Case Report

Pulmonary Nocardiosis and Scrub Typhus in an Immunocompromised Host

Isabella Princess, R Ebenezer[1], Nagarajan Ramakrishnan[2], S Nandini[3]

Departments of Microbiology and [1]Department of Critical Care Medicine, Apollo Speciality Hospitals, Vanagaram [2]Departments of Critical Care Medicine and [3]Department of Microbiology, Apollo Hospitals, Greams Road, Chennai, Tamil Nadu, India

Abstract

Pulmonary infections are not uncommon in patients with an underlying immunocompromised condition. Unusual combination of microorganisms causing concomitant infections among these patients has also been reported. However, certain rare dual occurrences are usually unanticipated as in the case we present here. This case highlights the importance of being aware of the possible coexistence of infections in immunocompromised patients. To the best of our knowledge, this is the first report of coinfection with *Nocardia otitidiscaviarum* and *Orientia tsutsugamushi* in a critically ill immunocompromised patient from South India.

Keywords: Coinfection, immunocompromised, *Nocardia otitidiscaviarum*, nocardiosis, scrub typhus

Introduction

Nocardia is an aerobic Gram-positive bacilli occurring ubiquitously in the environment, especially in soil, decomposing organic matter, vegetation, etc. The organism gains entry into the human body through inhalation or traumatic injury.[1] Based on the route of entry, nocardiosis commonly manifests as pulmonary, cutaneous, or central nervous system disease. It gets disseminated from the primary source of inoculation to various parts of the body.[2] Although commonly causing fatal disease in the immunocompromised, nocardiosis has also been reported in immunocompetent individuals.[3] Pulmonary manifestations of nocardiosis may be subacute to chronic onset of productive or nonproductive cough, shortness of breath, chest pain, hemoptysis, and pleural effusion.[1] Complications may include erosion of ribs and empyema necessitans.[4]

Scrub typhus is a tropical infection caused by the obligate intracellular organism *Orientia tsutsugamushi*. Its prevalence is more pronounced in the tsutsugamushi triangle of South East Asian region. India thus falls under the tsutsugamushi triangle.[5] Pulmonary manifestations in patients with scrub typhus include varying grades of bronchitis and interstitial pneumonitis progressing to acute respiratory distress syndrome.[6]

Access this article online

Quick Response Code:

Website: www.jgid.org

DOI: 10.4103/jgid.jgid_105_17

Clinical manifestations of both these infections can be nonspecific due to overlapping clinical features. Lack of availability of rapid tests for diagnosing these infections makes early diagnosis difficult. Herein, we present a case of dual infection with pulmonary nocardiosis and scrub typhus in our critical care unit with fatal outcome.

Case Report

A 51-year-old male from a suburban town in Tamil Nadu, India, presented to our emergency department with a history of high-grade, intermittent fever and cough with expectoration for 15 days and breathlessness of 1-day duration. He was treated before hospitalization with nebulized bronchodilators, steroids, and quinolones. Significant past medical history included hypertension and childhood onset bronchial asthma requiring chronic steroid therapy. On admission to the ward, his symptoms persisted; examination findings revealed tachycardia, tachypnea, and bilateral crepitations with wheeze, more pronounced on the left side of the chest than the right [Table 1].

Address for correspondence: Dr. Isabella Princess, Apollo Speciality Hospitals, Vanagaram, Chennai, Tamil Nadu, India. E-mail: drisabella_p@apollohospitals.com

How to cite this article: Princess I, Ebenezer R, Ramakrishnan N, Nandini S. Pulmonary nocardiosis and scrub typhus in an immunocompromised host. J Global Infect Dis 2018;10:108-11.

Table 1: Clinical history and findings of the patient

Features	Findings
Age	51 years
Presenting complaints	Fever, cough with expectoration, breathlessness
Past history	
Diabetes mellitus	No
Hypertension	Yes, for 25 years
Bronchial asthma	Yes, for 40 years (on chronic steroid therapy)
Tuberculosis	No
COPD	No
HIV 1 and 2 antibodies	Negative
Smoking	No
X-ray chest findings	Patchy and consolidative opacities noted in bilateral lung fields involving the mid and lower zone (left > right) obscuring the costophrenic angles and domes of diaphragm
CT chest findings	Diffuse consolidation of whole of the left lung and right lung lower lobe; diffuse nodular lesions in the right lung upper lobe; areas of lung destruction in the left lung lower lobe
Treatment	Doxycycline, azithromycin, cotrimoxazole, imipenem, caspofungin
Outcome of the patient	Patient died on 7th day after admission

COPD: Chronic obstructive pulmonary disease, CT: Computed tomography

Due to respiratory distress, he was shifted to the multidisciplinary critical care unit. A thorough examination in critical care unit revealed an eschar on the left side of the chest typical of scrub typhus. Initially, the patient was placed on noninvasive ventilatory support. Dual coverage for scrub typhus with azithromycin and doxycycline was started. Since an outbreak of H1N1 cases was present, he was also empirically started on oseltamivir and throat swab for H1N1 by real-time polymerase chain reaction (RT PCR), and sepsis workup was initiated. He was intubated on the same day in view of worsening respiratory distress and hypoxemic respiratory failure. Antibiotics were escalated to meropenem and teicoplanin. Computed tomography (CT) scan of the brain, thorax, and abdomen was done after intubation. CT chest findings revealed bilateral multifocal patchy consolidation in both lungs, minimal right-sided pleural effusion, and collapse of left lung fields with consolidation [Figure 1].

Tracheal aspirate sent for Gram stain showed moderate polymorphonuclear neutrophils with many branching filamentous bacilli suggestive of an actinomycete, probably *Nocardia* species [Figure 2]. This was confirmed by a positive 1% acid-fast stain (modified Kinyoun method) [Figure 2]. The patient was started immediately on cotrimoxazole and meropenem was changed to imipenem. Two further tracheal aspirates done consecutively also revealed similar Gram stain findings. All three tracheal cultures showed pure growth of dry chalky white colonies with pitting on blood agar and chocolate agar [Figure 3]. Gram stain and 1% acid-fast stain from all cultures were consistent with preliminary findings. The organism was susceptible to amikacin, ciprofloxacin, linezolid, imipenem, and ceftriaxone, resistant to cotrimoxazole and amoxicillin – clavulanate. Cotrimoxazole was stopped. Resistance to penicillin (10 U) was a supportive finding in identification of the organism [Figure 3]. The final identification of *Nocardia* species was done by matrix-assisted laser desorption ionization time of flight mass spectrometry

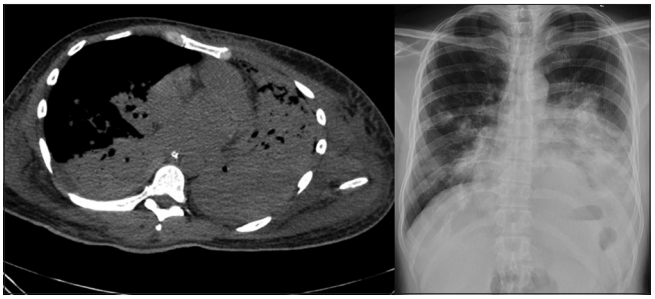

Figure 1: Computed tomography chest and X-ray images of the patient showing consolidation of the left lung with destruction of the left lung

(MALDI-TOF MS) as *Nocardia otitidiscaviarum* using standard protocols. MALDI-TOF MS works on the principle of mass spectrometry to identify microorganisms based on their mass to charge ratio. It has an excellent turnaround time for identifying multiple organisms within 3 h. In MALDI-TOF MS, the sample to be analyzed (bacterial colony) is mixed with another compound, called a matrix. Briefly, an isolated colony was picked up with a toothpick and spotted onto the MS slide. Once the colony dried, an on-plate extraction was performed using 1μl of 70% formic acid. Once this dried up, 1μl of HCCA matrix (α-Cyano-4-hydroxycinnamic acid) was added. The Vitek MS was set in the default IVD mode and spectra were analysed. Organism identification of 99.9% was considered correct to species level. The results are displayed as a series of lines (spectrum) which correspond to different fragments that have broken away from the original molecule.[7] A database is then used to compare this pattern with the known data of yeasts and bacteria in the test system.

Acid-fast stain for Mycobacteria was negative. HIV 1 and 2 antibodies were negative by chemiluminescence immunoassay. H1N1 RT-PCR was negative; oseltamivir was stopped. White blood cell counts were consistently high with a neutrophilic predominance. Progressive thrombocytopenia

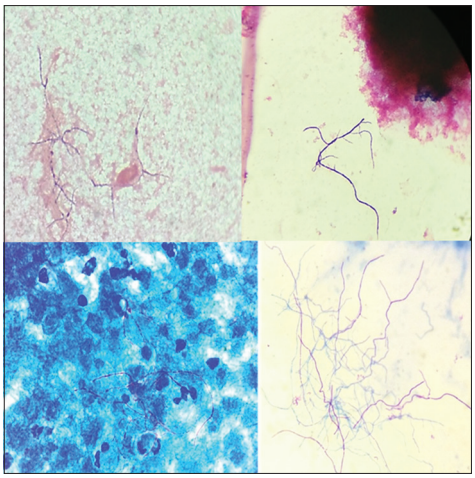

Figure 2: Gram-stain showing Gram-positive branching filamentous bacilli; modified 1% acid-fast stain – Kinyoun's stain showing branching filamentous pink acid-fast bacilli

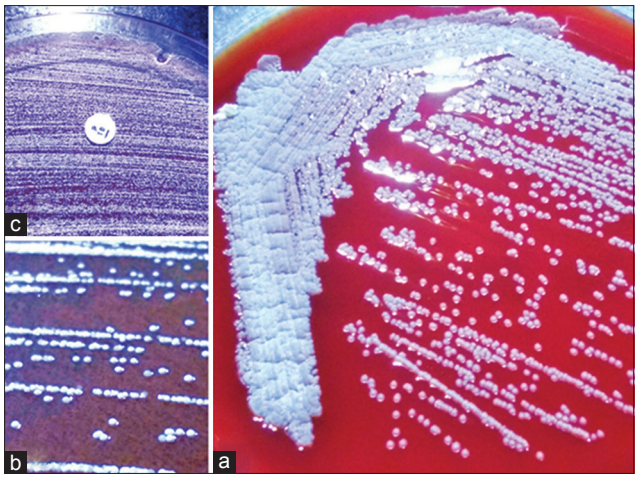

Figure 3: Blood agar and chocolate agar with dry chalky white pitting colonies of *Nocardia otitidiscaviarum* (a and b); no zone of inhibition around penicillin 10 U disk (c)

was noted (platelet count of 1.5 lakhs/mm^3 on the day of admission dropped to 40,000/mm^3). Scrub typhus IgM antibodies were positive by IgM ELISA (In Bios International, Inc., USA). The patient continued to require ventilatory support. Although transient improvement in hemodynamics was noted, there was subsequent deterioration with increasing inotropic requirement. Repeat blood cultures were sent on 5th day after intubation which revealed yeast-like cells on Gram stain within 24 h in the automated blood culture system (BD BACTEC-9050). [Table 2] Caspofungin was given since the patient was hemodynamically unstable. *Candida tropicalis* was reported after 48 h being susceptible to Amphotericin B, fluconazole, voriconazole, caspofungin, and micafungin using Vitek 2 compact system (bioMérieux Clinical Diagnostics). On the 7th day postadmission to the critical care unit, patient's condition remained critical with deranged renal parameters, liver function test, and coagulation profile. He was anuric with worsening metabolic acidosis and continued to deteriorate. Renal replacement therapy was initiated. The patient subsequently developed bradycardia followed by asystole and could not be resuscitated and was declared dead. The cause of death was sepsis with septic shock, multiorgan dysfunction, and community-acquired pneumonia – nocardiosis, scrub typhus, and candidemia.

Table 2: Significant microbiology laboratory findings

Laboratory parameters	Findings
Sample tracheal aspirate	
Gram stain	Moderate pus cells with moderate Gram-positive branching filamentous bacilli seen
Modified 1% acid-fast stain	Acid-fast bacilli seen
ZN stain	No acid-fast bacilli seen
KOH mount	No fungal elements seen
Culture	Chalky white colonies with pitting observed on blood agar and chocolate agar
Identification by MALDI-TOF MS	*Nocardia otitidiscaviarum*
Scrub typhus IgM ELISA	Positive
Blood culture (1 aerobic bottle)	*Candida tropicalis*

MALDI-TOF MS: Matrix-assisted laser desorption ionization time of flight mass spectrometry, ZN: Ziehl-Neelsen

Discussion

Commonly, coinfections occur among patients with an underlying background of immunocompromised condition such as solid organ transplantation, stem cell transplant, long-term corticosteroid therapy, and acquired immunodeficiency syndrome due to HIV.[6,8] Pulmonary nocardiosis as such is seen commonly in patients with an underlying chronic lung disease, thereby increasing the list of its differential diagnosis such as Mycobacterial infections, fungal infections (pulmonary aspergillosis and pulmonary zygomycosis), lung malignancy, and actinomycosis.[1] Coinfections have been commonly reported with tuberculosis and aspergillosis. A rare coinfection of nocardiosis with *Strongyloides stercoralis* has also been reported by authors from South India.[9] Keeping this in mind, a thorough literature search did not reveal any reports of coinfection of pulmonary nocardiosis with scrub typhus thus far.

It is necessary to identify *Nocardia* up to their species level as there are variations in the susceptibility patterns of each species of *Nocardia*.[10] Although cotrimoxazole is the first-line standard therapy of choice, the benefit of trimethoprim component is not clear.[11] A retrospective evaluation submitted to the center for disease control and prevention on antimicrobial susceptibility of *Nocardia* isolates showed 42% resistance of *Nocardia* species to cotrimoxazole.[12] The strain isolated from our patient was also resistant to cotrimoxazole. Our patient was treated with imipenem. According to two reviews on pulmonary nocardiosis, empirical combination

therapy with amikacin and imipenem (or meropenem) or a three-drug regimen comprising of sulfonamides, amikacin, and either a carbapenem or third-generation cephalosporin can be used in such high-risk patients.[2,13]

On the other hand, scrub typhus coinfection has been observed with other tropical infections such as dengue, leptospirosis, malaria, melioidosis, mycoplasma, and Q fever. These coinfections with scrub typhus have been reported mostly from immunocompetent and young individuals.[14-17] Drugs advocated for the treatment of scrub typhus with pulmonary involvement are doxycycline and azithromycin.[18] Our patient's empiric cover included both these antibiotics.

On reviewing three published case reports of nocardiosis with *Nocardia otitidiscaviarum,* one was from India and two from China, pulmonary involvement was seen in two cases, out of which one patient succumbed to the illness.[3,19,20] However, coinfection with other microorganisms was not present in any of these cases, unlike our patient. Fatal outcomes in immunocompromised patients with coinfections are not infrequent. Mortality rates of nocardiosis in immunocompromised individuals has been reported to be 42.4% and due to scrub typhus to be 30%.[21,22] In spite of appropriate antibiotic therapy given to our patient on admission, one would wonder if earlier diagnosis on outpatient basis could have improved outcome although suspicion of coexistence of such infections may not be on top of the list for treating physicians.

Conclusion

We would like to emphasize that when any immunocompromised patient in India presents with nonspecific respiratory symptoms with atypical progression, it is necessary to keep in mind the possibility of more than one infection. A detailed history coupled with a thorough physical examination, early diagnosis, appropriate targeted therapy, and heightened awareness for coinfections are crucial for good clinical recovery in immunocompromised individuals. However, outcomes of coinfections such as nocardiosis and scrub typhus in an immunocompromised individual are worse than the general population.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Wilson JW. Nocardiosis: Updates and clinical overview. Mayo Clin Proc 2012;87:403-7.
2. Shariff M, Gunasekaran J. Pulmonary nocardiosis: Review of cases and an update. Can Respir J 2016;2016:7494202.
3. Jiang Y, Huang A, Fang Q. Disseminated nocardiosis caused by *Nocardia otitidiscaviarum* in an immunocompetent host: A case report and literature review. Exp Ther Med 2016;12:3339-46.
4. Mandell L, Bennett E, Dollin R. Chronic pneumonia. In: Krehling H, editor. Principles and Practice of Infectious Diseases. 7th ed. Churchill Livingstone: Elsevier Publishers; 2010. p. 934.
5. Mandell L, Bennett E, Dollin R. Orientia tsutsugamushi (Scrub Typhus). In: Krehling H, editor. Principles and Practice of Infectious Diseases. 7th ed. Churchill Livingstone: Elsevier Publishers; 2010. p. 25-9.
6. Misra DP, Parida JR, Chowdhury AC, Agarwal V. Pulmonary co-infection with *Nocardia* and *Aspergillus* in a patient with adult-onset still's disease receiving steroids and tacrolimus. BMJ Case Rep 2014;2014. pii: bcr2014207335.
7. MALDI-TOF Mass Spectrometry. 2017. Available from: http://www.biomerieux.com/en/maldi-tof-mass-spectrometry. [Last accessed on 2017 Nov 21].
8. Ekrami A, Khosravi AD, Samarbaf Zadeh AR, Hashemzadeh M. *Nocardia* co-infection in patients with pulmonary tuberculosis. Jundishapur J Microbiol 2014;7:e12495.
9. Praharaj I, Sujatha S, Ashwini MA, Parija SC. Co-infection with *Nocardia asteroides* complex and *Strongyloides stercoralis* in a patient with autoimmune hemolytic anemia. Infection 2014;42:211-4.
10. Dawar R, Girotra R, Quadri S, Mendiratta L, Rani H, Imdadi F, *et al*. Epidemiology of nocardiosis – A six years' study from Northern India. J Microbiol Infect Dis 2016;6:60-4.
11. Karumanchi D, Oommen S, Sivan Pillai PM, Angel J. Nocardiosis in central Kerala: A case series. Int J Med Public Health 2015;5:384-6.
12. Uhde KB, Pathak S, McCullum I Jr., Jannat-Khah DP, Shadomy SV, Dykewicz CA, *et al.* Antimicrobial-resistant *Nocardia* isolates, United States, 1995-2004. Clin Infect Dis 2010;51:1445-8.
13. Paramythiotou E, Papadomichelakis E, Vrioni G, Pappas G, Pantelaki M, Kontos F, *et al.* A life-threatening case of disseminated nocardiosis due to *Nocardia brasiliensis*. Indian J Crit Care Med 2012;16:234-7.
14. Ahmad S, Dhar M, Bhat NK, Shirazi N, Mittal G. Rare co-infection of malaria, scrub typhus and dengue virus in an immunocompetent patient. Int J Curr Microbiol Appl Sci 2015;4:295-7.
15. Lu PL, Tseng SH. Fatal septicemic melioidosis in a young military person possibly co-infected with *Leptospira interrogans* and *Orientia tsutsugamushi*. Kaohsiung J Med Sci 2005;21:173-8.
16. Lee WS, Ou TY, Chen FL, Hsu CW, Jean SS. Co-infection with *Orientia tsutsugamushi* and *Mycoplasma pneumoniae* in a traveler. J Microbiol Immunol Infect 2015;48:121-2.
17. Lai CH, Chen YH, Lin JN, Chang LL, Chen WF, Lin HH, *et al.* Acute Q fever and scrub typhus, Southern Taiwan. Emerg Infect Dis 2009;15:1659-61.
18. Kaore SN, Sharma P, Yadav VK, Sharma R, Kaore NM. ARDS in scrub typhus. JK Science 2010;12:83-4. Available from: https://www.jkscience.org/archive/volume122/ARDSinscrubtyphus. [Last accessed on 2017 Aug 20].
19. Ramamoorthi K, Pruthvi BC, Rao NR, Belle J, Chawla K. Pulmonary nocardiosis due to *Nocardia otitidiscaviarum* in an immunocompetent host – A rare case report. Asian Pac J Trop Med 2011;4:414-6.
20. Liu C, Feng M, Zhu J, Tao Y, Kang M, Chen L, *et al.* Severe pneumonia due to *Nocardia otitidiscaviarum* identified by mass spectroscopy in a cotton farmer: A case report and literature review. Medicine (Baltimore) 2017;96:e6526.
21. Chedid MB, Chedid MF, Porto NS, Severo CB, Severo LC. Nocardial infections: Report of 22 cases. Rev Inst Med Trop Sao Paulo 2007;49:239-46.
22. Rapsang AG, Bhattacharyya P. Scrub typhus. Indian J Anaesth 2013;57:127-34.