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CASE REPORT

Disseminated nocardiosis with infective endocarditis of a transplanted heart

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SUMMARY

Nocardiosis is caused by various species of *Nocardia* and typically occurs as an opportunistic infection. It frequently disseminates, most often involving the lungs, subcutaneous tissues and central nervous system. It has rarely been reported to affect native heart valves. We report the case of a 64-year-old man with disseminated nocardiosis involving the brain, lungs, muscle and tricuspid valve of a transplanted heart. Following antimicrobial therapy, the patient improved clinically and there was no evidence of residual infection on follow-up imaging. This case highlights the presentation of nocardiosis, current therapeutic guidelines and the question of prophylaxis against *Nocardia* in immunocompromised patients.

BACKGROUND

Infective endocarditis is a relatively common condition. The typical organisms of native valve endocarditis include *Staphylococcus aureus*, coagulase-negative staphylococci, streptococci and enterococci. Acid-fast bacilli are a rare cause of endocarditis.[1] *Nocardia* has the ability to affect virtually any organ; however, literature describing cardiac disease is limited. This case demonstrates the disseminating potential of *Nocardia* and emphasises the importance of cardiac evaluation in affected patients. Questions remain about the optimal therapy for disseminated nocardiosis and the issue of prophylactic therapy in immunocompromised patients.

CASE PRESENTATION

A 64-year-old man with a history of chronic kidney disease and heart transplantation 3 months prior, for which he has since been treated with a stable immunosuppressive regimen (tacrolimus, prednisone and mycophenolate mofetil), was admitted to the hospital with fever and chills. Relevant history began 3 weeks prior to presentation when the patient experienced the onset of 'dull aching' pain in the right thigh. On the morning of admission, he developed fever and chills, prompting him to seek evaluation. There has been no recent escalation in the patient's immunosuppressive therapy and tacrolimus blood levels have predominantly been in the therapeutic range since transplantation. On examination, temperature was 38°C and heart rate 130 beats/min. There was a new grade 2/6 holosystolic murmur best heard over the left lower sternal border that augmented with inspiration. There was dullness to percussion and decreased breath sounds over the base of the right lung. The right thigh was tender to palpation.

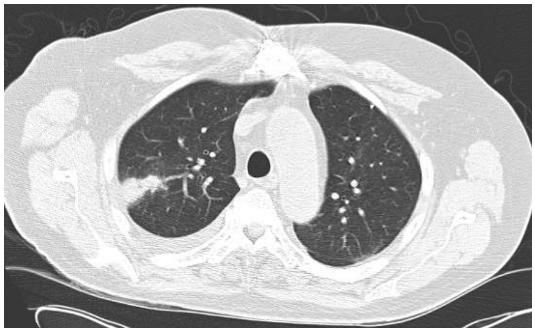

Figure 1 Chest CT demonstrating a 1.7 cm nodule in the periphery of the right lung with associated pleural effusion.

INVESTIGATIONS

Laboratory evaluation was notable for a peripheral white blood cell count of 3×10^9/L, which was stable from prior. CT imaging of the chest showed multiple peripheral lung nodules with a right-sided pleural effusion (figure 1). MRI of the right proximal leg demonstrated a 2×1.5×3 cm fluid collection consistent with abscess within the right vastus lateralis muscle (figure 2). Gram stain of the blood demonstrated the presence of Gram-positive bacilli. A transthoracic echocardiogram showed new moderate tricuspid regurgitation, but no clear vegetation. A transoesophageal echocardiogram revealed a small mobile mass on the tricuspid valve (figure 3). Blood cultures eventually returned positive for *Nocardia asteroides*. Given the evidence of endocarditis and the disseminating nature of *Nocardia*, a brain MRI was obtained and revealed a 9 mm ring-enhancing lesion in the right temporal lobe (figure 4).

TREATMENT

Given the immunocompromised status of the host, the Gram stain results triggered initiation of oral trimethoprim–sulfamethoxazole (TMP/SMX) to cover the possibility of infection with *Nocardia* species. When central nervous system (CNS) involvement was confirmed by neuroimaging, imipenem–cilastatin was added to the antibiotic regimen. At hospital discharge, imipenem–cilastatin was replaced with ceftriaxone based on microbial sensitivity, and oral TMP/SMX was continued.

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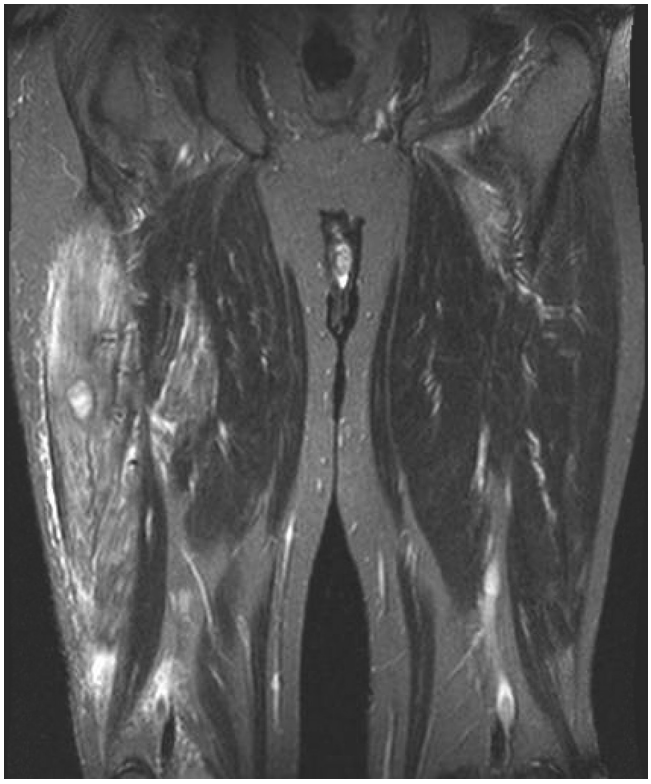

Figure 2 Right leg MRI demonstrating a 2×1.5×3 cm intramuscular collection within the vastus lateralis muscle, with adjacent muscle oedema and fascial fluid.

On development of nephrotoxicity 4 weeks after discharge, TMP/SMX was switched to linezolid. Intravenous ceftriaxone was continued for 12 weeks and then switched to oral minocycline for a planned 12-month course. However, minocycline was discontinued shortly thereafter due to gastrointestinal side effects. The patient was continued on linezolid monotherapy for 4 more months, bringing the total duration of antibiotic therapy to approximately 7 months.

OUTCOME AND FOLLOW-UP

The patient improved with treatment and there was no evidence of residual infection on follow-up imaging. On completion of therapy, a brain MRI revealed resolution of the abscess and an echocardiogram demonstrated stable tricuspid regurgitation.

DISCUSSION

Nocardia sp are aerobic Gram-positive bacteria that can cause localised or systemic disease in humans. The bacteria appear as filamentous branching rods that are weakly acid-fast staining. *Nocardia* is not part of normal human flora and can be found worldwide in soil, decaying vegetable matter and aquatic environments. Inhalation is the most common mode of entry.[2]

Nocardiosis is most often a disease of the immunocompromised; however, roughly one-third of those infected are immunocompetent.[3] *Nocardia* has the ability to disseminate, most commonly involving the lungs, subcutaneous tissues and CNS. It has rarely been reported to affect native heart valves.[4] In this case, cardiac examination revealed a new regurgitant murmur, leading to the discovery of a vegetation on the tricuspid valve and associated tricuspid regurgitation by echocardiography, confirming infective endocarditis in the setting of disseminated nocardiosis. In a large case-control study evaluating solid organ transplant recipients over a 10-year period, 35 patients out of 5126 (0.7%) were identified as having *Nocardia* infection. Within this subpopulation, 10 patients (29%) were heart transplant recipients.[5] These 10 cases occurred out of a total of 392 heart transplant recipients. Of all the patients with nocardiosis in this study, the lungs were the most frequent sites of infection. No cases of cardiac involvement were reported. A recent large-scale study of 54 cases of nocardiosis in solid organ transplant patients

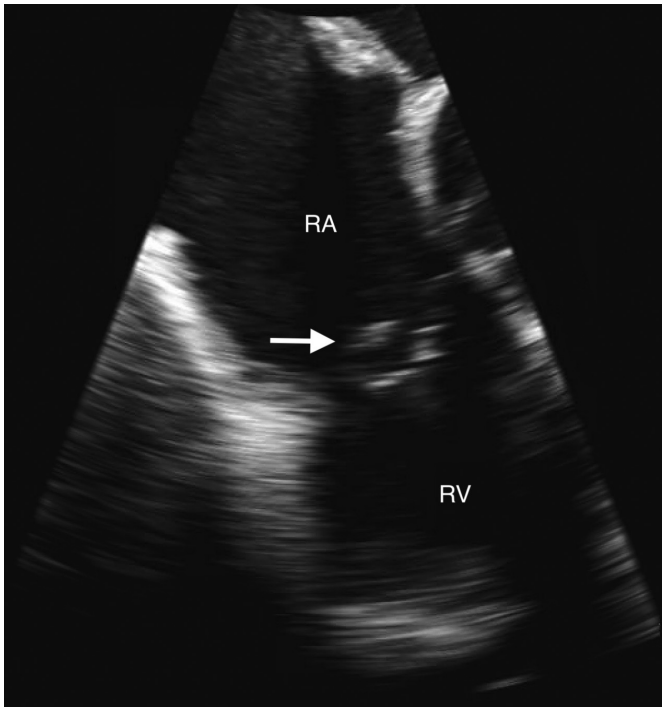

Figure 3 Transoesophageal echocardiogram demonstrating a small mobile mass on the tricuspid valve. RA, right atrium; RV, right ventricle.

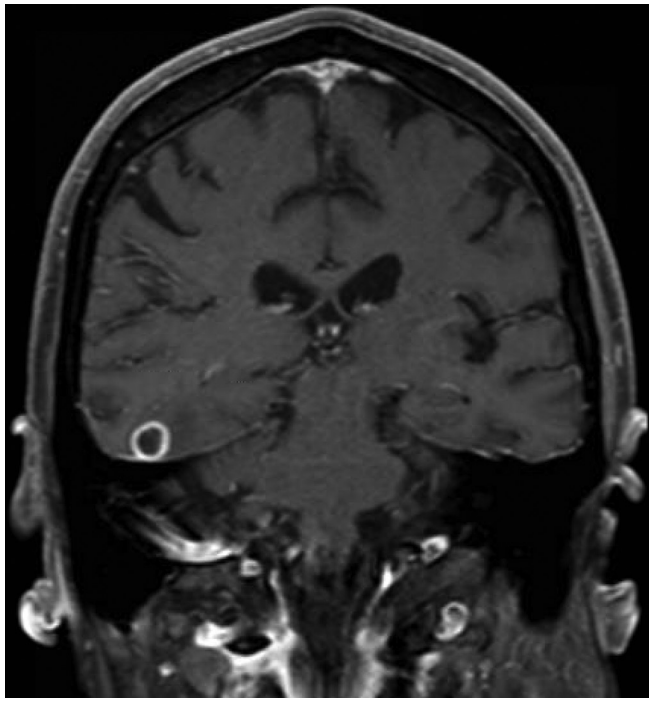

Figure 4 Brain MRI demonstrating a 9 mm ring-enhancing lesion in the right temporal lobe.

found a similar proportion of heart transplant recipients among the cases (37%).[6]

We identified a total of 10 case reports of nocardial endocarditis involving native heart valves from 1973 to 2017.[4 7–15] Two of those cases occurred in patients with a history of solid organ transplantation (liver and kidney). None of the cases occurred in a patient with a history of heart transplantation. The most common presenting feature in these patients was fever. The antibiotic treatment regimen used most frequency was imipenem/amikacin followed by a prolonged course of TMP/SMX. With treatment, 6 of the 10 patients (60%) survived.

Due to underlying chronic kidney disease, this patient was previously treated with pentamidine rather than TMP/SMX for *Pneumocystis jirovecii* prophylaxis (PJP). Although pentamidine does provide excellent coverage for PJP, it is not active against *Nocardia*. This clue from the patient's history raised suspicion for nocardiosis, which was reaffirmed when Gram-positive bacilli were found in the blood. Currently, there is no official recommendation for prophylaxis against *Nocardia* in immunocompromised hosts. It has traditionally been thought that TMP/SMX at doses used for prophylaxis against PJP provides at least some coverage against *Nocardia*. However, recent studies have shown that the use of TMP/SMX at prophylactic doses is not protective against nocardiosis.[5 16]

Due to lack of randomised trials, the most effective treatment for nocardiosis is not clear. Currently, standard therapy depends on the severity of disease; TMP/SMX is often the initial treatment of choice. When infection is severe (all cases of disseminated disease or CNS involvement as well as infections that involve more than one site in immunocompromised hosts), the combination of intravenous TMP/SMX and amikacin or imipenem is recommended.[17 18] Life-threatening infections may benefit from treatment with three intravenous antibiotics.[17] Therapy may be adjusted later depending on microbial susceptibilities. While linezolid may be effective against *Nocardia*, it should generally be avoided when possible given serious side effects such as peripheral neuropathy and myelosuppression.

The duration of therapy for nocardiosis depends on the severity of infection, but a typical regimen consists of 6–8 weeks of intravenous therapy followed by prolonged oral therapy.[18 19] In cases of disseminated disease in immunocompromised patients, or in any patient with CNS involvement, a duration of therapy of at least 1 year is recommended.[19] Efficacy of therapy is influenced by the extent of disseminated disease and underlying health of the host. Overall prognosis is improved with early diagnosis and prompt initiation of antibiotic therapy.[20] When the underlying cause of immunocompromise cannot be reversed, a higher dose of TMP/SMX for secondary prophylaxis should be considered in patients who recover from nocardiosis; however, more research is needed to determine whether higher doses of TMP/SMX would provide adequate coverage.[21]

Learning points

- Nocardiosis is most often a disease of the immunocompromised; *Nocardia* has the ability to disseminate, most commonly involving the lungs, subcutaneous tissues and central nervous system.
- Heart transplant recipients represent a large proportion of immunocompromised patients who become infected with *Nocardia*.
- Infective endocarditis should be considered in patients with disseminated nocardiosis. Physical examination is essential for the identification of regurgitant murmurs and other suggestive findings.
- Trimethoprim–sulfamethoxazole (TMP/SMX) at doses used for *Pneumocystis jirovecii* prophylaxis in immunocompromised patients may not provide coverage for *Nocardia*. Higher doses of TMP/SMX should be considered for secondary prophylaxis.
- The treatment strategy for nocardiosis depends on severity, but generally requires a long duration of intravenous and oral antibiotics.

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REFERENCES

1 Murdoch DR, Corey GR, Hoen B, *et al*. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective cohort study. *Arch Intern Med* 2009;169:463.
2 Goodfellow M, Williams ST. Ecology of actinomycetes. *Annu Rev Microbiol* 1983;37:189–216.
3 Beaman BL, Beaman L. Nocardia species: host-parasite relationships. *Clin Microbiol Rev* 1994;7:213–64.
4 Castelli JB, Siciliano RF, Abdala E, *et al*. Infectious endocarditis caused by Nocardia sp.: histological morphology as a guide for the specific diagnosis. *Braz J Infect Dis* 2011;15:384–6.
5 Peleg AY, Husain S, Qureshi ZA, *et al*. Risk factors, clinical characteristics, and outcome of Nocardia infection in organ transplant recipients: a matched case-control study. *Clin Infect Dis* 2007;44:1307–14.
6 Majeed A, Beatty N, Iftikhar A, *et al*. A 20-year experience with nocardiosis in solid organ transplant (SOT) recipients in the Southwestern United States: A single-center study. *Transpl Infect Dis* 2018;20:e12904.
7 Antonovich DD, Berke A, Grant-Kels JM, *et al*. Infectious eccrine hidradenitis caused by Nocardia. *J Am Acad Dermatol* 2004;50:315–8.
8 Antony SJ, Stivers M, Rivera JO. Endocarditis/endovascular infection associated with Nocardia. *Infect Med* 2006;23:262–6.
9 Cargill JS, Boyd GJ, Weightman NC. Nocardia cyriacigeorgica: a case of endocarditis with disseminated soft-tissue infection. *J Med Microbiol* 2010;59(Pt 2):224–30.
10 Chain S, Luciardi H, Feldman G, *et al*. [Nocardia endocarditis in aortic and tricuspid native valves]. *Medicina* 2007;67:279–81.
11 Kuretski J, Dahya V, Cason L, *et al*. Nocardia Bacteremia and Endocarditis in a patient with a Sulfa allergy. *Am J Med Sci* 2016;352:542–3.
12 Lazo Torres AM, Gálvez Contreras C, Collado Romacho A, *et al*. Nocardia endocarditis in a native mitral valve. *Rev Esp Cardiol* 2004;57:787–8.
13 Leonard A, Raij L, Comty CM, *et al*. Experience with endocarditis in a large kidney disease program. *Trans Am Soc Artif Intern Organs* 1973;19:298–301.
14 Niehues R, Schlüter S, Kramer A, *et al*. Systemic Nocardia asteroides infection with endocardial involvement in a patient undergoing immunosuppressive therapy. *Dtsch Med Wochenschr* 1996;121:1390–5.
15 Watson A, French P, Wilson M. Nocardia asteroides native valve endocarditis. *Clin Infect Dis* 2001;32:660–1.
16 Coussement J, Lebeaux D, van Delden C, *et al*. Nocardia infection in solid organ transplant recipients: a multicenter European case-control study. *Clin Infect Dis* 2016;63:338–45.
17 Brown-Elliott BA, Brown JM, Conville PS, *et al*. Clinical and laboratory features of the Nocardia spp. based on current molecular taxonomy. *Clin Microbiol Rev* 2006;19:259–82.
18 Lerner PI. Nocardiosis. *Clin Infect Dis* 1996;22:891–905.
19 Geiseler PJ, Andersen BR. Results of therapy in systemic nocardiosis. *Am J Med Sci* 1979;278:188–94.

20 Uttamchandani RB, Daikos GL, Reyes RR, *et al*. Nocardiosis in 30 patients with advanced human immunodeficiency virus infection: clinical features and outcome. *Clin Infect Dis* 1994;18:348–53.

21 Lebeaux D, Freund R, van Delden C, *et al*. Outcome and treatment of nocardiosis after solid organ transplantation: new insights from a European study. *Clin Infect Dis* 2017;64:1396–405.