A Puzzling Pulmonary Nodule in a Renal Transplant Recipient

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Case Presentation

A 52 year old gentleman; jeweller by profession, residing in rural Goa, was admitted to our institution in March 2013 with complaints of chest pain, fever and dry cough for 2 weeks prior to admission.

He was admitted to a hospital in Goa for two days prior to the present admission where he was found to have a raised WBC count of 18000/cm³ with a neutrophilic predominance. Chest x-ray showed a right upper zone para-tracheal nodular opacity (Figure 1). An HRCT chest revealed a 5.5 cm x 4.6 cm well-defined, dense, rounded mass of uniform density in the anterior segment of the right upper lobe with a few tiny, surrounding nodules (Figure 2). He was started empirically on IV piperacillin tazobactam and levofloxacin.

The patient had undergone a living-related renal transplant (mother-donor) in September 2009 following which he was on immunosuppression with tacrolimus, mycophenolate mofetil and deflazacort. In August 2012, he developed proteinuria and renal biopsy revealed acute cellular rejection. He received 3 doses of methylprednisolone 1g IV at this time. A month later he was re-admitted with chronic diarrhoea, persistent proteinuria and a rise in serum creatinine from a baseline post-transplant value of 2mg/dl to 5 mg/dl. Methylprednisolone was re-administered, mycophenolate mofetil was stopped in view of diarrhoea and azathioprine 100 mg/day was added. In addition, the dose of tacrolimus and deflazacort was increased. It was slowly tapered over the next few months and on the present admission he was receiving 6 mg and 12 mg of deflazacort on alternate days.
days. He had not received anti- lymphocyte antibody (ALA) therapy at any point. The patient was not on trimethoprim sulfamethoxazole (TMP SMX) or isoniazid (INH) prophylaxis during this period.

On admission to our institution, the patient’s general condition was satisfactory. He was hemodynamically stable, with normal oxygen saturation on ambient air. On enquiry he revealed that the current illness had started with a dull, right-sided chest pain 2 weeks prior to the onset of fever and dry cough. Auscultation of the chest revealed bronchial breath sounds with increased bronchophony in the right mammary and right inter-scapular areas. Other systemic examination was unremarkable. Piperacillin- tazobactam and levofloxacin were continued. However, daily spikes of high grade fever persisted.

Blood cultures drawn on admission were negative. Bronchoscopy revealed a normal transbronchial tree, bronchoalveolar lavage (BAL) galactomannan (GM) index was 0.9 and BAL cultures were negative. A transbronchial biopsy could not be performed as the lesion was peripheral. A CT guided lung biopsy was done; smears, fungal stain and culture of which were also negative. The patient remained persistently febrile with rising WBC counts despite the empirical antibiotic regime, and hence, a video assisted thoracoscopic (VATS) lung biopsy was performed. The lesion showed suppuration with necrosis and was difficult to excise. Hence, a right anterior segmental resection was carried out. Histopathology of the lung specimen revealed acute inflammation, microabscesses, histiocytic aggregates and giant cells, suggestive of pneumonia with abscess formation and organisation. No definite granulomas were seen. AFB, PAS and GMS failed to reveal any organism.

One week later, a diagnostic microbiological report was received.

Discussion

The pursuit of diagnostic testing and the management of infection in a transplant recipient must be guided by a number of principles:

- Immunocompromised hosts are difficult to evaluate as the factors which have rendered them so, interfere with inflammatory responses. However, prompt treatment is necessary as untreated infection disseminates rapidly and may be fatal. The range of pathogens involved is broad and so the diagnostic net has to be rather wide.

- These hosts generally have blunted clinical, pathological and radiological responses. Thus, more sensitive imaging techniques such as computed tomographic (CT) scans and magnetic resonance imaging (MRI) are essential for assessing the presence and nature of infectious and malignant processes.

- Therefore, direct detection of the pathogen, if necessary, by invasive procedures is helpful. These procedures provide tissue for culture and histology and are often preferable to empiric therapy that may be ineffective at best and toxic at worst.

- Serologic tests, indicating past exposure to certain pathogens, are useful in the pretransplant setting to assess risk for relapse of latent disease but are not generally useful after transplantation. Patients on immunosuppressive therapies do not reliably develop antibodies quickly enough during an active infection to enable a serologic diagnosis. Thus, quantitative tests that directly detect the protein products or nucleic acids of the organisms such as sandwich ELISA, direct immunofluorescence, or molecular assays (hybrid capture, PCR) should be utilized.

- Transplant recipients are particularly vulnerable to drug resistant organisms either from the hospital environment or through induction of antibiotic resistance in their flora during therapy. Sites at risk for colonization with resistant organisms (e.g. ascites, blood clots, drains, lungs) can be sampled so that information is available to guide empiric therapy at times of clinical deterioration.

- When undrained fluid collections, blood, or devitalized tissues are present, antimicrobials alone are inadequate. They merely delay clinical deterioration and promote the selection of resistant microorganisms. Early and aggressive surgical debridement of such collections is essential for successful care.

The concept of the “net state of immunosuppression” has been pivotal to the understanding of the incidence and spectrum of opportunistic infections in the organ transplant recipient. Infection-prevention and management strategies in solid organ transplantation (SOT) are based on the classic timetable originally proposed by Rubin et al. Although newer immunosuppressive and antimicrobial prophylactic regimens have affected the pattern and timing of specific infections, certain general observations still hold true.1

Within the first 30 days after transplantation, the patient is at greatest risk for healthcare-associated infections, often due to antibiotic-resistant organisms and often polymicrobial in etiology. Procedure or device-related, such as catheter-associated infections, ventilator-associated pneumonia, aspiration and surgical wound infections are common.

In the one to six months posttransplant period,
the patients are at greatest risk for the development of opportunistic infections. There is significant geographic and institutional variation in the occurrence of opportunistic infections which reflects local epidemiology, varying immunosuppressive strategies and the use of antimicrobial prophylaxis in the post-transplant period. The opportunistic infections most commonly seen are Pneumocystis jirovecii pneumonia, cryptococcal infections, histoplasmosis, tuberculosis, cytomegalovirus, herpesvirus, varicella zoster virus, Ebstein Barr virus, BK virus nephropathy, cryptosporidiosis, toxoplasmosis, strongyloidosis, listeriosis and nocardiosis.

After 6 months post SOT, patients fall into the following 3 groups:

1. **Eighty percent have adequate allograft functioning and minimal immunosuppression.** Infections in this group include community-acquired viral infections (eg, influenza, parainfluenza, respiratory syncytial virus, and human metapneumovirus), bacterial infections (eg, Streptococcus pneumoniae, Haemophilus influenzae) and asymptomatic cryptococcal infection (eg, asymptomatic pulmonary nodules).

2. **Approximately 15% have chronic viral infections** with adenovirus, polyomavirus BK, recurrent hepatitis C and human papillomavirus.

3. **About 5% have frequent rejection episodes with heightened immunosuppression.** They often present with opportunistic pathogens such as P jiroveci, Cryptococcus neoformans, Cytomegalovirus, Nocardia, Rhodococcus, and invasive fungi such as Aspergillus, Mucor, and other molds. Malignant neoplastic diseases that originate from or are modulated through infectious organisms can develop during periods of immunosuppression, albeit in the later post transplantation period (eg, EBV-related post transplantation lymphoproliferative disease, HPV-related skin or anogenital squamous cell cancers and human herpesvirus –8-related Kaposi sarcoma.)

Based on the duration post SOT, rejection episodes and increased immunosuppression; our patient falls into group 3 of the post 6 month period. It must be reiterated that these time frames though useful in clinical decision making are not water tight compartments.

Based on this patient’s history, characteristic host and epidemiological factors as well as the clinical

<table>
<thead>
<tr>
<th>Differential diagnosis</th>
<th>Points in favour</th>
<th>Points against</th>
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<tbody>
<tr>
<td><strong>Bacterial pneumonia</strong></td>
<td>- High WBC count</td>
<td>- Subacute onset (interval between chest pain and fever-2 weeks)</td>
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<td>- Streptococcus Pneumoniae</td>
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<td>- Dry cough</td>
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<td>- Rhodococcus (unlikely due to absence of skin, CNS involvement)</td>
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<td>- No dyspnoea, tachypnea or desaturation</td>
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<td>- Legionella</td>
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<td>- HRCT findings: dense nodule with no air bronchogram rather than a segmental consolidation</td>
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<td><strong>TB</strong></td>
<td>- Immunosuppressed</td>
<td>- No response to broad spectrum antibiotics</td>
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<td>- Not received INH prophylaxis</td>
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<tr>
<td><strong>Post-transplant lymphoproliferative disorder (PTLD)</strong></td>
<td>- Subacute onset</td>
<td>- HRCT: large, single, dense nodule</td>
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<td>- High dose calcineurin inhibitor for graft rejection</td>
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<tr>
<td><strong>Melioidosis</strong></td>
<td>- Rural Goa (lived in close proximity to paddy fields)</td>
<td>- 4 years post transplant</td>
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<td>- High WBC counts</td>
<td></td>
<td>- No ALA received</td>
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<td><strong>CMV</strong></td>
<td>- Immunosuppression</td>
<td>- Relatively well clinically</td>
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<td>- Illness began in dry, winter months, not in monsoon</td>
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<td>- Non DM, not an alcohol user</td>
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<tr>
<td><strong>Invasive fungal infection</strong></td>
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<td>- No other organ involvement</td>
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<tr>
<td>- Aspergillus</td>
<td>- Subacute onset</td>
<td>- HRCT: lung abscess rather than solid nodule is the more common presentation</td>
</tr>
<tr>
<td>- Cryptococcus</td>
<td>- Host factors-Solid organ transplant, high dose immunosuppression</td>
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<tr>
<td>- Dense nodule on HRCT</td>
<td>- BAL GM +ve</td>
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<tr>
<td><strong>Nocardiosis</strong></td>
<td>- Subacute onset</td>
<td>- High WBC count</td>
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<td>- Host factors- defect in cell mediated immunity</td>
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<tr>
<td>- HRCT: dense nodule</td>
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<td>- No skin, CNS involvement clinically</td>
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<tr>
<td>- Not receiving TMP SMX prophylaxis</td>
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and radiological features; our differential diagnosis is shown in Table 1.

The heightened immunosuppression post-renal transplant, radiological findings of a dense pulmonary nodule, albeit without the halo sign or cavitation and a positive BAL GM optical density (OD) index in our patient; favour the diagnosis of invasive pulmonary aspergillosis. Although the current cut off value for positive BAL GM is > 0.5, many authorities recommend a cut off value of 1 for BAL samples. Furthermore, this patient was on piperacillin-tazobactam which has been associated with false positive serum GM assays, especially with generic brands. False positivity is however less likely with BAL specimens.

Nocardiosis is not an uncommon infection in the post transplant setting and remains high on the list of differential diagnosis; however, certain confounding factors, despite multiple invasive procedures, in this case, could have given rise to diagnostic frustration.

The high peripheral leucocyte count despite treatment with Azathioprine, indicate a bacterial etiology. However, the long interval between chest pain and the onset of fever is suggestive of a subacute bacterial process such as Nocardia infection. Under compulsion to do “something,” empirical treatment was administered elsewhere, which possibly interfered with the microbiological yield from the BAL and tissue specimens. This patient underwent bronchoscopy, CT guided biopsy followed by VATS assisted segmentectomy of the involved lung in order to reach a definitive diagnosis. The solid nodule, which had not yet cavitated and the fact that the patient was on empirical treatment with piperacillin tazobactam and levofloxacin when the above investigations were carried out, reduce the chances of detection of the pathogen which may be somewhat susceptible to these drugs such as Nocardia.

Although this patient had undergone transplant four years prior to the onset of this infection, the augmented regime of immunosuppression including steroids that the patient has been receiving for graft rejection, would put him at an increased risk for infection such as Nocardia, which would otherwise be more common in the first year post transplant. In addition, the patient is not on TMP SMX prophylaxis during this period. It has been said however that 40% of patients who develop nocardiosis are on prophylaxis with TMP SMX.

Receipt of high dose steroids, cytomegalovirus disease in the preceding 6 months and a high median calcineurin inhibitor level in the preceding 30 days (>15 µg/mL for tacrolimus and >300 ng/mL for cyclosporine) are also found to be independently associated with subsequent Nocardia infection.

Based on the above compelling factors such as increased immunosuppression, absence of prophylactic therapy, clinical symptoms suggestive of a subacute bacterial process and certain confounding factors such as the presence of a nodule that has not yet cavitated and empiric antibiotic treatment which may have hampered the diagnostic yield of the organism; we feel that nocardia cannot be ruled out in this patient.

In our opinion, the diagnostic microbiological report, which was received after one week, is thus likely to be growth of Nocardia sp. after prolonged incubation of cultures.

**Diagnostic Report**

A single beaded organism was seen after diligent search on a smear of the excised tissue (Figure 3). Delayed and scanty growth of Nocardia species was obtained on culture (Figure 4). The same organism was eventually isolated from the CT guided biopsy which was done earlier.

![Fig. 3](image1.png)

**Fig. 3** A single beaded organism found on the smear of the excised tissue

![Fig. 4](image2.png)

**Fig. 4** Dry, chalky white colonies of Nocardia spp. on 5% sheep blood agar

**Management**

After this report, piperacillin tazobactam and levofloxacin were discontinued and the patient
was started on treatment for Nocardiosis with Tab. Trimethoprim sulfamethoxazole (160mg/800mg) with renal dose modification and Tab. Linezolid 600mg once daily. Amikacin was avoided in view of post renal transplant status. A third generation cephalosporin was not started empirically as we have noted increasing cephalosporin resistance in previous cases. An MRI brain was done which revealed no abnormality. The patient showed a marked clinical improvement and was discharged with advice to follow up with the Nocardia drug susceptibility test (DST). Based on the DST, treatment was changed to TMP SMX and Minocycline, which was planned to be continued as dual therapy for 6 months followed by a single drug for 1 year or longer.

The mainstay of treatment of Nocardial infections is antibiotic therapy. Initial selection of antibiotic therapy should take into account the site and severity of disease, the potential for toxicity, drug interactions and the likely susceptibility and resistance pattern of Nocardia species. Antimicrobial susceptibility testing is strongly recommended as resistance to standard therapy is increasingly seen. Therefore, the initial choice of combination therapy in this case, was based on our patient’s comorbidities as well as the resistance patterns noted in our setting. A reduction of immunosuppression may be a helpful adjunctive measure, particularly in progressive or severe disease. However, several authors have deemed this maneuver unnecessary, finding good treatment outcome despite continuing immunosuppressive agents without dosage adjustments. The optimal duration of treatment is unknown, but recommendations are based on site and severity of disease, the type and level of the patient’s immunosuppression and the adequacy of surgical source control.

At a six month follow up, the patient remains asymptomatic and is continued on TMP SMX.

Disclaimer

This case has been discussed briefly in ‘Casebook of Infectious Diseases’ by Rajeev Soman and Camilla Rodrigues, published by Rajeev Soman.

References