Nocardiosis and elevated beta-\(\text{d}-\)glucan in solid organ transplant recipients

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Beta-\(\text{d}-\)glucan (BDG) testing can expedite the diagnosis of invasive fungal infections in immunocompromised hosts. Elevated BDG levels have been reported in both in-vitro studies assessing cross-reactivity with Nocardia spp. and published cases of patients with nocardiosis, but there is little data on this association in solid organ transplantation (SOT) recipients. To explore this association, we conducted a case series of SOT recipients with culture-proven nocardiosis and BDG testing who received their care at our institution between 2016 and 2021. We found thirteen cases of nocardiosis in SOT recipients, of which three cases met our case definition of an elevated BDG. Their clinical courses are detailed in the present report. We found that BDG may be elevated in SOT with nocardiosis with no identified cause of false positive BDG, though a causal association cannot be determined. Future prospective studies that better evaluate the association between nocardiosis and BDG are warranted, as are studies that better characterize the possible variability in reactivity amongst Nocardia spp.

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Introduction

Nocardia spp. are well-recognized pathogens that can lead to a range of infectious syndromes in immunocompetent [1] or immunocompromised [2] hosts, including solid organ transplant (SOT) recipients [3]. The diagnosis of nocardial infections rests on a combination of host, clinical, and radiographic factors along with the isolation of Nocardia spp. in culture from a suspected site of infection [3]. A definitive diagnosis of nocardiosis often requires tissue sampling, a process that can prove challenging.

Invasive fungal infections (IFI) present an analogous dilemma. Antigen assays have resolutely been developed to assist in the diagnosis of several IFI including cryptococcosis [4] and endemic mycoses [5]. In particular, the beta-\(\text{d}-\)glucan (BDG) assay detects a component of the cell wall of most fungi [6] and can be useful in a variety of clinical contexts [7–9]. In a large meta-analysis, the sensitivity and specificity of BDG for IFI were 76.8% and 85.3%, respectively [9].

Since the clinical presentations of IFI and nocardiosis are often overlapping, patients diagnosed with Nocardia infection may undergo testing with BDG for work-up of IFI. Interestingly, elevated BDG levels (>60 pg/mL) have been reported in both in-vitro studies assessing cross-reactivity with Nocardia spp. [10] and published cases of patients with nocardiosis (Table 1) [10–12]. To our knowledge, BDG testing has not been previously described in the setting of nocardiosis in SOT recipients. To further explore this association, we conducted a case series of SOT recipients with culture-proven nocardiosis and BDG testing who received their care at our institution between 2016 and 2021.

Case reports

We retrospectively reviewed the electronic medical records of SOT recipients with positive Nocardia cultures treated at Yale New Haven Hospital between October 2016 and March 2021. Cases were identified by querying our institution’s laboratory information system. For purposes of our study, we defined cases as (1) SOT recipients who had (2) a positive culture for Nocardia spp., (3) a clinical syndrome compatible with nocardiosis, and (4) underwent testing with the Fungitell® BDG assay (Associates of Cape Cod, MA, USA) as part of their workup. An elevated BDG was defined as > 60 pg/mL [13]. The Yale University Institutional Review Board approved this study (HIC#2000023859).

We identified thirteen cases of microbiologically-proven nocardiosis in SOT recipients (Fig. 1). Ten of thirteen cases underwent...
Table 1

| Age/sex | Relevant comorbidities | Antimicrobial prophylaxis | Diagnoses | Symptoms | Diagnostics methods | Speciation methods | Species | Antimicrobial therapy | Outcome |
|---------|------------------------|---------------------------|-----------|----------|---------------------|-------------------|---------|-----------------------|---------|
| 62/F    | None                   | None                       | Nocardia abscessus | Pulmonary | Serology, 16S ribosomal DNA sequencing | Histopathology, 16S rRNA sequencing | Nocardia abscessus | Antibiotics, TMP-SMX, ceftriaxone, azithromycin | Chronic respiratory failure, then death from aspiration pneumonia |
| 62/F    | Diabetic mellitus      | None                       | Nocardia abscessus | Pulmonary | Serology, 16S ribosomal DNA sequencing | Histopathology, 16S rRNA sequencing | Nocardia abscessus | Antibiotics, TMP-SMX, ceftriaxone, azithromycin | Chronic respiratory failure, then death from aspiration pneumonia |

Abbreviations: BDD, beta-D-glucan; CNS, central nervous system; CSF, cerebrospinal fluid; DNA, deoxyribonucleic acid; RNA, ribosomal ribonucleic acid.

BDG testing during their clinical courses, and BDG results were available for nine cases. Three of nine cases had elevated BDG (>60 pg/mL) (Table 2), and their clinical courses are detailed below.

Case 1. - Nocardia nova/africana

A 51-year-old man with a history of focal segmental glomerulosclerosis underwent kidney transplantation with allobumulin induction. His post-transplant course was complicated by acute cellular rejection (three weeks post-transplantation) treated with anti-thymocyte globulin and methylprednisolone. His immunosuppressive regimen consisted of tacrolimus, mycophenolate mofetil (MMF), and prednisone (5 mg/day). Post-transplant prophylaxis included azaquone and acyclovir.

Two months post-transplantation, he presented with acute-onset pleuritic chest pain, productive cough, and fever at an outside hospital. A chest radiograph demonstrated right middle lobe consolidation consistent with pneumonia. He was given ceftriaxone and azithromycin. Due to fever (38.9°C) on hospital day (HD) 2, antimicrobial therapy was broadened to cepfepine, doxycycline, micafungin, and vancomycin. On HD3, serum BDG drawn on day of admission resulted as >500 pg/mL (reference range <60 pg/mL). On HD4, a computed tomography (CT) scan of the chest revealed a large cavitary pulmonary lesion, several pulmonary nodules, and bilateral ground-glass opacities. On HD7, bronchoscopy was performed, and bronchoalveolar lavage (BAL) cultures grew Nocardia nova/africana prompting a switch in antimicrobial therapy to trimethoprim-sulfamethoxazole (TMP-SMX) and meropenem. Subsequently, magnetic resonance imaging (MRI) of the brain was obtained and ruled out central nervous system involvement. BAL studies including fungal culture, bacterial and mycobacterial culture, Pneumocystis jirovecii polymerase chain reaction (PCR), and galactomannan testing were negative. In addition, serum cryptococcal antigen and urine Histoplasma antigen were negative. After review of the cumulative data, the elevated BDG was attributed to nocardiosis.

Approximately one-month post-hospital discharge, his regimen was switched to TMP-SMX and ceftriaxone when susceptibility results were made available. He completed 10-weeks of combination therapy before transitioning to TMP-SMX monotherapy. One month after transitioning, his symptoms improved, and imaging with a CT scan of the chest demonstrated a stable cavitary lesion in the left upper lobe with improvement in the left lower lobe nodule.

Case 2. - Nocardia abscessus

A 62-year-old woman with a history of pancreas and kidney transplant due to type 1 diabetes mellitus (eleven years prior) presented with lower extremity edema, fatigue, and dysphagia. At time of presentation, she was on MMF, prednisone (5 mg/day), and tacrolimus. Her post-transplant course had been complicated by renal graft failure requiring hemodialysis.

A CT scan of the chest was ordered to work-up the dysphagia and revealed mediastinal lymphadenopathy. Due to concern for a bacterial infection, piperacillin-tazobactam was empirically started. Blood cultures, sputum culture, Coccioidies serology, serum galactomannan, Histoplasma urine antigen, and BDG were negative. On HD3 she developed worsening respiratory status and left thigh pain. Creatine kinase was found to be elevated (4552 U/L). An MRI of the left femur revealed left thigh myositis, and a left thigh muscle biopsy revealed necrotizing fibers and non-specific acute inflammation with negative stains and cultures for microorganisms. Due to progressive respiratory decline, bronchoscopy was performed, and BAL cultures grew Nocardia abscessus. Additionally, intravenous immunoglobulin (IVig) was administered due to concern for a paraneoplastic or progressive neurological process.

One-week post-IvIG, serum BDG measured >500 pg/mL. Antimicrobial therapy was empirically switched to TMP-SMX and meropenem. Further imaging revealed a right upper lobe pulmonary...
mass likely due to nocardiosis. Five weeks after the last dose of IVIG, serum BDG remained elevated at 331 pg/mL. Two months into her hospital stay, she died from cardiogenic shock after undergoing mitral valve surgical repair.

Case 3. – Nocardia asteroides/Nocardia pseudovaccinii

A 64-year-old man underwent liver transplantation for alcoholic cirrhosis, without the need for induction immunosuppression, and was on maintenance MMF, prednisone (5 mg), and tacrolimus. Notably, his post-transplant course was complicated by acute cellular rejection 1 month after transplant which was treated with methylprednisolone. Two years post-transplantation, he presented with failure to thrive, diarrhea, and a perineal rash involving the penis and gluteal folds.

The rash was due to Herpes simplex virus 2 (HSV-2) as determined by HSV-2 PCR of a skin swab from the affected area. He underwent sigmoidoscopy as part of his work-up for diarrhea. Cytomegalovirus (CMV) immunostaining of biopsied rectal tissue was positive and confirmed the diagnosis of CMV proctitis. Valganciclovir therapy was initiated. On HD8, he developed subcutaneous abscesses in the left calf and left elbow. Wound cultures obtained by incision and drainage of multiple abscesses grew Nocardia spp. identified as either Nocardia asteroides or Nocardia pseudovaccinii by 16S rRNA sequencing. An MRI of the brain was obtained due to concern for disseminated nocardiosis and revealed multiple non-specific hypodensities concerning for abscesses. A transthoracic echocardiogram was negative for vegetations. He was placed on a treatment dose of TMP-SMX and meropenem. He later developed worsening liver function which peaked on HD25 with elevated aspartate aminotransferase 907 U/L (reference range 11–33 U/L), alanine aminotransferase 996 U/L (reference range 6–34 U/L), and alkaline phosphatase 1766 U/L (reference range 9–122 U/L). Liver biopsy was performed and revealed cholestatic hepatitis and bile duct injury consistent with drug-induced liver injury. TMP-SMX was considered a possible cause and switched to linezolid. He developed cytopenias on HD37 attributed to linezolid, so it was substituted with moxifloxacin and minocycline.

On HD51, he had a witnessed tonic-clonic seizure, and a repeat MRI revealed parenchymal enhancement suggestive of worsening nocardiosis or a new infectious process. A lumbar puncture was performed, and cerebrospinal fluid (CSF) studies revealed 0 nucleated cells/μL (reference range <6 cells/μL), glucose 81 mg/dL (reference range 40–70 mg/dL), and protein 69.2 mg/dL (reference range 15–45 mg/dL). CSF bacterial cultures were negative. A serum BDG was obtained to assess for a fungal infection due to unclear etiology of the MRI findings and returned elevated at >500 pg/mL. The patient was empirically started on anidulafungin; however, blood cultures, galactomannan, and CSF fungal and mycobacterial cultures were negative. On HD70, anidulafungin was discontinued, and the elevated BDG was attributed to nocardiosis. He was discharged with a plan to complete 6 months of therapy for nocardiosis. Unfortunately, he died 3 months later due to toxic metabolic encephalopathy complicated by aspiration pneumonia and acute renal failure.

Discussion

The utility of BDG as a diagnostic tool for IFI was first explored among patients with hematological malignancies [8,9], and the literature surrounding interpretation and applicability of BDG assays has since expanded to other populations, including SOT recipients [14]. In SOT recipients with a compatible clinical syndrome, an elevated BDG can be highly suggestive of an IFI; however, elevated BDG has also been reported in association with non-fungal organisms, particularly Nocardia species both in in-vitro studies and in case reports [10–12]. Notably, Nocardia can produce disease that is clinically indistinguishable from a fungal infection in an immunocompromised population. Despite this clinical and microbiological overlap, the diagnostic utility of the BDG assay for the diagnosis of nocardiosis has not been explored in a clinical setting. Indeed, there are no prior published reports describing elevated BDG in SOT recipients infected with Nocardia, and the American Society of Transplantation guidelines on nocardial infections did not include the BDG assay [3]. This case series builds on prior data in the non-transplant population suggesting that nocardiosis may be associated with elevated BDG and expands this observation to the setting of SOT.

In addition to cross-reactivity with certain bacteria, there are other established reasons for falsely elevated BDG levels. These include hemodialysis with cellulose membranes [15], IVIG [16], and other established reasons for falsely elevated BDG levels. These include hemodialysis with cellulose membranes [15], IVIG [16],...
| Age/sex | Relevant comorbidities | Immunosuppression | SOT induction therapy | Antimicrobial prophylaxis | Time since SOT | Diagnosis | Species | Diagnostic methods | Negative fungal diagnostics | Peak BDG level | Potential BDG confounders | Outcome |
|---------|------------------------|-------------------|-----------------------|--------------------------|-----------------|-----------|---------|------------------|----------------------------|---------------|-----------------------------|---------|
| 51/M    | Kidney transplant      | Tacrolimus, mycophenolate mofetil, prednisone (5 mg/daily) | Alemtuzumab             | Atovaquone, acyclovir    | 2 months        | Pulmonary | Nocardia nova/aficana | BAL culture                  | >500 pg/mL | None                         | Clinical improvement |
| 64/M    | Liver transplant       | Tacrolimus, mycophenolate mofetil, prednisone (5 mg/daily) | N/A                    | None                     | 2 years         | Disseminated (skin abscess and CNS) | Nocardia asteroides/N. pseudovaccini | Abscess I&D and nocardia culture | >500 pg/mL | None                         | Deceased due to shock and decompensated cirrhosis |
| 62/F    | Kidney-pancreas transplant | Tacrolimus, mycophenolate mofetil, prednisone (5 mg/daily) | N/A                    | None                     | 11 years        | Disseminated (pulmonary and cardiac) | Nocardia abscessus | BAL culture                 | >500 pg/mL | IVIG (1 week prior to initial BDG; BDG 5 weeks after last IVIG dose was 331 pg/mL) | Deceased due to cardiogenic shock after mitral valve repair |
| 52/M    | Kidney transplant      | Mycophenolate mofetil, prednisone (5 mg/daily), belatacept monthly, eculizumab biweekly | Thymoglobulin           | Atovaquone, valganciclovir | 10 weeks        | Disseminated (CNS, pulmonary, and skin) | Nocardia farcinica | Blood and deep wound cultures | Serum cryptococcal antigen | 46 pg/mL | None                         | Clinical improvement |
| 57/F    | Heart transplant       | Tacrolimus, mycophenolate mofetil, prednisone (5 mg/daily) | Basiliximab            | Atovaquone, acyclovir    | 2 months        | Skin abscess | Nocardia farcinica | Abscess I&D and nocardia culture | N/A                      | <31 pg/mL | None                         | Clinical Improvement |
| 53/F    | Kidney transplant      | Tacrolimus, mycophenolate mofetil, prednisone (3 mg/daily) | N/A                    | None                     | 17 years        | Disseminated (CNS, pulmonary and skin) | Nocardia spp. | Abscess I&D and nocardia culture | N/A                      | <31 pg/mL | None                         | Clinical Improvement |
| 66/M    | Kidney transplant      | Tacrolimus, mycophenolate mofetil, prednisone (5 mg/daily) | Alemtuzumab            | None                     | 3 years         | CNS        | Nocardia farcinica | Brain abscess drainage with tissue culture | N/A                      | <31 pg/mL | None                         | Clinical stability at follow up (2 months after discharge) |

(continued on next page)
| Age/se x | Re lev ant comorbidities | Immunosuppressi on therapy | SOT induction therapy | Time since SOT | Antimicrobial prophylaxis | Species | Diagnosis | Peak BDG level | Potential BDG confounders | Outcome |
|----------|-------------------------|-----------------------------|----------------------|----------------|---------------------------|---------|-----------|---------------|---------------------------|---------|
| 50/M     | Kidney transplant       | Belatacept, mycophenolate   | Alemtuzumab          | None           | 8                         | Nocardia spp. complex | Disseminated nocardiosis | <31 pg/mL | None                      | Clinical and radiologic improvement |
| 65/M     | Kidney transplant       | Tacrolimus, mycophenolate   | Alemtuzumab          | 1 year         | 1 year                     | Nocardia spp. complex | Pulmonary nocardiosis     | <31 pg/mL | None                      | Clinical and radiologic improvement |

Abbreviations: BAL, bronchoalveolar lavage; BDG, beta-D-glucan; CNS, central nervous system; CSF, cerebrospinal fluid; I&D, incision and drainage; IVIG, intravenous immunoglobulin; SOT, solid organ transplantation.

Although these patients were on hemodialysis at the time of admission, our institution uses non-cellulose dialysis membranes which are not known to interfere with BDG levels [19]. Therefore, hemodialysis was not deemed to be a confounder of BDG testing. Notably, Case 2 did receive IVIG one week prior to measurement of serum BDG, but the BDG level remained significantly elevated (331 pg/mL) for >5 weeks after IVIG. In an analysis of 21 pediatric patients receiving IVIG, BDG normalized in 64% and 100% of patients at one and three weeks, respectively [20]. Given the sustained positivity in our case, it is unclear whether or not IVIG played a significant role in confounding the results.

It is interesting to note that all three cases of \textit{Nocardi a farcinica} (maximum BDG 46 pg/mL; Table 2) at our institution did not satisfy the case definition of BDG elevation (>60 pg/mL). This is consistent with an \textit{in-vitro} study performed by Sawai et al. [12] that evaluated \textit{N. farcinica} isolated in a brain specimen and reported mild elevation of BDG levels to about 20 pg/mL compared to control (pure blood agar). Other published studies suggest that levels of BDG may vary across infection with different \textit{Nocardi a} spp. [10–12] Whether species heterogeneity is related to variations in cell-wall content or to other pathogen or host factors is unclear and deserves further investigation.

Our case series is limited by its modest size, retrospective design and descriptive format, which precludes any causal inference. Additionally, the small number of nocardiosis cases in SOT recipients with BDG results available limits our ability to characterize BDG variation across \textit{Nocardi a} spp. The intent of the report is not to establish a causative relationship between BDG elevation and nocardiosis. Rather, this report serves to highlight an association that is poorly known in the clinical setting of transplantation.

In light of the abovementioned results, SOT recipients with elevated BDG, no identified cause of false positive BDG, and clinical concern for IFI with a negative comprehensive workup (including microbiology, histopathology, serology and antigen testing) may merit a work-up for infection with \textit{Nocardi a} spp. This series has important implications for the diagnostic utility of BDG for the diagnosis of nocardiosis in SOT. Future prospective studies that better evaluate the association between nocardiosis and BDG, are warranted, as are studies that better characterize the possible variability in reactivity amongst \textit{Nocardi a} spp.

**Ethical approval**

The Yale University Institutional Review Board approved this study (HIC#2000023859).

**Consent**

Need for informed consent was waived by our institution’s IRB.

**CRediT authorship contribution statement**

\textbf{Matthew Ringer}: Writing – original draft, Conceptualization, Methodology. \textbf{Christopher Radcliffe}: Writing – original draft, Conceptualization, Methodology. \textbf{Christopher A. Kerantzas}: Data curation, Writing – review & editing. \textbf{Maricar Malinis}: Conceptualization, Methodology, Supervision, Writing – review & editing. \textbf{Marwan M. Azar}: Conceptualization, Methodology, Supervision, Writing – review & editing.

**Declarations of Competing Interest**

None.
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