CASE REPORT

First reported case of disseminated *Nocardia kroppenstedtii* sp nov. infection presenting with brain abscess and endocarditis in an immunocompromised patient with mantle cell lymphoma: challenges in diagnosis and treatment

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SUMMARY

A 72-year-old man with a history of blastoid variant stage IV relapsed refractory mantle cell lymphoma presented with new central nervous system (CNS) symptoms. Brain imaging was positive for rim-enhancing lesions along with a mitral valve mass on the echocardiogram. It was a challenge to establish the exact aetiology of these lesions in this patient. He was empirically treated with chemotherapy on the presumption that the brain lesions were secondary to progressive malignancy. However, brain biopsy was negative for malignancy and blood cultures were found positive for *Nocardia kroppenstedtii* sp nov. He subsequently improved with antibiotic therapy. Disseminated *Nocardia* can present with multiorgan involvement. Clinical and microbiological diagnosis can be challenging. Antimicrobial treatment-related side effects require close monitoring, and dosage changes or therapy adjustments may be necessary.

BACKGROUND

Nocardia is a soil borne aerobic actinomycete. It is a Gram-positive branching filamentous bacillus which is weakly acid fast. *Nocardia* bacteraemia is quite rare. Infection with *Nocardia kroppenstedtii* sp nov. is extremely rare, with only one other report described in a case of an immunosuppressed lung transplant recipient in 2014.¹ Diagnosis of nocardiosis is difficult to establish clinically and microbiologically.² *Nocardia* can disseminate to multiple sites in the body and can mimic many other conditions, such as advanced cancer. The other challenge in diagnosis is the slow growth of *Nocardia* on culture media, as the organism may take weeks before positive identification. Pulmonary nocardiosis is the most common clinical presentation of infection, while central nervous system (CNS) infection is the most common extrapulmonary location for nocardiosis.³ Since patient populations are changing, with more numerous and advanced immunosuppressant therapies available for various conditions, the significance of *Nocardia* infections may increase. Here, we describe the challenges in diagnosis and treatment of a case of advanced refractory mantle cell lymphoma complicated by disseminated nocardiosis, with *Nocardia*

kroppenstedtii sp nov. bacteraemia, evidence of infective endocarditis and brain abscess. To the best of our knowledge, this is the first case of brain abscess and endocarditis from this *Nocardia* spp.

CASE PRESENTATION

A 72-year-old Caucasian man presented with a progressive blurry vision and right foot drop for 1 week. His medical history was significant for mantle cell lymphoma and he was on combination chemotherapy with Bendamustine, and Rituximab plus Bortezomib. Unfortunately, his disease progressed and a follow-up lymph node biopsy showed progression of the mantle cell morphology to a blastoid form. Thus, the BTK inhibitor ibrutinib was added to his chemotherapy regimen. The patient underwent an MRI of the brain and spinal cord for the investigation of his new neurological symptoms which revealed multiple intracranial rim-enhancing lesions (figures 1), along with enhancing lesions of the right C7 lamina. The brain lesions were not present on a previous MRI, although the cervical cord lesion was noted on a previous positron emission tomography/CT. On transthoracic echocardiography, a (1.2×0.69 cm) mass was seen on the anterior leaflet of the mitral valve (figure 2). A transesophageal echo study was done to further delineate the disease, and mitral regurgitation was noted. Since blood cultures were negative to that point, consideration of culture negative infective endocarditis was raised.

On the basis of the MRI findings of the CNS, the brain lesions were felt to be most likely consistent with multiple metastatic lymphoma lesions based on an oncology and neurology review. Brain biopsy was recommended at this stage, but not performed. The patient was empirically started on high-dose intravenous methotrexate with methylprednisolone to decrease intracranial oedema. The patient was not a candidate for cardiac surgery regarding the mitral valve lesion due to comorbidities, brain lesions and the advanced stage of aggressive refractory mantle cell lymphoma. Subsequently, a follow-up MRI of the brain 1 week later revealed an increase in size of the multiple intracranial rim-enhancing lesions. The infectious disease service strongly recommended brain biopsy

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Figure 1 MRI of the brain with contrast showing multiple intracranial rim-enhancing lesions with associated central restricted diffusion and surrounding oedema.

Figure 2 Two-chamber view of echocardiogram showing a 1.2x0.69 cm mass on the anterior leaflet of the mitral valve.

at this stage. Pathology from the biopsy showed scattered multi-focal acute inflammatory cells and focal necrosis, but no malignant cells were identified.

After 11 days of hospitalisation, blood cultures returned positive by the BacT/Alert microbial detection system. Gram stain showed Gram-positive rods resembling the *Nocardia* spp, which were weakly acid fast on the Ziehl-Neelsen stain. For further speciation, the specimen was sent to an outside laboratory, where Matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI TOF MS) was used. This technique is a newer advanced test allowing rapid identification of micro-organisms comparing the molecular spectra of the sample to known small molecule libraries. In our case, the MALDI TOF MS database was limited to the 10 most common *Nocardia* spp (*Nocardia kroppenstedtii* sp nov. was not included in the database). The closest match for this test suggested an identification of *Nocardia farcinica*. Subsequently, 16s ribosomal sequencing was performed and a 100% match was found for *Nocardia kroppenstedtii* sp nov. These two *Nocardia* spp have a 99.8%

16s gene sequence similarity, which explained the difficulty in the mass spectrometry test.

INVESTIGATIONS

CT scan of the chest showed a left upper lobe pulmonary opacity measuring up to 3.1 cm, consistent with disease of an infectious or inflammatory aetiology. Cerebrospinal fluid (CSF) studies revealed 1 white cell count, glucose of 61 mg/dL and a total protein of 37 mg/dL. CSF was sent for infectious workup and flow cytometry was performed for evaluation of brain involvement with lymphoma. Infectious workup included serum and CSF testing with cytomegalovirus PCR, coccidioidomycosis IgG/IgM titres, cryptococcal antigen, Treponema testing, bacterial and fungal cultures, and toxoplasma PCR. These tests were all negative.

DIFFERENTIAL DIAGNOSIS

The brain lesions were initially suspected to be due to metastasis from the lymphoma. However, the brain biopsy and lack of response to chemotherapy suggested another aetiology. One possibility included septic emboli from the mitral vegetation that was present on the echocardiogram suggesting endocarditis. In that context, the lung lesion could also have represented an infection with septic emboli versus worsening cavitory lymphoma. Other causes for brain lesions prompted brain biopsy for full evaluation.

TREATMENT

Treatment was initiated with meropenem and trimethoprim-sulfamethoxazole (TMP/SMX) pending susceptibilities for disseminated nocardiosis with lesions involving the brain and heart valves. Owing to the patient's progressive pancytopenia and with the help of susceptibility data, TMP/SMX was replaced with levofloxacin and linezolid. On this therapy, the patient's pancytopenia worsened, so the antibiotic regimen was replaced once more with ceftriaxone, minocycline and ciprofloxacin.

OUTCOME AND FOLLOW-UP

The clinical state of the patient improved slightly after starting treatment, but later in the course, the patient opted for home hospice care and expired shortly thereafter.

DISCUSSION

Nocardia is a ubiquitous environmental saprophyte, found in soil, organic material, water and air. It is an aerobic, partially acid-fast staining, filamentous Gram-positive rod. It can cause a localised infection in the dermis, or lungs, or it can disseminate haematogenously to other organs and cause systemic nocardiosis.⁴ *Nocardia* was first described by Edmond Nocard in 1888 and represents a large group of bacteria with more than 80 species. Of these, up to 30 different species are known to cause infection in humans. Since the recent advent of antibiotic resistance testing and genetic studies of ribosomal components, there has been a great increase in the number of *Nocardia* spp described. *Nocardia* infection is fairly uncommon with only up to 500–1000 cases of nocardiosis reported yearly in the USA.⁵ Most strains possess the cord factor (trehalose 6–6'-dimycolate), which is an important virulence factor for *Nocardia* spp. Other virulence factors include the enzymes catalase and superoxide dismutase. However, *Nocardia* is generally considered an organism of low intrinsic virulence and is usually found as an opportunistic pathogen.

Nocardia kroppenstedtii sp nov. is a newly discovered *Nocardia* spp that was first identified in a lung transplant

recipient in 2014, and has not been reported since then. This makes our case the second case of *Nocardia kroppenstedtii* sp. nov. infection reported until now. It is also the first reported case of infectious endocarditis and brain abscess. *Nocardia kroppenstedtii* sp. nov. was described as a separate species based on chemotaxonomic and morphological properties, though it shares 99.8% of its genome with *N. farcinica*.¹ This helps explain the MALDI TOF MS findings, which required 16s ribosomal sequencing for definitive identification. The serious nature of disease and resistance to the newer cephalosporins suggest a clinical need for proper laboratory identification of *Nocardia* spp.⁶

Nocardia spp. usually infect immunocompromised individuals or those with underlying chronic medical illnesses. Interestingly, up to 15% of cases have been found in apparently healthy individuals with no predisposing conditions.⁷ Infection is more common in patients with impaired cell-mediated immunity, such as those with underlying haematological malignancies, patients with transplant on immunosuppression, patients with HIV/AIDS, or those on long-term steroid therapy.⁸ An increase in the incidence of *Nocardia* in immunosuppressed patients appeared due to increased heart and liver transplantation procedures after 1980. In 1989, Wilson *et al.* reviewed clinical and epidemiological data in solid organ transplants. The frequency of *Nocardia* in different centres varied from 0% to 20% with a mean of 2.8%.⁹ In more recent times, it appears that the overall incidence of *Nocardia* infection in transplant recipients has decreased since the introduction of cyclosporine. In one study, there was a reduction in the incidence of *Nocardia* infection at Stanford University from 13% to 4.2%.¹⁰ In another study, 69% patients who were taking prophylaxis with TMP/SMX developed *Nocardia* infection, concluding that chemoprophylaxis was not fully protective.¹¹

The most common *Nocardia* infections include pulmonary and skin infections. Pulmonary infections are the most common (43%). Extrapulmonary involvement occurs quite frequently with CNS infections comprising 30% and wound infections 15%. However, *N. farcinica* is rarely isolated from blood and urine.¹² This multiorgan involvement results in challenges in the diagnosis of *Nocardia*, as infection with this genus may mimic a wide variety of conditions. Therefore, a low threshold for suspicion must be kept in the appropriate clinical setting. *Nocardia* infections have increased recently, as more effective immunosuppressants have resulted in many more immunocompromised patients. Our patient was suffering from advanced B-cell non-Hodgkin's lymphoma and had received rituximab and ibrutinib followed by another multiagent cytotoxic chemotherapy. Rituximab is known to induce B-cell lymphopenia for many months' duration, which predisposes patients to opportunistic infections.¹³

In the appropriate clinical setting, the diagnosis of *Nocardia* can be made by the demonstration of organisms in culture or tissue histology. *Nocardia* can also be visualised by methenamine silver and Gram staining, even though the latter is usually weak. *Nocardia* can be found by acid-fast staining, though it is not reliable. However, PCR can be used for the rapid diagnosis of *Nocardia*, as cultures may take up to 5 days. PCR is more accurate and also helps to differentiate the various species of *Nocardia*. Analysis by 16s ribosomal sequencing or restriction analysis of hsp65 genes is highly accurate and is considered the gold standard in identifying *Nocardia* spp.^{14 15} *N. farcinica* and related species can be differentiated from other species using this technique.⁷ This has clinical significance, as intrinsic antibiotic resistance may be a factor among the various *Nocardia* spp.

Current recommendations to treat *Nocardia* infection are to start empiric treatment with either TMP-SMX or other agents such as amikacin or linezolid, with adjustment of medication as appropriate based on the final sensitivities.^{16–18} However, as in our case, side effects such as allergic reactions and bone marrow suppression may require discontinuation and use of alternative therapy. Most *Nocardia* spp. are susceptible to TMP-SMX, moxifloxacin, linezolid, minocycline and amikacin, and demonstrate variable susceptibility to ciprofloxacin and imipenem-cilastatin.^{19–24} In the case of severe infections, combination antibiotic regimens are recommended, with TMP-SMX in association with a third-generation cephalosporin or a carbapenem.¹¹ A minimum of 6 months and up to 12 months of treatment is recommended if there is involvement of the CNS.²⁵

Our patient showed a good response to antibiotics, once the appropriate therapy was instituted. However, systemic nocardiosis is a serious condition with a high mortality rate, with some reports of case fatality over 50%.^{26–28} CNS nocardiosis has a very high mortality overall, approaching 50%.¹⁷

Learning points

- ▶ *Nocardia kroppenstedtii* sp. nov. is a newly discovered species of *Nocardia* with only one previous reported case.
- ▶ This is the first report of a brain abscess and infective endocarditis caused by *Nocardia kroppenstedtii* sp. nov.
- ▶ *Nocardia* infection is an uncommon opportunistic infection that is most commonly seen in immunocompromised patients, though rarely it is found in healthy individuals.
- ▶ Neurological symptoms in the setting of diffuse large B-cell lymphoma or other malignancy are not always due to central nervous system (CNS) metastasis. CNS nocardiosis, although uncommon, should be considered in the differential diagnosis of mass lesions in the brain.
- ▶ *Nocardia* infection can be treated with a long course of TMP-SMX; however, in the case of suppressed haematopoiesis or pancytopenia, non-myelosuppressive drugs such as ceftriaxone and ciprofloxacin may be better suited to treat nocardiosis.

Contributors AM and MAM were responsible for writing the case presentation, summary and background. HMAA and WU were responsible for writing the discussion and learning points.

Competing interests None declared.

Patient consent Obtained.

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