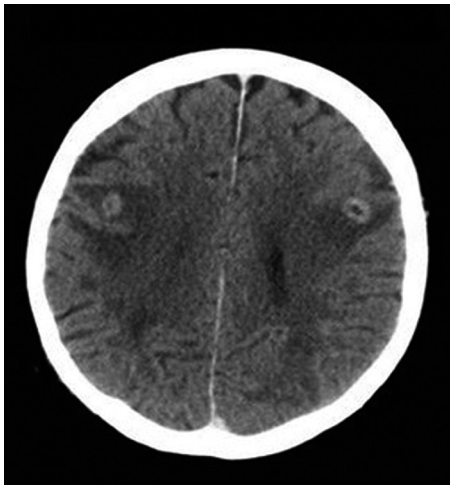
Disseminated nocardiosis in a liver transplant patient

Introduction

Nocardiosis is an uncommon opportunistic infection caused by the Gram-positive actinomycetes of the genus Nocardia which is found worldwide in soil as well as in aquatic environments. Most nocardiosis occurs in patients who are immunosuppressed, notably those receiving glucocorticoids or other immunosuppressant therapies.

Nocardiosis carries high mortality rates. It can affect multiple body systems and causes localized or disseminated disease. It displays little pathognomy, rendering its clinical diagnosis difficult. The population of immunosuppressed patients has increased significantly in recent decades owing to novel therapies and increasing numbers of organ transplantations. It is thus important for clinicians to include nocardiosis as a differential diagnosis in such patients who present with localized or systemic symptoms of infection.

Figure 1. Computed tomography of the head demonstrating bilateral ring-enhancing lesions with surrounding oedema.



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Discussion

Nocardiosis is caused by infection with the bacteria actinomycetes of the genus Nocardia. *Nocardia* spp are filamentous, Gram-positive rods. Worldwide, *N. farcinica* and *N. nova*

CASE REPORT

A middle-aged man presented to hospital with 24 hours of new onset holocranial headache and an episode of convulsion. He had a 4-month history of lassitude and weight loss (1 stone), without fever. He had attended hospital 1 month earlier complaining of a productive cough and was given oral antibiotics to treat a presumed chest infection.

The patient had no contact with animals at home or at work or unwell persons and had no travel history. He had had a liver transplant 4 years earlier. He was immunosuppressed with tacrolimus. His drug history also included valganciclovir for recent cytomegalovirus viraemia.

On examination, the patient was cachectic. His temperature was 37.5°C, and he required 2 litres of oxygen to maintain his saturations above 94%. Auscultation of his chest revealed reduced air entry at the right base. A well-healed rooftop incision was noted on his abdomen which was otherwise normal. His Glasgow coma score was 15/15 although his speech was dysarthric. His power and tone were normal in all four limbs but past-pointing was noted in his left arm.

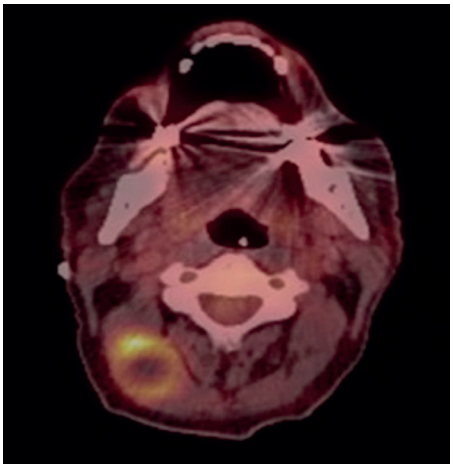
Blood tests revealed a haemoglobin level of 90 g/litre, white cell count of 6.69×10^9/litre with a lymphopaenia of 0.45×10^9/litre and a C-reactive protein level >200 mg/litre. Chest X-ray revealed right lower zone minor linear atelectasis. Computed tomography of the head revealed multiple bilateral ring-enhancing lesions with surrounding oedema (*Figure 1*). Blood and urine cultures were negative. HIV and syphilis serology was negative, as were toxoplasma IgM, galactomannan, beta-D-glucan and cryptococcal antigen tests. His lumbar puncture revealed an opening pressure of 12 mmHg, no white cells, a negative Gram-stain and a mildly elevated protein. CSF culture, tuberculosis polymerase chain reaction and viral polymerase chain reaction were negative.

A F-18 fluorodeoxyglucose positron emission tomography-computed tomography scan revealed numerous intracranial, pulmonary and intramuscular lesions demonstrating increased rim fluorodeoxyglucose uptake and central photopenia suggesting central necrosis. One of these, a 34 mm avid intramuscular lesion in the right posterior neck (*Figure 2*), was aspirated. Microscopy of the pus revealed branching Gram-positive rods. Modified Ziehl-Neelsen stain was negative and no fungal elements were seen. After 48 hours pinpoint white colonies appeared. Spectrometry was performed on these via matrix-assisted laser desorption/ionization – time of flight, identifying *Nocardia farcinica*.

The differential diagnosis of this presentation is wide and includes bacterial (streptococcal/staphylococcal abscesses, tuberculosis), fungal (cryptococcus, aspergillosis), parasitic (toxoplasmosis, cysticercosis), viral (JC virus), and neoplastic causes (CNS lymphoma) (Nelson et al, 2011). The patient was initially started on anti-tuberculous therapy, meropenem for broad-spectrum bacterial abscess cover, ambisome for antifungal cover, and pyrimethamine and sulphadiazine to treat toxoplasmosis. He was initiated on dexamethasone for cerebral oedema and levetiracetam for seizure treatment.

Once the diagnosis of nocardiosis was confirmed, his antimicrobial therapy was rationalized to intravenous ceftriaxone, amikacin and co-trimoxazole while awaiting sensitivities. The patient's clinical progress was remarkable. He had no further seizures, progressively gained weight, and his neurological symptoms improved, but repeat magnetic resonance imaging of the head showed only minimal improvement at 6 weeks, therefore he was discharged on intravenous ceftriaxone and co-trimoxazole, for a planned treatment duration of 1 year. An oral switch will be dictated by further clinical progress and follow-up brain imaging.

Figure 2. Positron emission tomography-computed tomography demonstrating right posterior intramuscular neck lesion with central photopenia.



are the most common pathogenic species (Mandell et al, 1995). Human infection is largely secondary to cutaneous inoculation or inhalation.

The majority of those who suffer nocardiosis are immunosuppressed (Beaman and Beaman, 1994). Specifically in transplant patients, risk factors include elevated median calcineurin inhibitor levels in the preceding 30 days and cytomegalovirus disease (Peleg et al, 2007).

Nocardiosis can affect multiple body systems, most commonly the lungs, CNS and skin (Beaman and Beaman, 1994; Mandell et al, 1995; Peleg et al, 2007). In pulmonary disease, abscesses, pneumonias and empyemas have all been described (Mandell et al, 1995). In the CNS it usually causes brain abscesses. In the skin, nocardiosis may present as a primary cutaneous lesion (e.g. ulcer, abscess) or cellulitis; lymphocutaneous disease may occur (Satterwhite and Wallace, 1979). It is a recognized cause of mycetoma.

Diagnosis relies on identification. *Nocardia* spp. grow on most routine bacterial culture media, but they are fastidious and growth can take up to 21 days (Beaman and Beaman, 1994; Lederman and Crum, 2004). It is therefore important that laboratory staff are aware of the suspected diagnosis so that culture time can be extended. There are increasing reports of identification using matrix-assisted laser desorption/ionization – time of flight (Blosser et al, 2016).

Untreated disseminated nocardiosis carries a 100% case fatality rate (Beaman and Beaman, 1994). Treatment should be directed by isolate sensitivities. An empirical combination of co-trimoxazole, amikacin and a beta-lactam can be used to treat disseminated disease with CNS involvement before sensitivity acquisition. Treatment usually consists of a 6-week induction period with intravenous antibiotics, and providing improvement is observed, a maintenance period is continued with oral antibiotics for the remaining course. Treatment duration is empiric, but given the relapsing nature of nocardiosis treatment in the immunosuppressed is usually given for at least 1 year (Mandell et al, 1995; Lerner, 1996). **BJHM**

LEARNING POINTS

- Nocardiosis results from infection by the environmental Gram-positive rod actinomycete of the genus Nocardia.
- The majority of those affected are immunosuppressed.
- The disease can affect multiple body systems, most commonly the lungs, and has a propensity to cause disseminated disease.
- Diagnosis is based on isolation of the organism, although it can take up to 21 days to be cultured. Susceptibility testing is important given varying resistance patterns.
- Treatment is based on organism sensitivities but empirical therapy includes a 6-week induction period with more than one intravenous antibiotic, usually followed by oral therapy to complete 1 year given the high relapse rate.

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