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Disseminated *Nocardia asiatica* infection in an immunocompromised individual: A rare entity needs careful vigilance

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ABSTRACT

Nocardia asteroides complex and *Nocardia brasiliensis* are common etiological agents of disseminated nocardiosis among immunocompromised individuals. Here we reported an uncommon case of disseminated nocardiosis with the involvement of lung, brain, soft tissue & pancreas by a rarely isolated species *Nocardia asiatica* in a HIV infected individual. Diagnosis was initially misinterpreted as tuberculosis based on the clinical and radiological findings. The isolate was identified to the species level with a 16S rRNA gene analysis & in vitro susceptibility was done as resistance is not uncommon among them. Clinical cure & radiological regression of lesions was observed except for brain after treatment with meropenem, amikacin & cotrimoxazole.

Contents

Introduction

Nocardia species are aerobic, Gram-positive, branching and filamentous bacteria. They are unusual pathogens and mostly affect immunosuppressed individuals. They cause either localized or disseminated infection [1]. Disseminated nocardiosis is an infection of two or more organs with or without bacteremia caused by it [2]. In the immunocompromised patient, the lung is the primary focus, before spreading haematogenously to the central nervous system (CNS) or other organs [3]. Disseminated *Nocardia asiatica* infection is a rare disease which can present with varied forms [4]. The highly diverse clinical presentation, and low general awareness are adding to the underreporting of the disease, which largely remains underdiagnosed in India. Here, we are reporting a case of disseminated nocardiosis by *N.. asiatica* in an HIV infected individual, presenting with pancreatic & paraspinal abscesses. To the best of our knowledge, this rare clinical entity has not been documented in the literature, and the same is highlighted with literature review (Table 1).

Case report

A 37 years old man with the retroviral disease presented to our tertiary care hospital with persistent diffuse abdominal pain and vomiting for last 2 months, along with swelling in the back since 15 days, and high grade, intermittent fever with chills and rigor for the past 2 days. He also complained of anxiety for last many years.

His past history included HIV antibodies positive status with CD4 count 55cells/mm^3 and he was on anti-retroviral therapy with

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Table 1
Nocardia asiatica infection reported in the literature.

Case Reports	Age(in yrs)	Underlying predisposing conditions	Site(s)of infection	Therapy given	Outcome
1. Haussaire et al. [2]	63/M	Seborrheic pemphigus on steroids	Lung, brain	Trimethoprim sulfamethoxazole, carbapenem, cefotaxime for 32 weeks + surgery	Neurological sequelae
2. Iona et al. [5]	45/M	HIV	Skin	Cotrimoxazole for 3 months & doxycycline for 5 months	Cured
3. Verfaillie et al. [6]	57/F	COPD	Lung	Linezolid	–
4. Matsumoto et al. [7]	60/M	Malignancy	Lung	Cotrimoxazole & meropenem	Cured
5. Ambrosioni et al. [3]	49/M	Myasthenia gravis Malignant thymoma	Heart, brain, anterior mediastinum	Imipenem, amikacin, and trimethoprim sulfamethoxazole for 9–12 months	CURED
6. Leitner et al. [8]	66/M	NIL	Olecrenon bursa	Cotrimoxazole for 10 days & Linezolid for 20 days	Cured
7. Saraya T et al. [9]	66/M	COPD on steroid	Lung	Amikacin & imipenem	Cured
8. Okawa et al. [10]	64/F	NIL	Lung	trimethoprim-sulfamethoxiazole for 9 months	Cured
9.Suemori et al. [11]	76/M	ANCA associated Vasculitis, old PTB, steroids	Lung	Doripenem, Cotrimoxazole	Cured
10. Uneda et al. [12]	65/M	AIHA on steroids	Lung, Brain	Cotrimoxazole for 5 months and further follow up continued	CURED
11.Jeong et al. [13]	51/M	SLE on steroids	Brain	Cotrimoxazole, Ceftriaxone for ten months	Expired
12. Present case	37/M	HIV infection	Lung, brain, skin & pancreas	Amikacin & meropenem for 3 months followed by trimethoprim sulfamethoxazole continued & asked for follow up visit	Cured except brain lesion

tenofovir (300 mg), lamivudine (300 mg) and efavirenz (600 mg) for past one month. At the same time, he was misdiagnosed for pulmonary tuberculosis. On the basis ofclinical featureslike chronic cough & intermittent fever, suggestive radiological picture like right & left upper zone opacities and cytolological finding of the lymph node aspirate, the patient was started with antitubercular therapy. CT(computed tomography) chest also showed, cavity in the left upper zone and multiple necrotic mediastinal lymph nodes (Fig. 3). On fine needle aspiration cytology (FNAC)necrotic areas along with few granulomas in the lymph node were seen. But his sputum was negative for *Mycobacterium tuberculosis* by acid fast stain & GeneXpert (Cepheid).

During current visit, he was febrile (39.7 °C) with tender, erythematous cystic swelling of $6 \times 4\,cm^2$ was present at the paraspinal region. MRI thoracolumbar spine and brain showed well defined peripherally enhancing collection in the subcutaneous plane of the thoracolumbar region from D11-L1with diffuse disc bulging at the level of L4-5 & L5-S1 (Fig. 2) and multiple intracerebral space occupying lesions respectively (Fig. 1). In CT abdomen and pelvis, well defined peripherally enhancing cystic lesion with enhancing septa within, measuring $7.4 \times 7.0 \times 7.2\,cm^3$ was noted in the body and proximal part of the tail of the pancreas. CT chest findings remained same as previous visit. No regression of the lesion was seen.

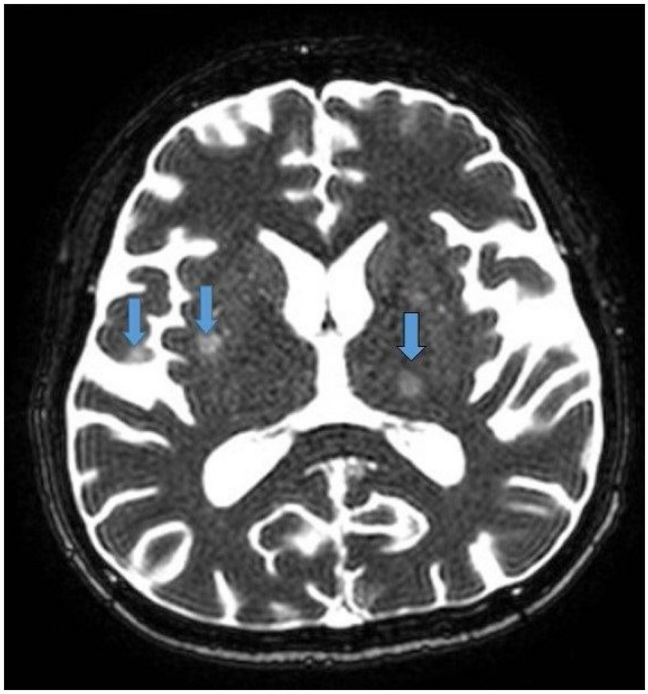

Fig. 1. Multiple intracerebral space occupying lesions.

Laboratory findings

Multiple pus samples collected from paraspinal region & pancreatic lesions showed many pus cells & plenty of Gram positive filamentous bacilli which were acid fast by modified Kinyoun stain. Culturing on chocolate & nutrient agar for 48 h at 37 °C under aerobic conditions yielded white, rough, and dry colonies. Pus was also put into the Robertson's cooked meat (RCM) broth intraoperatively and showed no growth after 7 days of anaerobic incubation. For the speciation of the isolate battery of biochemical tests like hydrolysis of casein, tyrosine, hypoxanthine, urease and growth at 45 °C was performed. But we could not come to any conclusive species identification from these tests. The isolate hydrolysed casein & urease, utilized citrate, and fermented glucose & trehalose. Bile esculin test was positive. The strain was finally identified using 16 s rRNA sequencing. BLAST analysis was used to screen sequence databases for the isolate. The sequence of the PCR obtained was compared with those stored in GenBank. Strain had shown to have >99% sequence similarity with *N. asiatica*. (http://www.ncbi.nlm.nih.gov/BLAST/). Antimicrobial susceptibility testing was performed by Kirby Bauer Disk diffusion method which was sensitive to amikacin, ceftriaxone, cotrimoxazole, gentamycin, doxycycline, linezolid, piperacillin–tazobactum, meropenem and resistant to ciprofloxacin and erythromycin. Blood culture was sterile. GeneXpert of pus samples & bronchoalveolar lavage fluid were negative for tuberculosis. He remained positive for HIV antibodies. The patient was treated with injection amikacin & meropenem for 3 months in the hospital & on discharge continued with oral cotrimoxazole & anti-retroviral therapy. Anti-tubercular treatment was discontinued after the final diagnosis came within 8 days of

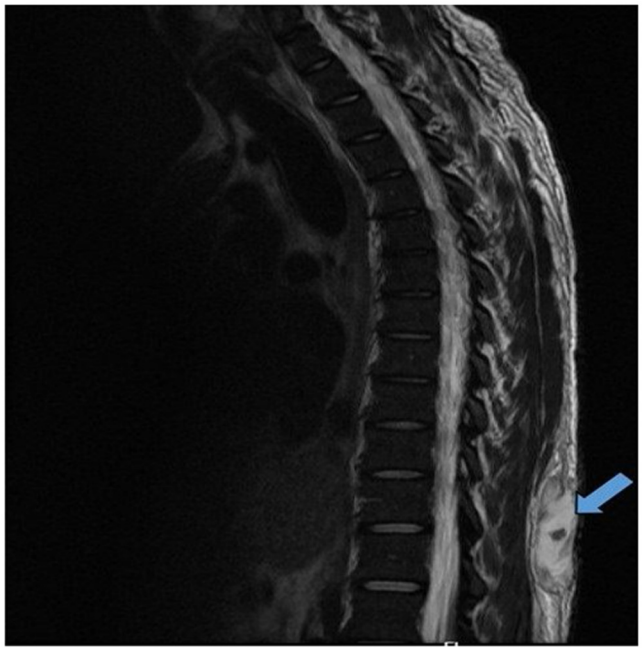

Fig. 2. MRI Thoracolumbar spine showing well-defined peripherally enhancing collection in the subcutaneous plane of the thoracolumbar region with multiple incomplete septations within, extending from D11-L1.

admission. On follow up visit, after 2 months, he was cured clinically. Radiologically all lesions regressed except in the brain. His CD4 count was raised to 118 cells/mm^3. Antiretroviral therapy and oral cotrimoxazole were continued until the next visit.

Discussion

This study reports the first case of disseminated nocardiosis by *N. asiatica* from India. *N. asteroids* complex is the most frequent etiological agent of disseminated nocardiosis [14]. Till now very few cases of disseminated infection reported by *N. asiatica* in the literature. Here we analyzed 11 cases of *N. asiatica* infection along with our example (Table 1). We found, out of 11 cases reported in the literature, 5 presented with an isolated lung infection [6,7,9–11]. Disseminated infection was observed in 3 cases and the brain was the most common site of dissemination [2,3,12]. In the present case, other than the brain, soft tissue and pancreas were the disseminated sites. Isolated infection of brain and skin were also reported in the literature [5,8,13]. The pancreatic abscess was a rare presentation in our case. So far very few cases of pancreatic abscess by *Nocardia* spp. like cyriasigeorgia & asteroides had been reported [15].

Nocardiosis is more prevalent in male patients than female. It is familiar with a mean age of 60 years having underlying immunocompromised conditions like HIV, malignancy, long-term steroid therapy, organ transplant [2]. Out of 11 cases *N. asiatica* described herein, 80% of them were immunocompromised. The common underlying predisposing condition was long-term steroid therapy (50%). In our case, HIV was the underlying risk factor. HIV patient with CD4 count <200 cells/mm^3 are more prone to having impaired neutrophil function, and antiretroviral therapy improves their function [5]. In our case, although the patient was on antiretroviral treatment for past one month, but his CD4 count was only 55 cells/mm^3 at the time of admission which explains poor compliance to the therapy that may have led to disseminated nocardiosis.

Disseminated nocardiosis commonly observed in immunosuppressed patients and lung is the primary localization site among them [16,17]. The cases reviewed for species asiatica documented the similar finding. Primary pulmonary nocardiosis mimics both clinically and radiologically as pulmonary tuberculosis [5]. In Chest radiography, several pictures like consolidation, irregular nodules, cavitary lesion, and interstitial infiltration, etc. can be observed [2,4,16]. In our case, clinical presentation, cavitary lesion on chest radiology, and granuloma of mediastinal lymph nodes led the diagnosis towards tuberculosis during his initial visit with initiation of treatment for pulmonary tuberculosis . Howeve his chest lesion did not resolve with the antitubercular therapy. It can be emphazsized therefore that a classic radiological picture of pulmonary tuberculosis that is unresponsive to anti-tubercular medication should raise the suspicion of Nocardia infection, especially in an immunocompromised patient.

Like other *Nocardia* spp, brain was found to be a common site of dissemination from the lung [18]. The most common clinical picture in the brain is a formation of multilocular abscess [19]. In differential diagnosis disseminated toxoplasmosis, tuberculosis and aspergillosis should be considered in an immunocompromised patient having both lung and brain foci. But none of the cases had any detail microbiological workup. The present case was misdiagnosed as disseminated brain abscess of tubercular origin [20].

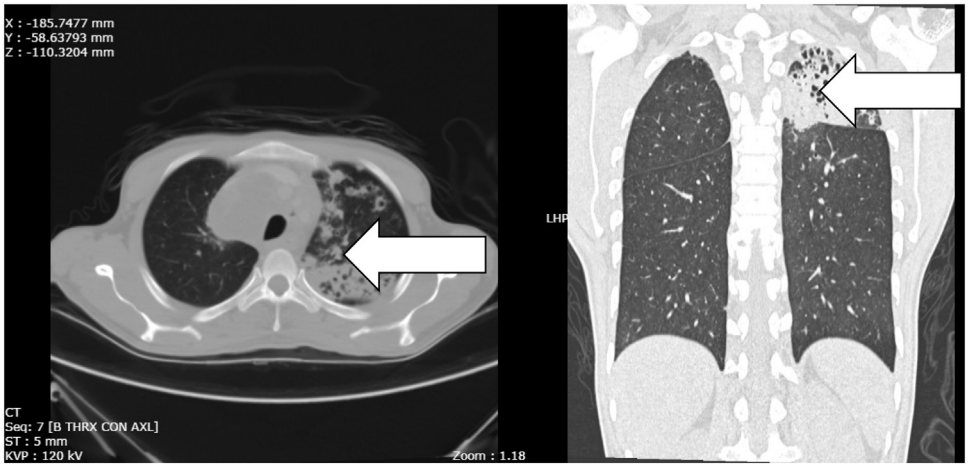

Fig. 3. HRCT AND CONTRAST CT STUDY OF THORAX showing Left upper zone cavity and multiple conglomerated peripherally enhancing lymphnodes with non-enhancing central necrotic areas noted in the pre and paratracheal, subcarinal and a few small in peripancreatic region largest measuring ~6.2 × 5.6 cm in the right lower paratracheal region.

We had to go through a challenging laboratory methods to identify the isolate at species level and perform the antimicrobial susceptibility testing in order to provide diagnosis at the earliest. Biochemical tests gave very inconclusive result and failed to discriminate between different species [7]. So final identification of species asiatica was accomplished by 16S rRNA sequencing, which along with sequencing of hsp65 gene may only give the correct differentiation of *Nocardia* species [21].

Standard therapy for nocardiosis depends on the degree of various organ involvement. Treatment of severe disseminated infection with the evidence of CNS involvement, consists of intravenous TMP-SMX or imipenem, combined with amikacin. An alternative to sulfa drug linezolid can be given for CNS infection [15]. Medical therapy should be combined with surgical drainage whenever required. All the disseminated *N. asiatica* infection treated with cotrimoxazole & carbapenem. Amikacin was combined with them in our case & case no. 2 [1]. Surgical drainage was done only in case 1 & 3 [2,4].

In an immunosuppressed patient, it requires 6–12 months of treatment to prevent recurrence and mortality [22]. During the follow up visit of around 5 months, most of the cases, except one, cured clinically and radiologically. In our patient, during the follow up visit after 2 months, a persistence of few lesions was observed in the brain. No new lesion or recurrence was found.

Conclusion

Disseminated *N. asiatica* infection is a rare disease which can mimic tuberculosis. So it may easily misdiagnosed by the clinician as tuberculosis as it is highly endemic. We report the first case of disseminated infection in India presented with a para-spinal & pancreatic abscesses in an HIV infected patient. Combination treatment with TMP-SMX, amikacin, and meropenem resulted in clinical cure while radiologicall regression of CNS lesions was not observed. So periodic radiological follow up is required to decide the treatment duration and to look for any new lesion or relapse.

References

[1] Wilson JW. Nocardiosis: updates and clinical overview. Mayo Clin Proc 2012.
[2] Haussaire D, Fournier PE, Djiguiba K, Moal V, Legris T, Purgus R, et al. Nocardiosis in the south of France over a 10-years period, 2004-2014. Int J Infect Dis 2017;57:13–20.
[3] Ambrosioni J, Lew D, Garbino J. Nocardiosis: updated clinical review and experience at a tertiary centre. Infection 2010;38:89–97.
[4] El-Herte RI, Kanj SS, Araj GF, Chami H, Gharzuddine W. First report of Nocardia asiatica presenting as an anterior mediastinal mass in a pa-tient with myasthenia gravis: a case report and review of the literature. Case Rep Infect Dis 2012;325767:1–4.
[5] Iona E, Giannoni F, Brunori L, de Gennaro M, Mattei R, Fattorini L. Isolation of Nocardia asiatica from cutaneous ulcers of a human immunodeficiency virus-infected patient in Italy. J Clin Microbiol 2007.
[6] Verfaillie L, De Regt J, De Bel A, Vincken W. Nocardia asiatica visiting Belgium: nocardiosis in a immunocompetent patient. Acta Clin Belg 2010;65(6):425–7.
[7] Matsumoto T, Shimizu T, Aoshima Y, Oda H, Kikuchi K, Katsura H, et al. Endobronchial hamartoma with obstructive pneumonia due to Nocardia asiatica. Gen Thorac Cardiovasc Surg 2011;59(2):141–4.
[8] Leitner E, Valentin T, Hoenigl M, Lanz P, Flick H, Zollner-Schwetz I, et al. First report of Nocardia asiatica olecranon bursitis in an immunocompetent traveler returning to Austria. J Clin Microbiol 2013;51(7):2461–2.
[9] Saraya T, Ohkuma K, Kikuchi K, Tamura M, Honda K, Yamada A, et al. Cytomegalovirus pneumonia in a patient with interstitial pneumonia and Nocardia asiatica presenting as cavitary lung lesions. Intern Med 2013;52(5):593–7.
[10] Okawa S, Sonobe K, Nakamura Y, Nei T, Kamio K, Gemma A. Pulmonary nocardiosis due to nocardia asiatica in an immunocompetent host. J Nippon Med Sch 2015;82(3):159–62.
[11] Suemori K, Miyamoto H, Murakami S, Yamazaki H, Ishizaki J, Matsumoto T, et al. Pulmonary Nocardiosis due to Nocardia asiatica in a Patient with ANCA-associated Vasculitis. Kansenshogaku Zasshi 2015;89(4):470–5.
[12] Uneda A, Suzuki K, Okubo S, Hirashita K, Yunoki M, Yoshino K. Brain abscess caused by Nocardia asiatica. Surg Neurol Int 2016;7:74.
[13] Jeong JH, Moon SM, Park PW, Ahn JY, Kim KH, Seo JY, et al. Multiple brain abscesses caused by Nocardia asiatica in a patient with systemic lupus erythematosus: the first case report and literature review. Ann Lab Med 2017;37(5):459–61.
[14] Shivaprakash MR, Rao P, Mandal J, Biswal M, Gupta S, Ray P, et al. Nocardiosis in a tertiary care hospital in North India and review of patients reported from India. Mycopathologia 2007;163(5):267–74.
[15] Martínez TR, Menéndez VR, Reyes CS, et al. Pulmonary nocardiosis: risk factors and outcomes. Respirology 2007;12:394–400.
[16] Singh A, Chhina D, Soni RK, Kakkar C, Sidhu US. Clinical spectrum and outcome of pulmonary nocardiosis: 5-year experience. Lung India 2016;33:398–403.
[17] McNeil MM, Brown JM. The medically important aerobic actinomycetes: epidemiology and microbiology. Clin Microbiol Rev 1994;7:357.
[18] Mamelak AN, Obana WG, Flaherty JF, Rosenblum ML. Nocardial brain abscess: treatment strategies and factors influencing outcome. Neurosurgery 1994;35:622–31.
[19] Lin YJ, Yang KY, Ho JT, Lee TC, Wang HC, Su FW. Nocardial brain abscess. J Clin Neurosci 2010;17:250–3.
[20] Meier B, Metzger U, Mller F, Siegenthaler W, Lthy R. Successful treatment of a pancreatic Nocardia asteroides abscess with amikacin and surgical drainage. Antimicrob Agents Chemother 1986;29(1):150–1.
[21] Rodríguez-Nava V, Couble A, Devulder G, Flandrois JP, Boiron P, Laurent F. Use of PCR-restriction enzyme pattern analysis and sequencing database for hsp65 gene-based identification of Nocardia species. J Clin Microbiol 2006;44:536–46.
[22] Rosman Y, Grossman E, Keller N, Thaler M, Eviatar T, Hoffman C, et al. Nocardiosis: a 15-year experience in a tertiary medical center in Israel. Eur J Intern Med 2013;24:552–7.