CASE REPORT

Multidrug-resistant *Nocardia pseudobrasiliensis* presenting as multiple muscle abscesses

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Accepted 10 April 2015

SUMMARY

A 79-year-old Caucasian man presented with multiple leg abscesses due to *Nocardia pseudobrasiliensis*. He was on chronic steroid therapy for myasthenia gravis. We present the difficulties in diagnosis and treatment of this rare organism. *N. pseudobrasiliensis* is a new emerging species that was previously thought to belong to the *N. brasiliensis* species. The distinction between the two species is extremely important given the different antibiotic susceptibility pattern and association of *N. pseudobrasiliensis* with more invasive and disseminated disease.

BACKGROUND

Nocardiosis is a localised or disseminated infection caused by an aerobic actinomycete belonging to the genus *Nocardia*.¹ *Nocardia asteroides* is the predominant organism within the genus followed by *N. brasiliensis*. *N. pseudobrasiliensis* is an emerging pathogen within the *Nocardia* genus that can cause invasive and disseminated disease.² *N. pseudobrasiliensis* shares morphological features with *N. brasiliensis*, however, the latter causes less serious infections and has a different antibiotic susceptibility pattern.² We describe a 79-year-old Caucasian man who presented with multiple leg abscesses due to *N. Pseudobrasiliensis*.

CASE PRESENTATION

A 79-year-old Caucasian man was hospitalised for evaluation of multiple leg abscesses. He had a medical history of myasthenia gravis and had been taking chronic steroid therapy for the past 2 years. He started having pain in the left leg 3–4 weeks before presentation and developed multiple leg swellings for the past 2 weeks. Within the preceding year, he had a history of Achilles tendon septic bursitis and left hand cellulitis that required several courses of antibiotic therapy. He denied having fever, chills, cough, cold, shortness of breath, sweating, abdominal pain and/or night sweats. His other medical history included coronary artery disease, hypertension and paroxysmal atrial fibrillation.

On admission, the patient was afebrile. Pertinent findings on examination included the presence of multiple tender swellings in his legs. The largest swelling was located on the posterior medial left thigh, which was warm and tender. Lungs were clear to auscultation. He had elevated white cell count of 12 400/mL with 81.7% neutrophils, 10% monophils, 8% lymphocytes and no bands. Blood

cultures collected at the time of admission were negative. An admission chest radiograph showed minimal pleural effusion on the right side. The patient was started initially on vancomycin and piperacillin-tazobactam. MRI study of the legs showed multifocal complex lesions and fluid collections within the muscle beds of both legs, left more than right. The largest lesion measured 10 cm×8 cm in the left mid biceps femoris muscle complex (figure 1). There was no involvement of bone. The largest abscess was drained with the aspiration of 300 mL of bloody pus that was sent to the microbiology laboratory for culture. Other abscesses were also drained.

The organism recovered from culture was initially thought to be suspicious for an *Actinomyces* based on its Gram's stain and colonial morphology. The patient's antibiotic therapy was changed to ampicillin. A modified acid-fast stain of the isolate was positive, suggestive of *Nocardia* species. The antibiotics were switched to ceftriaxone and doxycycline to provide therapeutic coverage for *Nocardia* and *Actinomyces*. The isolate was identified by the GenBank database sequence of the Hsp65 gene and it was found to be 100% homologous with that of *N. pseudobrasiliensis* (figure 2) reference strain DSM44290. The region hsp65 gene contains sufficient polymorphisms for comprehensive *Nocardia* species identification. Broth microdilution was used to test susceptibility for this isolate and found to be

Figure 1 MRI of bilateral lower extremities showing abscesses.

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To cite: Veerappan Kandasamy V, Nagabandi A, Horowitz EA, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2014-205262

Nocardia pseudobrasiliensis strain DSM 44290 heat shock protein 65 (hsp65) gene, partial cds

Sequence ID: [gb|JN041758.1](#) Length: 401 Number of Matches: 1

Range 1: 1 to 401

Score	Expect	Identities	Gaps	Strand
741 bits(401)	0.0	401/401(100%)	0/401(0%)	Plus/Plus
Query 1	CGCCAAGGAGATCGAGCTCGAGGACCCCTACGAGAAGATCGGCGCCGAGCTGGTCAAGGA	60		
Sbjct 1	CGCCAAGGAGATCGAGCTCGAGGACCCCTACGAGAAGATCGGCGCCGAGCTGGTCAAGGA	60		
Query 61	AGTCGCCAAGAAGACCGACGATGTCGCGGGCGACGGCACCACCACCGCCACCGTGTCTCGC	120		
Sbjct 61	AGTCGCCAAGAAGACCGACGATGTCGCGGGCGACGGCACCACCACCGCCACCGTGTCTCGC	120		
Query 121	TCAGGCGCTGGTGC GCGAGGGGCTGCGCAACGTGCGGGCCGGTGC GAACCCGCTGGGTCT	180		
Sbjct 121	TCAGGCGCTGGTGC GCGAGGGGCTGCGCAACGTGCGGGCCGGTGC GAACCCGCTGGGTCT	180		
Query 181	GAAGCGCGGCATCGAGAAGGCCGTGAGGCCGTACCAACCGCCTGCTCGACTCGGCCAA	240		
Sbjct 181	GAAGCGCGGCATCGAGAAGGCCGTGAGGCCGTACCAACCGCCTGCTCGACTCGGCCAA	240		
Query 241	GGAGGTGAGACCAAGGAGCAGATCGCCGCCACCGCCGCGATCTCCGCCGCGACCAAGTC	300		
Sbjct 241	GGAGGTGAGACCAAGGAGCAGATCGCCGCCACCGCCGCGATCTCCGCCGCGACCAAGTC	300		
Query 301	CATCGGTGAGCTCATCGCCGAGGCCATGGACAAGGTCGGCAAGGAAGGTGTCATACCGT	360		
Sbjct 301	CATCGGTGAGCTCATCGCCGAGGCCATGGACAAGGTCGGCAAGGAAGGTGTCATACCGT	360		
Query 361	CGAGGAGAGCAACACCTTCGGCCTCCAGCTGGAGCTGACCG	401		
Sbjct 361	CGAGGAGAGCAACACCTTCGGCCTCCAGCTGGAGCTGACCG	401		

Figure 2 Genetic analyser results showing a perfect match for *Nocardia pseudobrasiliensis*. BLAST systems were used for the alignments.

susceptible to moxifloxacin and linezolid, and resistant to penicillin, cephalosporin and trimethoprim (TMP)/sulfamethoxazole (SMX).

A CT scan of the chest showed the presence of ground-glass, right upper lobe opacities suggestive of infection. MRI of the brain did not show the presence of any intracranial abscesses. Based on the patient's clinical presentation and radiographic scan results, it was concluded that the patient had pulmonary nocardiosis with dissemination secondary to immunosuppression due to chronic steroid use. The patient was started on linezolid but this drug was discontinued within 3 weeks when the patient developed thrombocytopenia. He was then started on moxifloxacin, which was continued for a total of 6 months. The patient improved at the end of therapy and he was doing well without any recurrent abscesses at 1 year follow-up.

DISCUSSION

N. pseudobrasiliensis is an emerging species of *Nocardia* that was first identified in 1996.³ Only a few cases have been reported so far. This case emphasises the difficulties in the diagnosis of *Nocardia* infection. To our knowledge, this is the first case of multidrug-resistant *N. pseudobrasiliensis* infection presenting with multiple muscle abscesses.

The genus *Nocardia* has more than 80 species that have been characterised by phenotypic and molecular methods.^{4 5} *N. pseudobrasiliensis* is a new species that was thought to belong to the *N. brasiliensis* species. *N. pseudobrasiliensis* is similar to *N. brasiliensis* phenotypically, but it decomposes adenine, and has nitrate reductase activity.³ Genotypically, this new taxon was confirmed to constitute a new species of *Nocardia* on the basis of 16S rRNA gene sequence analysis and DNA-DNA hybridisation.³ Furthermore, *N. pseudobrasiliensis* exhibits a specific restriction pattern in PCR restriction fragment length polymorphism analysis of the 65 kDa heat shock protein gene.^{2 3}

The distinction between these two species is important given their different antibiotic susceptibility patterns and the association of *N. pseudobrasiliensis* with more invasive and disseminated disease. Although *N. brasiliensis* and *N. pseudobrasiliensis* can be distinguished by adenine hydrolysis and nitrate reductase,³ these tests are not commonly available for use in the speciation of *Nocardia* in most clinical microbiology laboratories. Therefore, 16S rRNA gene sequencing is desirable as a next step to differentiate between *N. brasiliensis* and *N. pseudobrasiliensis*.

It is also important for microbiology laboratories to distinguish between *Actinomyces* and *Nocardia* species. On the basis of the Gram stain, *Nocardia* and *Actinomyces* species are morphologically indistinguishable. *Nocardia* species can exhibit a distinct variably acid-fast property with modified acid-fast staining.^{6 7} Furthermore, growth under aerobic conditions should arouse the suspicion of the isolate being a possible *Nocardia* spp.

A recent study² demonstrated that 60% of apparent *N. brasiliensis* associated with pulmonary or disseminated disease belonged to a new taxon named *N. pseudobrasiliensis*. Because of the association of this organism with invasive or disseminated disease and a different antibiotic susceptibility pattern, it seems prudent to recommend the screening of all *N. brasiliensis* isolates to rule out the possibility of the isolate being *N. pseudobrasiliensis*. Antibiotic susceptibility testing to ciprofloxacin by the disk-diffusion method provides a rapid screening test, as 95% of *N. pseudobrasiliensis* strains are susceptible to ciprofloxacin compared with 100% of *N. brasiliensis* strains being resistant.²

Wallace *et al*,² in a study of 43 isolates of a novel species of *Nocardia* (*N. pseudobrasiliensis*) in 1995, described different anatomical sites of infection but reported a strong association with invasive disease, including involvement of the lungs in 70% of the cases, of the brain and/or meninges in 23%, of skin and/or soft tissue in 30%, of joints in 7% and disseminated disease in 37%. Most of these patients presented with underlying immunosuppression, with 92% (excluding patients with

Table 1 Review of *Nocardia pseudobrasiliensis* cases in the literature

Case number	Author and reference citation	Age/sex	Predisposing factor	Type or site of infection	Positive site for <i>N. brasiliensis</i> culture	Therapy (final)	Outcome
1	Mongkolrattanothai <i>et al</i> ⁷	9/F	None	Ventriculitis	Ventricular fluid	TMP-SMX	Survived
2	Kageyama <i>et al</i> ⁸	71/M	Oesophageal and stomach cancer on chemotherapy	NA	NA	NA	NA
3	Lebeaux <i>et al</i> ⁹	55/M	Allogeneic haematopoietic stem cell transplantation for multiple myeloma	Pulmonary/disseminated	BAL	CIP, GM (TMP-SMX)	Died
4	Brown <i>et al</i> ¹⁰	33/M	AIDS	Disseminated	Sputum, right hand, knee aspirate	CLIN, AMIK, IMI, TMP-SMX and AMP-B	Died
5	Seol <i>et al</i> ¹¹	57/F	Chronic steroid therapy for microscopic polyangitis	Disseminated	Biopsied tissues from mycetomas on the patient's scalp, right arm and right leg	AMPI/SUL. Switched to AMOX/CLAV at discharge and continued for 6 months	Survived
6	Harent <i>et al</i> ¹²	37/M	Cardiac transplantation	Pulmonary	BAL	CTX, CIP for 4 weeks, then CIP for 12 months	Survived
7	Javaid <i>et al</i> ¹³	86/M	None	disseminated	Joint, abscess fluid	CIP, TMP-SMX	Survived

AMIK, amikacin; AMOX/CLAV, amoxicillin/clavulanate; AMP-B, amphotericin B; AMPI/SUL, ampicillin/sulbactam; BAL, bronchoalveolar lavage; CIP, ciprofloxacin; CLIN, clindamycin; CTX, ceftriaxone; F, female; GM, gentamycin; IMI, imipenam; M, male; NA, no data; TMP-SMX, trimethoprim/sulfamethoxazole.

Table 2 Antimicrobial susceptibility

Drug	Our case	Case 1 ⁷	Case 3 ⁹	Case 4 ¹⁰	Case 5 ¹¹	Case 7 ¹³
Ciprofloxacin	0.5 (S)	0.5 (S)	0.125 (S)	<0.5 (S)	<0.12 (S)	(S)
Moxifloxacin	<0.25 (S)				<0.25 (S)	
Gatifloxacin		<0.12 (S)				
Clarithromycin	0.5 (S)		0.125 (S)	<0.5 (S)	0.25 (S)	(S)
Linezolid	<1.0 (S)	0.5 (S)			<1 (S)	(S)
TMP-SMX	4/76 (R)	8/152 (R)		<32 (S)*	8/152 (R)	(S)
Imipenam	64 (R)	>32 (R)	>32 (R)		64 (R)	(R)
Amox-Clav	32/16 (R)		2 (S)	>8/2 (R)	32/16 (R)	(R)
Cefepime	>32 (R)				16 (S)	
Cefoxitin					>128 (R)	
Cefotaxime				<32 (S)		
Ceftriaxone	>64 (R)	>64 (R)		<32 (S)	8 (S)	(R)
Minocycline	8 (R)			>8 (MS –R)	>8 (R)	(R)
Doxycycline	16 (R)				16 (R)	(R)
Amikacin	16 (R)	8 (S)		4–16 (S)	4 (S)	(S)

*SMX only.

Amox/Clav, amoxicillin/clavulanate; MS, Moderately susceptible; R, resistant; S, susceptible; TMP-SMX, trimethoprim/sulfamethoxazole.

HIV infection and those suffering from alcoholism) receiving corticosteroid therapy.

Review of the literature

MEDLINE and Cochrane database searches were performed for collecting all published case reports on *N. pseudobrasiliensis*. A total of seven cases have been published to date. The clinical details of these seven cases are shown in table 1. In our review, *N. pseudobrasiliensis* affected all age groups ranging from 9 to 86 years. Five patients were male and two were female. All but two cases had a predisposing condition causing immunosuppression. Disseminated disease was present in three of the cases.

Antimicrobial susceptibility

Nocardia species can vary in their antimicrobial susceptibility patterns. Therapeutic efficacy in individual patients depends on the species that is responsible for infection and the results of in vitro susceptibility studies. The majority of *N. pseudobrasiliensis*

originally described by Wallace *et al*² were susceptible to ciprofloxacin (95%), clarithromycin (91%), cefotaxime (78%) and ceftriaxone (69%). However, 34 of 37 isolates (92%) were

Learning points

- Based on the above case studies and the susceptibility patterns reported, we strongly recommend that additional testing be performed to rule out *Nocardia pseudobrasiliensis* as a cause of disease in all disseminated cases of infection allegedly caused by *N. brasiliensis*, particularly if the patient is immunocompromised.
- Ciprofloxacin is the antibiotic of choice in patients suspected of having an infection caused by *N. pseudobrasiliensis*.
- The antibiotic susceptibility pattern of *N. pseudobrasiliensis* is different from *N. brasiliensis*.

resistant to a 25 µg TMP-SMX by disk diffusion. However, most of these isolates (29 of 31 isolates, 94%) were susceptible to SMX by minimum inhibitory concentration determination (MIC $\leq$ 32 µg/mL). This finding may reflect the low concentration of SMX in the disk resulting in the discrepancy between the disk diffusion and MIC results.² The antibiotic susceptibility results were reported in four of the studies reported so far. The antimicrobial susceptibility results are summarised in table 2. The reported results show uniform susceptibility to ciprofloxacin, moxifloxacin, clarithromycin and linezolid.

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Contributors VVK, the corresponding author, primarily prepared the manuscript and reviewed it. AN contributed with the images, helped in preparation and review of the manuscript. RV and EAH were attending physicians in the infectious disease department, and mentored the preparation of the manuscript and reviewed it.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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