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Case Report

Disseminated nocardiasis by *Nocardia farcinica*: Review and first case report from Central India

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ARTICLE INFO

Article history:

Received 2 August 2018

Accepted 20 November 2018

Keywords:

Nocardia farcinica

Disseminated

Infection

Systemic lupus erythematosus

This case of disseminated nocardiosis is reported to emphasise that *Nocardia farcinica*, a rare isolate, can cause severe infection and, if diagnosed timely and appropriately managed, can prevent morbidity and mortality.

Case report

A 42-year-old female patient, a known case of systemic lupus erythematosus (SLE) presented with altered mental sensorium since 3 days at Jan Swasthya Sahyog (JSS), Ganiyari; a 70-bedded rural hospital in Chhattisgarh in March 2017. She also had difficulty in breathing for the past 15 days, and cough with expectoration, right-sided chest pain, low-grade intermittent fever for the past 2 months.

The patient was on cyclophosphamide, hydroxy-chloroquine and diuretics for treatment of SLE since October 2016. Despite the therapy, patient remained proteinuric with reduced appetite, pedal oedema and gradually developed lupus nephritis. Since mid of January 2017, she developed chest pain on right side and cough with expectoration. Differential diagnosis of pulmonary tuberculosis and lupus serositis was considered. Accordingly, thoracocentesis was done twice before, which was fluid negative for *Mycobacterium tuberculosis* by Cartridge-based nucleic acid amplification technique-Gene Xpert *Mycobacterium tuberculosis*/Rifampicin (MTB/RIF).

On clinical examination, the patient was disoriented with time, place and person and had neck stiffness, anasarca with pedal oedema and bilateral subcutaneous nodules in infra-axillary region which were firm, 4 × 4 cm in size and tender.

Introduction

Nocardiae are aerobic actinomycetes found ubiquitously in nature across the world, with more propensity in warm and humid regions. Primary mode of its transmission is air through respiratory tract.¹ *Nocardiae*, primarily an opportunistic pathogen, produces infections in immunocompromised individuals, but sometimes it can cause infections in immunocompetent patients as well.² The spectrum of infections caused by *Nocardia* ranges from indolent cutaneous and subcutaneous lesions to life-threatening disseminated infections, involving two or more body sites with or without nocardemia.¹

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<https://doi.org/10.1016/j.mjafi.2018.11.006>

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The Central Nervous System (CNS) examination indicated left-sided hemiplegia (Grade 2/5) with brisk reflexes on left side and bilateral extensor plantar reflex. Respiratory system examination revealed right lower lobe consolidation with pleural effusion. The patient was managed with prednisolone, hydroxychloroquine, furosemide and intravenous broad-spectrum antibiotics. On the second day of in-patient stay, she had one episode of generalised seizures for which phenytoin was added to the treatment protocol.

Haematological and biochemical investigations of blood revealed total leucocyte count at 22,400 cells/mm³ with 86% neutrophils, normal blood sugar and deranged renal function tests. CSF examination showed no cells, protein: 24 gm/dl and sugar: 56 gm/dl. No abnormality was detected in routine urine examination. Viral markers for human immunodeficiency virus (HIV), hepatitis B and hepatitis C virus were non-reactive.

Computed tomography (CT) head showed multiple rim-enhancing parenchymal lesions consistent with abscesses (Fig. 1). Chest radiograph and CT chest findings were suggestive if abscess is in the lower zone of the right lung (Fig. 2).

Thoracentesis was performed to drain pleural fluid, and the sample collected was immediately transported to the Department of Microbiology, AIIMS Raipur, for complete microbiological analysis. Gram stain of pleural fluid showed plenty of pus cells and gram-positive fine beaded, branching filamentous bacteria (Fig. 3), which were partially acid fast with modified Ziehl-Neelsen (ZN) stain (Fig. 4). Same morphology of bacteria was observed with Gram stain and modified ZN stain of Fine Needle Aspiration Cytology (FNAC) material obtained from infra-axillary subcutaneous nodules.

Preliminary report of *Nocardia* was informed to the treating physician. Empiric antibiotic therapy with intravenous ceftriaxone was started.

Culture of pleural fluid on blood agar showed non-haemolytic, dry, white, chalky irregular colonies following 48 h of incubation at 37 °C (Fig. 5). The isolate was presumptively identified as *Nocardia* spp. by standard laboratory biochemical tests. The antibiotic therapy of the patient admitted at JSS was changed to meropenem and amikacin with oral trimethoprim-sulfamethoxazole (TMP-SMX).

Gram stain or modified ZN staining of the patient's sputum and CSF was negative for nocardia. No pathogen was isolated from blood, CSF and sputum culture either.

The bacterial isolate from the pleural fluid was sent to Post Graduate Institute of Medical Education and Research, Chandigarh, where it was identified as *N. farcinica* by matrix-assisted laser desorption-ionisation time of flight mass spectrometry (MALDI-TOF-MS; Make—Vitek—MS, Biomerieux, France). The pure bacterial colony was tested by MALDI-TOF MS after formic acid-acetonitrile extraction, and mass spectra was acquired with a MALDI-TOF MS score of 2.1. A cut-off of MALDI-TOF MS score ≥ 1.9 was taken for identification to the species level.³ The isolate was confirmed, and the patient was finally diagnosed as a case of disseminated nocardiosis by *N. farcinica*.

Patient was discharged 20 days later with significant clinical improvement. Meropenem, amikacin, and TMP-SMX was continued for a total of 2 months, followed by monotherapy with TMP-SMX for 1 year (continued till April 2018). Prednisolone was withdrawn completely after tapering with no recurrence of nephritis.

During her recent consultation at JSS in December 2017, complete resolution in chest symptoms was noted. Chest radiograph image also revealed complete clearing (Fig. 6). There were no neurological complaints; normal mental functions, grade 5 power in both upper and lower limbs of right side. She was able to perform all her daily activities and chores independently.

Discussion

Nocardiosis is an opportunistic, localised or granulomatous infection caused by several species of the genus *Nocardia*. Among the pathogenic species, *Nocardia asteroides* complex and *Nocardia brasiliensis* are most commonly associated with human disease.¹ In 1888, Nocard isolated an actinomycete from cows, which was characterised and named as *N. farcinica*, grouped with *N. asteroides*.⁴ In 1969, Wallace et al demonstrated that *N. farcinica* formed an independent species distinct from *N. asteroides*.⁵ The *N. asteroides* complex was separated on the basis of antibiotic susceptibility pattern into five different series.⁶ This study also set a base for other investigator to perform drug susceptibility testing for *Nocardia* isolates. All the *Nocardia* groups described by Wallace are capable of causing pulmonary nocardiosis while *N. asteroides* type VI is capable of causing cutaneous nocardiosis.⁷

Morphologically, *Nocardia* are thin, filamentous gram-positive bacilli that exhibit varying degrees of acid-fastness. The bacteria grow readily over most of the routine laboratory media such as blood agar, brain heart infusion agar, Sabouraud's dextrose agar and Lowenstein–Jensen agar. Species identification can be done by conventional biochemical methods such as ability to grow in lysozyme broth, growth at 45 °C, catalase, urease and pyrolydonyl arylamidase production, in addition to hydrolysis of casein, tyrosine, xanthine, gelatin, esculin and hypoxanthine; acid production from different sugars; citrate utilisation and nitrate reduction and/or newer techniques such as molecular methods or MALDI-TOF MS.⁸ The laboratory work-up for isolation of *Nocardia* warrants collection of many samples as only one-thirds of them may reveal *Nocardia*.⁹

N. farcinica is distinct from other species in its clinical behaviour. It is more virulent, has a tendency to disseminate, especially to neural tissue and shows more resistance to antibiotics. The hosts usually have some underlying predisposing condition in 85% cases. The infection often spreads to the brain, kidney, joints, bones and eyes. Pulmonary or pleural infections (43%) are commonest, followed by brain abscesses (30%).¹⁰ In our case, *N. farcinica* was isolated from pus from pleural cavity and Fine needle aspirated (FNA) material from subcutaneous nodules.

The relative frequency of *N. farcinica* among clinical nocardial isolates is difficult to determine because of inadequate reporting and may vary geographically. *N. farcinica* is one of the least common clinical isolate among all pathogenic species of *Nocardia*. However, in Germany, the prevalence of *Nocardia farcinica* is twice as common as other nocardia species.¹¹

Disseminated infections were reported in 37.5% cases. Among the patients with disseminated infections, 88% had

Fig. 1 – Computed tomography of head showing multiple rim-enhancing parenchymal lesions consistent with abscesses.

one or more predisposing factors or risk factors leading to immunocompromised state such as solid organ transplant, malignancy, HIV infection, SLE, diabetes, etc.¹² Our case also has a comorbid condition of SLE, treated with immunosuppressive therapy predisposing her to disseminated infection with *N. farcinica*.

Several cases of *N. farcinica* infections have been reported from India as well. Chaudhari et al. reported brain abscess in an immunocompetent individual.¹³ A case of brain abscess because of *N. farcinica* has been reported in a patient of chronic demyelinating neuropathy on steroid therapy from Kerala.¹⁴ The present case also had multiple brain abscesses by *N.*

Fig. 2 – Computed tomography of chest showing right-sided loculated fluid collection with air fluid level consistent with abscess.

Fig. 3 – Gram staining of empyema pus ($\times 1000$)—showing Gram-positive, unevenly stained, thin, filamentous branching bacteria, suggestive of *Nocardia*, in the background of polymorphonuclear leucocytes.

Fig. 4 – Modified Ziehl–Neelsen staining of empyema pus ($\times 1000$) using 1% sulphuric acid as decolouriser showing thin, filamentous, branching partially acid-fast bacteria, suggestive of *Nocardia*, in a background of many polymorphonuclear leucocytes.

Fig. 5 – Non-haemolytic, dry, white, chalky irregular colonies of *Nocardia* spp. on blood agar culture medium.

Fig. 6 – Chest Radiograph after 8 months of therapy showing no signs of abscess or fluid collection in pleural cavity signifying complete resolution.

farcinica. The patient however survived with no morbidity due to timely appropriate diagnosis and proper management. There are also reports of pulmonary nocardiosis both from immunocompromised as well as immunocompetent patients caused by *N. farcinica* from different parts of the country.^{15–17}

To the best of authors' knowledge, it is the first case of disseminated nocardiosis involving two or more sites, i.e. lungs, brain and subcutaneous tissue/lymphatics, by *N. farcinica* in a patient of SLE, from Central India.

There are no diagnostically specific signs because the clinical presentation has a full spectrum of either acute or chronic infection, either in pulmonary or CNS nocardiosis. It is therefore difficult to diagnose and treat. Radiology, especially CT scan and magnetic resonance imaging, plays an important role in identifying and locating such lesions. However, aetiological diagnosis would require laboratory confirmation.⁵

The treatment options and antibiotic susceptibility pattern among different species of *Nocardiae* have wide variations. It is found to be resistant to most β -lactam antibiotics, aminoglycosides and susceptible to ciprofloxacin, imipenem and TMP-SMX.⁵ Currently TMP-SMX is accepted as drug of choice. In a recent treatment guideline released by Indian Council of Medical Research (ICMR), TMP-SMX and combination of imipenem-cilastin are mentioned as empiric antibiotic for treating brain abscess or subdural empyema due to *Nocardia* spp.¹⁸ So far as duration of therapy is concerned, it is recommended that a patient of disseminated nocardiosis should be treated for at least 6 months. If brain is involved, the duration of therapy should be extended to 12 months.¹⁸

Conclusion

It is concluded that *N. farcinica* is not so rare bacterial species and is fast emerging as an important pathogen which may be attributed to the wide use of immunosuppressive drugs, improved diagnostic tests and increased awareness among microbiologists and health professionals. It may also happen that nocardiosis may be missed in the event of concomitant occurrence of more prevalent chronic infectious disease such as tuberculosis in developing countries like India. It is also important to accurately detect and identify *Nocardia* species for prediction of antimicrobial susceptibility because different species have emerged in terms of their antibiotic susceptibility pattern, virulence and epidemiology. A differential diagnosis of nocardial infections should be considered while dealing with indolent infections that are not responding to third generation cephalosporins, especially when multiple sites are involved. Gram stain and modified ZN stain are excellent, rapid and economical tests as they can provide timely relevant information to the clinician and help initiate empirical therapy. Newer technique such as MALDI-TOF MS provides a rapid and precise assay for speciation of *Nocardia*, as compared with conventional techniques that are tedious, require expertise and are time- and labour-intensive.

Conflict of interest

The authors have none to declare.

Acknowledgement

The authors acknowledge the help of Prof. Pallab Ray for providing species identification of the *Nocardia* isolate in the Department of Bacteriology, PGIMER, Chandigarh by MALDI-TOF MS.

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