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Nocardiosis in solid-organ transplant recipients: Spectrum of imaging findings

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Abstract

Nocardiosis is an infrequent but severe infection that primarily affects the lung and thence is able to produce disseminated disease. Prompt diagnosis of pulmonary and disseminated nocardiosis is of utmost importance in solid-organ transplant recipients to reduce mortality. Knowledge of the different radiological manifestations in the appropriate clinical setting is key to successful management of these patients. The aim of this review is to describe the radiological features of nocardiosis in immunosuppressed patients, particularly in solid-organ transplant recipients.

Introduction

In an age of sophisticated immunosuppressive regimens, rejections in solid-organ recipients are observed less frequently, giving rise to opportunistic infections. Bacteria are the most prevalent pathogens in the early postsurgical stage. *Nocardia* spp. are Gram-positive, aerobic, slowly growing agents (Actinobacteria) with a reported prevalence of 0.7–3.6%. *Nocardia* infections are uncommon but frequently fatal, with a related mortality of up to 80%.^{1–4} *Nocardia cyriacigeorgica*, formerly known as *Nocardia asteroides* type IV, is now the most frequently detected pathogen in nocardiosis patients worldwide.²

Nocardiosis occurs predominantly, but not exclusively, in immunosuppressed patients. A high-dose corticosteroid regimen is the most frequent risk factor for infection, and solid-organ transplantation is the most common underlying condition.² The incidence is highest in lung transplant recipients followed by heart, kidney, and liver transplanted patients.^{1,5}

Usually, once the host has been infected via the respiratory tract as the primary entry site, *Nocardia* spp. invade the circulatory system, which may result in dissemination.^{6,7} Therefore, two general nocardiosis subtypes can be distinguished: pulmonary and disseminated nocardiosis.

The course of disease can be acute, subacute, or chronic, and is often complicated by exacerbations.⁸ Nocardiosis characteristically requires a substantial amount of time to establish diagnosis; time to diagnosis has been reported to be as high as 6 weeks.⁸

Trimethoprim/sulfamethoxazole (TMP-SMZ) has traditionally been considered the treatment of choice exhibiting a favourable response in a vast majority of pulmonary nocardiosis cases.⁶ Although recently other drugs have become increasingly used due to the development of TMP-SMZ resistance in up to 10.8% of the treated patients.² If resistance is encountered, imipenem and amikacin are considered alternative options.⁸ Treatment can take more than 6 months and even longer for disseminated nocardiosis.¹ Abscess formation and empyema may require percutaneous drainage or surgical treatment.

As pathogen identification by isolation in culture can take several weeks, patients would benefit from a rapid diagnosis by radiological means. Early detection during the period of primary pulmonary involvement could spare patients disseminated disease. This is of paramount importance given a high mortality rate.⁴

Due to its bivalent pathogenesis resulting in both granulomatous and suppurative manifestations, nocardiosis presents with a high range of radiological findings.⁹ The objective of this review is to describe the different radiological manifestations of pulmonary nocardiosis, as well as of disseminated disease with extrapulmonary involvement.

Pulmonary nocardiosis

Nocardia spp. are soil-borne pathogens that are usually inhaled, making use of the lung as a primary entry site. Involvement of the lung has been reported in 60–70% of all cases.² The following findings have been described in pulmonary nocardiosis in immunosuppressed patients^{10,11} and particularly in solid-organ recipients¹²: air-space consolidation (with a reported frequency of 64%), variable-sized nodules (57%), masses (21%), pleural effusion (28%), and mediastinal and hilar lymphadenopathy (15%).^{13,14} Although most of the imaging findings can be depicted by means of thoracic x-ray, computed tomography (CT) enables better characterization of lesions, to define the extent of the disease precisely and to guide tissue biopsy whenever necessary.

Pulmonary nodules and masses do not exhibit specific anatomical distribution,¹⁰ and present either with well or ill-defined margins (Figs 1–3). Chest radiography tends to show round nodules with well-defined borders, whereas CT frequently identifies spiculate margins (Fig 2).¹⁵ In addition, cluster formation can occur (Fig 2).^{6,16} *Nocardia* lesions may demonstrate cavitation (40%; Fig 2), and be accompanied by pleural and septal thickening. Cavitation occurring in pulmonary masses or nodules has characteristically been described as thick walled,⁶ and usually presents a halo of ground-glass opacity. Bronchial wall thickening, tree-in-bud pattern, and centrilobular nodules, reflecting endobronchial spread, can also be found (Fig 2).

Pulmonary nocardiosis can present as air-space consolidation with (Fig 4) or without cavitation (Fig 5). It is usually multifocal, involves large areas, and is not restricted to anatomic pulmonary segments.¹⁰

Pleural effusion is a frequent finding (Figs 1,6,7),¹² which can be loculated and present signs of chronicity. However, some can be attributed to surgical causes, particularly in the early postoperative period.¹²

Features more infrequently observed are chest wall extension with abscess formation, pleural and septal thickening, hilar and mediastinal lymph node enlargement, and mediastinitis with concomitant superior vena cava syndrome.¹⁰ Local spread resulting in rib destruction and sinus tract formation has been reported.¹⁵

A small number of patients might be infected without showing symptoms or radiological manifestations.¹⁵

In a solid-organ transplant patient who presents with nodules, consolidation, or cavitary lesions, the primary concern would be infection or lymphoproliferative disease. The diagnosis of infectious diseases by means of radiological findings suffers from poor specificity, but correlating disease patterns and progression of disease with clinical history can often give crucial diagnostic clues.

Whenever pulmonary nodules in solid-organ recipients are accessible to biopsy, tissue should be retrieved in order to obtain rapid diagnosis. In addition, CT allows for monitoring during follow-up and enables diagnosis of potential complications.

Disseminated nocardiosis

Central nervous system involvement

The central nervous system (CNS) is the most common extrapulmonary site of *Nocardia* infection. Forty-four percent of patients with systemic disseminated disease experience subsequent invasion of the CNS resulting in brain abscesses. Mortality is 30%, three-times higher than that of any other bacterial abscess. However, if multiple foci are present, which often applies to *Nocardia*, mortality dramatically increases to 66% and even to >80% if an intraventricular rupture of the brain abscess occurs.^{6,17} Patients presenting without neurological signs but *Nocardia* infection, should be considered for brain imaging as brain abscesses can be clinically silent. Spinal cord intramedullary abscess formation and subacute or chronic meningitis are less common CNS manifestations.¹⁸

Contrast-enhanced magnetic resonance imaging (MRI) is the diagnostic technique of choice, because CT may be unable to detect subtle findings, particularly small lesions or those affecting posterior fossa. Radiological features include ring-enhancing lesions with occasional surrounding oedema (Fig 8). Mass effect with midline shift can be present depending on the size of the lesion.¹⁶

The presence of ring-enhancing brain lesions in transplant recipients should trigger the diagnosis of CNS infections (nocardiosis or other infections such as toxoplasmosis) and malignancies (particularly lymphoma).^{19,20}

Soft-tissue and organ involvement

Although CNS involvement is the most common extrapulmonary manifestation, systemic spread with abscess formation can be present affecting almost every organ. Hepatic (Fig 9), splenic, renal, adrenal (Fig 9), and muscular (Fig 10) abscesses, as well as skin ulceration and subcutaneous tissue abscesses have been described.^{6,7,9} Surgical or CT/ultrasound guided biopsy and/or drainage may be required to treat and identify the underlying organism.

Conclusion

Prompt diagnosis of pulmonary and disseminated nocardiosis is of utmost importance in solid-organ transplant recipients. This article familiarizes the reader with the different radiological manifestations of infections with *Nocardia* spp. Although non-specific, knowledge of these findings together with a high index of suspicion in the appropriate clinical setting are key to successful management of these patients.

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Figure 1. Pulmonary nocardiosis in a 61-year-old female liver transplant recipient for cryptogenic cirrhosis. Axial contrast-enhanced thoracic CT image shows a well-defined enhancing mass in the left upper lobe (asterisk). Para-aortic mediastinal lymphadenopathy (arrow) and bilateral pleural effusion are also seen. CT-guided tissue sample of the lung mass revealed *Nocardia nova*.

Figure 2.

Pulmonary nocardiosis in a 51-year-old male patient status post-liver transplant and history of common variable immune deficiency. Thoracic CT images (a, b) show a cluster of multiple well-defined nodules (arrows) within the left lower lobe and a spiculate mass with a small area of cavitation (arrowhead) in the same lobe. Bilateral pleural effusion is also seen. This patient presented disseminated nocardial disease with pulmonary, hepatic, adrenal, brain, scalp, and muscular involvement. A tissue biopsy culture of the intramuscular abscess revealed *Nocardia nova*.

Figure 3. Pulmonary nocardiosis in a 58-year-old male right lung transplant recipient who presented with respiratory infection. Axial chest CT image shows several small ill-defined centrilobular nodules (arrows) in the apical segment of the right lower lobe. Diffuse bronchial wall thickening and bronchiectasis throughout the right lung (arrowheads) as well as severe left lung emphysematous changes are seen. Right pleural effusion was also present (images not shown). Bronchoalveolar lavage cultures revealed *Nocardia nova*.

Figure 4. Pulmonary nocardiosis in a 45-year-old female patient status post-kidney transplant. Thoracic CT image (a) shows an air-space consolidation in the left lower lobe with central cavitation (arrow). Mediastinal and left axillary lymphadenopathy (arrows) are also seen (b). Bronchoalveolar lavage cultures revealed *Nocardia cyriacigeorgica*.

Figure 5. Pulmonary nocardiosis in a 54-year-old male kidney and pancreas transplant recipient. Thoracic CT images show bilateral air-space consolidations with air-bronchogram in the lower lobes and the right upper lobe. CT-guided aspirate of the right upper lobe and sputum culture revealed *Nocardia nova*.

Figure 6.

Pulmonary nocardiosis in a 46-year-old male renal transplant recipient. He presented 5 years after his transplant with chest discomfort. Thoracic CT images show a left lower lobe air-space consolidation (arrows; a) and a left pleural effusion (b). A small, lobulate nodule is also seen in the left upper lobe (arrow). Calcified lymph nodes probably related to previous granulomatous disease are also seen in (a). Surgical treatment consisted of left thoracotomy, decortication, and pulmonary wedge resection. Cultures of the empyema fluid revealed *Nocardia cyriacigeorgica*.

Figure 7. Pleural nocardiosis in a 54-year-old man post-renal transplant for hypertensive nephropathy. Thoracic CT image shows a loculated right pleural effusion (asterisk) with thick, calcified wall, suggesting chronicity. Mediastinal lymphadenopathy (arrows) is also present. Calcified lymph nodes probably related to previous granulomatous disease are also seen. No parenchymal abnormalities were noted. Cultures of the empyema fluid revealed *Nocardia cyriacigeorgica*.

Figure 8.

Disseminated nocardiosis with CNS involvement in a 51-year-old male patient status post-liver transplant (same patient as Fig 2). MRI images reveal multiple parenchymal and a subcutaneous abscess. T2-weighted image (a) shows multiple bilateral white matter hyperintense lesions (arrows). Coronal contrast-enhanced T1-weighted image (b) shows ring enhancement of the lesions (arrows) and surrounding oedema. Diffusion-weighted images show restricted diffusion of the brain lesions (arrows; c) and of the subcutaneous right temporal abscess (arrowhead; d).

Figure 9.

Disseminated nocardiosis with abdominal involvement in a 51-year-old male patient status post-liver transplant (same patient as Fig 2). MRI images revealed multiple liver and bilateral adrenal abscesses. Contrast-enhanced fat-suppressed (FS) T1-weighted MRI image shows two small round hypointense lesions with peripheral ring enhancement in segment IVa (arrow; a). Splenomegaly and a splenic infarct (arrowhead) are also seen. Contrast-enhanced FS T1-weighted image (b) shows a right adrenal nodule with hypointense centre and peripheral enhancement (arrow). A left adrenal abscess was also present (not shown).

Figure 10. Pyomyositis and intramuscular abscess in a 65-year-old man status post-right lung transplant who presented with a 1-week history of left leg pain. Axial short-tau inversion recovery (STIR) MRI image of the pelvis shows a hyperintense complex fluid collection within the left gluteus maximus muscle (arrow; a). Coronal contrast-enhanced FS T1-weighted image shows peripheral and septal enhancement of the lesion (arrows; b). Post-surgical gluteal abscess culture revealed *Nocardia farcinica*.