CASE REPORT

Immunosuppression and a serious opportunistic infection: an unfortunate price to pay

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SUMMARY

A 57-year-old woman with diabetes mellitus type 1, status postcadaveric pancreas transplant alone 11 years ago, on chronic immunosuppression, and dialysis-dependent end-stage renal disease, presented with 2 months of progressive generalised weakness, lumbar back pain with right lower extremity radiculopathy and episodic symptomatic hypotension. Preliminary infectious disease work up was unremarkable. She was discharged following symptomatic improvement. She represented 3 days later with continued functional decline and leucocytosis. Chest X-ray demonstrated diffuse pulmonary nodules, confirmed on chest CT scan. CT-guided biopsy of a right upper lobe nodule was performed; studies confirmed *Nocardia farcinica*. Further imaging revealed bilateral white matter intracranial lesions, and extensive *Nocardia*-positive fluid collections in the right gluteal and vastus musculature, requiring periodic surgical debridement. She was treated with multiple antimicrobials, including trimethoprim-sulfamethoxazole, amoxicillin/clavulanate and moxifloxacin. She was discharged after a 6-month hospitalisation.

BACKGROUND

This case highlights challenges in timely diagnosis of opportunistic infections, such as *Nocardia farcinica*. This bacterium is a ubiquitous environmental saprophyte that primarily affects hosts with defects in cell-mediated immunity, including solid organ transplant recipients and immunosuppressed individuals. Clinical presentation may be rather non-specific. Even though pulmonary involvement is most common, chest radiographs are often variable and inconclusive. There can be widespread organ involvement with significant-associated morbidity and mortality, if timely and appropriate treatment is not initiated. While *Nocardia* infection has been seen in kidney/pancreas recipients, we describe for the first time, to the best of our knowledge, presence of *Nocardia* infection in a patient who has undergone pancreas transplant alone (PTA).

CASE PRESENTATION

A 57-year-old woman presented with 2 months of functional decline characterised by progressive weakness, back and right lower extremity (RLE) pain, non-healing RLE ulcers, fatigue and intermittent fevers, with lightheadedness that was most notable after dialysis. Her medical history included PTA 11 years ago for diabetes mellitus type 1, with cystopancreatic shunt, as well as dialysis-dependent end-stage renal disease from calcineurin-inhibitor

toxicity. Of note, her induction immune suppression included antibody therapy with renal antithymocyte globulin-thymoglobulin as well as mycophenolate mofetil 1000 mg two times per day, tacrolimus 3 mg two times per day and a prednisone taper. Her initial tacrolimus target level was 15–18 ng/mL; over the years, the target level was decreased to 5–7 ng/mL. Other than rarely positive C4d immunostain in a needle biopsy of her pancreas allograft 8 years following transplant, there was no evidence of donor-specific antibodies.

Physical examination was significant for a loud triphasic pericardial friction rub on cardiac auscultation, and chronic ulcers on the RLE. At the time of admission, the patient's immunosuppressive regimen consisted of mycophenolate mofetil 500 mg two times per day, tacrolimus 2 mg in the morning and 1.5 mg at night and prednisone 5 mg daily. Initial laboratory parameters were significant for anaemia with haemoglobin of 7.9 g/dL, normal white cell count, elevated creatinine of 4.2 mg/dL and negative troponins. Tacrolimus level was initially supratherapeutic at 12.9 ng/mL (goal 5–7 ng/mL). Blood cultures were negative, urine was positive for coagulase negative *Staphylococcus* (determined to be a contaminant) and RLE ulcers confirmed *Enterococcus*. The patient was discharged with a diagnosis of 'multi-factorial weakness' and negative infectious work up, but was readmitted several days later for continued functional decline, RLE pain, increased fatigue and intermittent confusion.

INVESTIGATIONS

Laboratory evaluation on readmission revealed leucocytosis to $18 \times 10^9/L$. The patient was treated with broad antimicrobial coverage, including piperacillin/tazobactam and vancomycin. Abdominal X-ray and CT were consistent with pseudo-obstruction, likely secondary to immobility and narcotic pain medications for her RLE pain.

Blood cultures remained negative, prompting discontinuation of antimicrobial therapy. Urine cultures continued to grow coagulase negative *Staphylococcus*, thought to be chronic. Given the negative blood cultures, her antibiotics were discontinued after 48 h. The following day, she was tachycardic and hypotensive, with leucocytosis. Antibiotics were restarted and further infectious disease work up was initiated. Chest X-ray followed by a chest CT revealed bronchovascular micronodules in both lungs without an apical basal gradient, felt to be most consistent with miliary spread of an opportunistic fungal or mycobacterial

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infection, given her immunocompromised status (figure 1). Blood cultures remained negative, as did additional tests including Epstein-Barr virus and cytomegalovirus (CMV) DNA PCR. Fungal serologies were obtained, and were negative; a positive Fungitell assay (which is able to detect (1→3)- β -D-glucan, a cell wall component of medically important fungi)¹ was felt to be a false positive secondary to piperacillin/tazobactam. Transoesophageal echocardiogram was negative for endocarditis.

Bronchoalveolar lavage (BAL) of the right upper lobe and transbronchoscopic biopsy were performed. Tests for *Mycoplasma*, *Pneumocystis carinii*, adenovirus, *Legionella*, *Histoplasma*, *Blastomyces* and tuberculosis were negative; however, candida and herpes simplex virus (HSV) 1 were positive. The BAL demonstrated a negative Gram stain, acid-fast smear, fungal smear and nocardia stain. While positive HSV-1 PCR was thought to be secondary to oropharyngeal contamination, acyclovir was initiated given the patient's immunocompromised state.

Finally, CT-guided biopsy was performed on one of the lung nodules in her right upper lobe, and grew organisms morphologically suggestive for *Nocardia* on mycobacterial culture.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses considered in our patient included dehydration from overaggressive dialysis, electrolyte abnormalities, anaemia, opportunistic infection in the setting of immunosuppression and recurrent fevers, local infection of the patient's non-healing skin ulcers or dialysis catheter site, underlying malignancy, medication toxicity and hypothyroidism. Her initial presentation was thought to be multifactorial, given her many comorbidities. It was only during her subsequent presentation, with persistent symptoms along with abnormal objective parameters such as hypotension and leucocytosis, that increased concern for infection as a primary contributor was aggressively entertained.

TREATMENT

Histopathological examination using specific stains and 16S DNA sequencing from the lung biopsy confirmed the organism as *Nocardia farcinica*. Intravenous trimethoprim-sulfamethoxazole was initiated. MRI of the brain revealed multiple discrete multifocal cerebral lesions highly suggestive for disseminated central nervous system (CNS) nocardiosis (figure 2). MRI of the RLE was obtained, which showed extensive cystic changes and fluid collections in the right gluteal and vastus musculature (figures 3 and 4). An aspirate taken during surgical exploration

Figure 1 CT angiography of the chest showing bilateral bronchovascular micronodules along with focal consolidative opacity in the right upper lobe posteriorly, likely representative of coalescence of multiple nodules consistent with miliary spread of a likely opportunistic fungal or mycobacterial infection.

Figure 2 MRI of the brain: T2 fluid attenuated inversion recovery image revealing hyperintense area (arrow) in mid right centrum semiovale, the largest of four seen; this corresponds to an area of restricted diffusion on diffusion weighted imaging (not shown). Lesions involve white matter of both cerebral hemispheres.

revealed *Nocardia*. The patient underwent numerous incision and drainage procedures, as well as RLE debridement, over the course of her hospitalisation. Moxifloxacin and amoxicillin/clavulanate were added in addition to trimethoprim-sulfamethoxazole.

OUTCOME AND FOLLOW-UP

The patient remained hospitalised for approximately 6 months on trimethoprim-sulfamethoxazole, amoxicillin/clavulanate and moxifloxacin. She was dismissed on this regimen with a plan to continue the medication for at least 1 year. Her immunosuppressive regimen had been notably de-escalated during the course of her hospital stay, weighing the risk of transplant rejection versus the risk of opportunistic infection. Mycophenolate mofetil and tacrolimus were discontinued. Infusions of Intravenous immunoglobulin were added and prednisone dose

Figure 3 MRI of the lower extremities: T2-weighted axial image revealing cystic change/fluid collections in the right quadratus femoris, vastus medialis, intermedius and lateralis musculature.

Figure 4 MRI of the pelvis: T2-weighted axial image revealing cystic change/fluid collections, which have largely replaced the right gluteal musculature.

was increased to 10 mg. Of note, pancreatic enzymes were serially followed to monitor for signs of pancreatic allograft rejection. The patient's regimen was adjusted periodically by the kidney transplant team based on her clinical status and laboratory findings, in an attempt to find an optimal balance between immune suppression and adequate host defence.

DISCUSSION

In this case report we present a middle-aged woman with PTA, on chronic immunosuppressive anti-rejection therapy, who presented with non-specific symptoms, including progressive weakness. She was found to have disseminated *Nocardia* after multiple evaluations. Notably, her non-specific presentation rendered the case a diagnostic challenge.

Nocardia farcinica is a ubiquitous environmental, aerobic saprophyte that appears as a Gram-positive filamentous bacterium microscopically.² *Nocardia* is primarily considered an opportunistic infection, and is most often diagnosed in individuals with defects or impairments in cell-mediated immunity, notably solid organ transplant recipients, and in those who are chronically immunosuppressed.³ Most frequently, patients present with pulmonary symptoms, including cough, shortness of breath, fever, weight loss and progressive fatigue, which may be subacute to chronic in nature.⁴ Extrapulmonary manifestations of nocardiosis include CNS and subcutaneous tissue involvement, among others.⁵

In organ transplant recipients overall, the incidence of *Nocardia* infection appears to be less than 1%; however, higher frequency has been seen with specific organ transplantations.^{6–9} Peleg *et al*⁸ showed, while comparing 30 solid organ transplant recipients (lung, heart, kidney, liver, intestine) to 70 controls, that risk factors for *Nocardia* in individuals who have undergone organ transplantation include high-dose steroids, CMV disease in the prior 6 months and high levels of calcineurin inhibitors in the antecedent month. These independent risk factors have been further validated in another series.¹⁰ Interestingly, our patient does not have any of these specific risk factors.

Importantly, an accurate diagnosis of *Nocardia* (and species) allows for institution of appropriate treatment. Furthermore, susceptibility testing is important, given the 'variable in vitro antimicrobial susceptibility patterns'⁴ in *Nocardia* spp. Sulfonamides constitute the therapeutic agent of choice, though other antimicrobials can be used. Often, more than one agent is

used for effective therapy.⁴ While our patient was originally on trimethoprim–sulfamethoxazole and a carbapenem, her medication regimen now includes trimethoprim–sulfamethoxazole, moxifloxacin and amoxicillin/clavulanate, to be continued for a protracted course.

Non-specific presenting symptoms, less common overall incidence rates and absence of red flag symptoms were potential diagnostic challenges in our patient. This case highlights the importance of a high index of suspicion and aggressive testing for opportunistic infections, such as *Nocardia*, in the right clinical setting, of chronically immunosuppressed patients with organ transplantation.

Learning points

- ▶ *Nocardia* is primarily considered an opportunistic infection, and is most often seen in individuals with defects or impairments in cell-mediated immunity, notably solid organ transplant recipients, and in those who are chronically immunosuppressed.
- ▶ Presentation of *Nocardia* infection is most often in the form of pulmonary nocardiosis; however, symptoms may be non-specific and chest imaging findings may be variable.
- ▶ The central nervous system and its accompanying neurological symptoms comprise the most commonly involved extrapulmonary site for *Nocardia* infection.
- ▶ Treatment of *Nocardia* infection often requires a protracted antibiotic course.

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