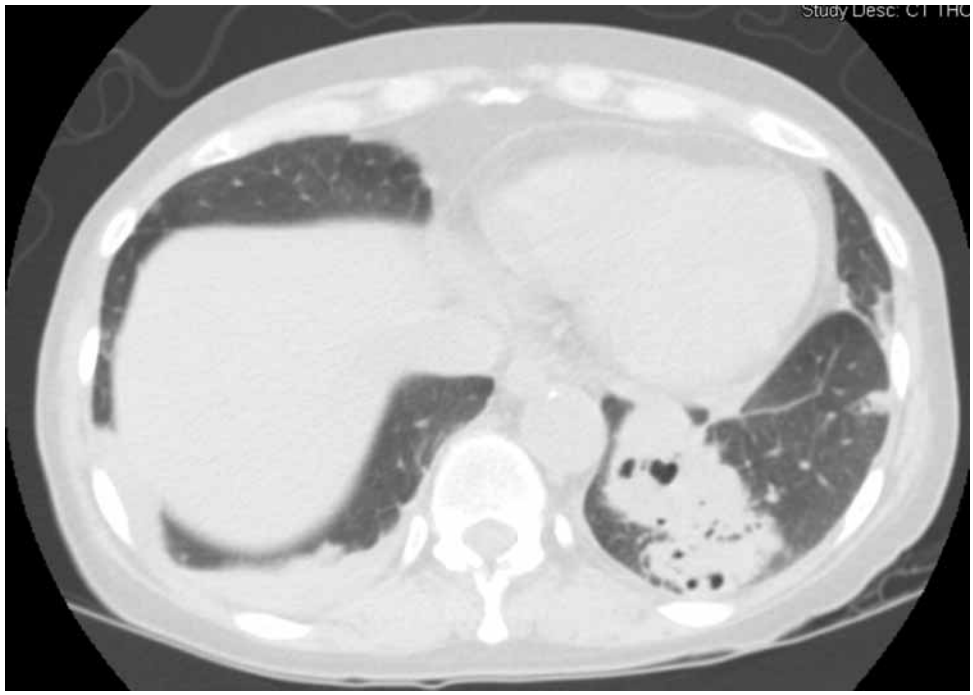
Slika 1.

piration of the inflamed sub-mandibular lymph node was performed, revealing numerous neutrophils and necrotic debris as well as numerous branching gram positive bacilli. Resection and drainage of the largest cerebral abscess in the right frontal lobe was performed via craniotomy; the brain tissue also showed branching, filamentous gram positive bacilli. All three of these cultures grew the same organism, *Nocardia farcinica*.

Due to the severity of her disease, this patient was initially treated with a combination of intravenous high-dose trimethoprim-sulfamethoxazole, intravenous ceftriaxone, and oral minocycline. Resistance testing revealed that she had two different strains of the organism with slightly different resistance patterns. Combined, the two strains were resistant to ciprofloxacin, clarithromycin, imipenem, ceftriaxone, and minocycline but were sensitive to trimethoprim-sulfamethoxazole, linezolid, and amikacin. Once her sensitivity pattern became available and she clinically improved, her antibiotic regimen was switched to oral trimethoprim-sulfamethoxazole and linezolid.

This patient's case became further complicated when, one month after discharge, she noted a week-long gradual onset of blindness in her right eye. Ophthalmologic evaluation revealed evidence of endophthalmitis, likely due to nocardia as well. She was treated with intravitreous injections of amikacin into the affected eye.

After 2 months of treatment for her condition, the patient continues to have significant cerebral disease on repeat brain imaging and has little improvement in her right eye vision. She is, however, ambulatory, and continues to be treated as an outpatient at this time.



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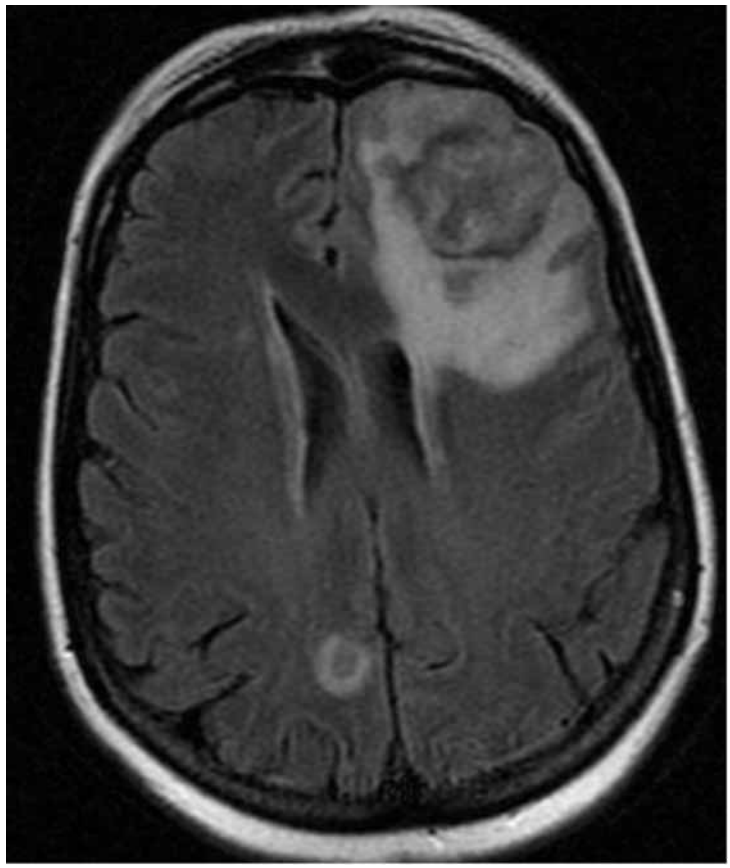

Figure 3.

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Discussion

Microbiology

As aerobic actinomycete bacteria, *Nocardia sp.* appear on gram stain as beaded, branching, filamentous gram positive bacilli. The organisms are also weakly acid-fast on Fite staining. The genus *Nocardia* contains numerous species, only some of which are known to cause human disease. Of these, the most significant are *N. asteroides*, *N. brasiliensis*, *N. transvalensis*, and *N. farcinica*. Individual species are often identified through 16S rRNA gene sequencing [1].

Nocardia sp. are ubiquitous environmental bacteria found in soil, water, and organic material. Human disease often occurs through either pulmonary inhalation or inoculation via a wound [1].

Pathophysiology

Nocardia sp. can affect both immunocompetent and immunocompromised hosts. During infection, neutrophils and monocytes initiate the host defense against nocardial infection. However, the bacteria have distinct cell wall protein complexes which create varying levels of virulence amongst the different strains, both amongst and between bacterial species. As a result, bactericidal activity is variable when neutrophils first encounter *Nocardia*, as determined by the cell wall structure of the organism [2]. Pus and abscess formation are often seen clinically as a result of the neutrophil response.

In immunocompetent hosts, cellular immunity typically plays the greatest role in controlling and clearing infection. Though the precise mechanisms of T cell and cytokine function against *Nocardia* are not completely known, data exist which suggest there is some interaction involving T cells, IL-1, and TNF. T cells have been shown to recruit macrophages to sites of infection. In addition, T cells have also been implicated in direct bactericidal activity [2, 3]. While the details of immunologic clearance of *Nocardia* are not fully understood, it does appear that T cells and cellular immunity play an important role in clearing the organisms.

With the role of cellular immunity established in immunocompetent hosts, several populations of at-risk immunocompromised hosts can be identified. Individuals receiving immune-modulating agents are thus at highest risk. These populations include individuals on chronic corticosteroids [4], solid organ and stem cell transplantation recipients, and individuals on immunomodulators such as tumor necrosis factor blockers [5]. AIDS patients are susceptible to nocardiosis as well, but, interestingly and for unexplained reasons, do not often develop nocardial infections [6]. All these groups are at higher risk for overwhelming disseminated infection due to their suppressed cellular immunity.

Both immunocompetent and immunocompromised individuals can develop cutaneous nocardial infection or disseminated, invasive nocardiosis. Disease manifestation in each individual depends on a combination of route of acquisition of infection, virulence of the specific nocardial strain, and immunocompetence of the affected host. Animal studies suggest that more virulent strains have a predilection for lung and brain tissue and several factors affect the degree of invasiveness of the organisms [7].

Disease Manifestations

In humans, nocardial infection can present in a variety of forms, ranging from localized cutaneous disease to disseminated, multi-organ invasion. Cutaneous or lymphocutaneous disease is typically seen in immunocompetent individuals, but can occur in the immunocompromised as well. All the pathogenic *Nocardia* species are capable of causing cutaneous disease, but *N. brasiliensis* and *N. asteroides* most commonly present this way. Cutaneous nocardial infections occur after inoculation from a wound, such as after a puncture or laceration. Wound contamination is often from an environmental source. The lesions typically appear as a nodular lymphangitis, also known as sporotrichoid lesions, with erythematous, indurated suppurative nodules advancing along lymphatic tracts [1]. These lesions rarely become invasive, but can occasionally be a source of systemic disease. Diagnosis can typically be made via wound culture.

Pulmonary nocardiosis typically occurs after inhalation of environmental organisms. In one study, 40 % of reported cases of nocardial infection were pulmonary, with 90 % of those being due to *N. asteroides* [2]. Fever, malaise, cough, dyspnea, and pleuritic chest pain are common manifestations of pulmonary disease; however, many immunocompromised patients can develop severe disease and be virtually asymptomatic due to their lack of appropriate inflammatory immune response. Radiographic signs of disease can vary, but often include diffuse nodular opacities, consolidation, and cavitation. A particular hallmark of *Nocardia sp.* (though not pathognemonic), is the ability of the organism to cross tissue planes and invade adjacent structures, creating fistulas [1]. Diagnosis of pulmonary disease can be made from sputum culture, but often requires bronchoscopy with direct culturing of the lung lesions.

Some virulent *Nocardia* strains are particularly adept at invading through the lung tissue and disseminating via the bloodstream. Dissemination can occur in both immunocompetent and immunocompromised hosts, but is often much more severe and rapidly progressive in the latter group. The brain is a particular site of dissemination, which may be explained in part by the organism's molecular preference to invade brain tissue. Symptoms of brain involvement, such as focal neurological deficits, seizure,

and obtundation are broad and nonspecific; infected individuals can in fact be asymptomatic as well [1]. Central nervous system disease can be rapidly progressive and fatal. Often numerous metastatic infectious lesions will be seen throughout the brain parenchyma.

Treatment

Several drugs are potentially available to treat nocardiosis, though resistance patterns can differ amongst species and between strains within a species. Sulfonamides have traditionally been the primary option for therapy. Typically, initial therapy is intravenous, with higher doses of sulfonamide in pulmonary or disseminated disease. Due to reports of sulfonamide monotherapy failure, severe cases of nocardiosis are often treated with two or more agents [8]. Often therapy can be transitioned to oral antibiotics after 3 to 6 weeks of intravenous therapy; this decision, however, is usually made at the discretion of the treating clinician [1]. In some cases, due to resistance, allergies, or drug toxicities, alternative agents to sulfonamides are available. Active drugs against *Nocardia* include fluoroquinolones, tetracyclines (particularly minocycline), carbapenems, and ceftriaxone, though resistance patterns can vary for each isolate [1]. Linezolid, a newer oxazolidinone antibiotic, has been shown to have adequate clinical efficacy with good activity against all *Nocardia* and little documented resistance at this time [9, 10].

Surgical management is often indicated in complement to antibiotic therapy. In particular, large, easily accessible brain abscesses may require surgical drainage, especially if there is no apparent response after 4 weeks of antibiotic therapy [11]. Drainage of other large pus collections is often at the discretion of the treating clinician, using general criteria for bacterial abscesses.

Once appropriate parenteral therapy is initiated, infected individuals typically show a clinical response within the first 5 to 7 days. Usually, 3 to 6 weeks of intravenous therapy is required before switching the patient to appropriate oral antibiotics [1]. If possible, immunosuppressive drugs are occasionally tapered or removed to promote clearance of the organisms, though adequate treatment can be achieved without changing immunosuppressive regimens [1]. Cutaneous lesions in immunocompetent patients typically take up to 3 months of total antibiotic therapy until resolution. More invasive disease often requires 12 months or longer of antimicrobial therapy [1]. Immunocompromised patients, particularly those with severe disease and high levels of immunosupression, may end up on long-term therapy or prophylaxis for life, at the discretion of the treating clinician.

The outcome is usually good in patients with isolated cutaneous disease, with one study quoting nearly a 100 % cure rate. The same study notes a 90 % cure rate in those with isolated pulmonary disease, 63 % in disseminated disease, and 50 % in those with brain abscesses [8]. Another study notes a 31 % mortality rate in individuals diagnosed with brain abscesses, rising to 55 % in the immunocompromised population [11].

Nocardia farcinica

Originally described as a bovine pathogen, *N. farcinica* is being increasingly recognized as an agent of disseminated human nocardiosis. As early as 1975, the species was found to be a potential cause of disease in humans [12]. Many of the case reports on human disease relate to disseminated disease, particularly in immunocompromised hosts. Nonetheless, the organism can cause the same spectrum of disease as the other pathogenic *Nocardia sp.*

A distinguishing feature of *N. farcinica* is its tendency to be resistant to numerous antibiotics [13]. Several studies over the years suggest that this species of *Nocardia* has innate resistance to 3rd generation cephalosporins, erythromycin, tobramycin, gentamicin, kanamycin, and beta-lactam antibiotics [14, 15]. In vitro data suggests that two newer antibiotics, imipenem and linezolid, have activity against *N. farcinica* [16, 17]. The organism, however, appears to have variable resistance patterns to drugs in the carbapenem class. Treatment success has been reported with the quinolone antibiotic moxifloxacin [18]. Sulfonamides remain the mainstay of therapy against *N. farcinica* infection.

Conclusion

Nocardiosis can be a difficult infection to identify and treat. While cutaneous disease is often noted early, invasive disease in immunocompromised individuals is often diagnosed late in the disease course. Delayed diagnosis can lead to a poor outcome. In addition, *N. farcinica* presents the unique treatment challenge of being resistant to many of the common drugs used to treat other *Nocardia* species. Nocardial infection should be considered early in the differential diagnosis of all immunosuppressed patients with fever and pulmonary or CNS lesions.

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