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The Journal of
Heart and Lung
Transplantation

http://www.jhltonline.org

Concomitant pulmonary infection with *Nocardia transvalensis* and *Aspergillus ustus* in lung transplantation

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KEYWORDS:
Nocardia;
aspergillus;
opportunistic pathogens;
lung transplantation;
resistant organisms

Lung infections with *Nocardia* and *Aspergillus* spp in lung transplant recipients (LTRs) create diagnostic and therapeutic challenges. The present case illustrates the difficulties in identifying these pathogens in LTRs. A high degree of clinical suspicion and aggressive early management are required to ensure good outcomes. Although prospective data on treating these conditions are scarce, the empiric use of combination broad-spectrum anti-microbials initially seems prudent.
J Heart Lung Transplant 2010;29:900–3

Survival after lung transplantation has improved little despite advances in surgical techniques, immunosuppression and opportunistic infection management. According to the registry of the International Society for Heart and Lung Transplantation, non-cytomegalovirus infections are among the most common causes of death in lung transplant recipients (LTRs), especially in the first year, and significantly contribute to overall morbidity and mortality.[1]

Concomitant opportunistic infections in LTRs are well described. One report noted 7 of 11 LTRs with *Nocardia* spp lung disease had at least one co-infecting organism, with *Aspergillus* spp accounting for 27%.[2] A similar report described 6 of 10 LTRs with *Nocardia* spp pulmonary disease co-infected with *Aspergillus* spp, of whom half had an additional pathogen isolated.[3]

In this report we describe the clinical presentation, diagnostic strategy and therapeutic approach to pneumonia caused by synchronous *Aspergillus ustus* and *Nocardia transvalensis* in a LTR. A review of key clinical and epidemiologic characteristics of both opportunistic pathogens is summarized.

Case report

A 65-year-old Hispanic man with idiopathic pulmonary fibrosis underwent right single-lung transplantation. The recipient and donor were seropositive against cytomegalovirus. Induction immunosuppression consisted of equine antithymocyte globulin followed by maintenance tacrolimus, azathioprine and prednisone. Anti-microbial prophylaxis consisted of trimethoprim–sulfamethoxazole (TMP-SMX) given 3 times weekly and valganciclovir and itraconazole given daily. His lung function and clinical symptoms steadily improved.

Five months after transplantation he developed progressive anorexia, dyspnea and a productive cough with a commensurate decline in lung mechanics and 6-minute walk distance.

High-resolution computed tomography (HRCT) of the thorax showed right middle and lower lobe nodular opaci-

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1053-2498/$ -see front matter
doi:10.1016/j.healun.2010.04.016

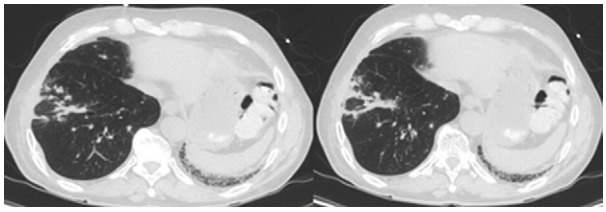

Figure 1 High-resolution computed tomography showing multiple nodular opacities.

ties (Figure 1). Bronchoalveolar lavage (BAL) cytopathology revealed filamentous organisms therefore empiric treatment including high-dose TMP-SMX, imipenem–cilastatin and voriconazole for suspected drug-resistant *Nocardia* and *Aspergillus* spp was started. Four weeks later, BAL cultures grew *Aspergillus fumigatus* and *Aspergillus flavus.* Imipenem–cilastatin was discontinued and anidulafungin was added for 4 weeks (Figure 2).

The patient improved until 8 months post-operatively, with recurrence of symptoms and decline of lung function. Repeat bronchoscopy with transbronchial lung biopsies showed no rejection. BAL showed neutrophilia with branching, filamentous bacilli identified by Grocott–Gomori methenamine (Figure 3) and Gram–Weigert stains (Figure 4), and weakly acid-fast bacilli identified by modified Kinyoun stain, suggestive of *Nocardia* spp.

Amikacin, imipenem–cilastatin and anidulafungin were added to high-dose TMP-SMX and voriconazole for empiric treatment against drug-resistant *Nocardia* and *Aspergillus* spp with significant clinical and functional improvement.

Two and 3 weeks after repeat bronchoscopy, *A ustus* and *N transvalensis,* were cultured from BAL, respectively. *N transvalensis* isolate was susceptible to TMP-SMX, ciprofloxacin, linezolid and amoxicillin–clavulanate, but was resistant to amikacin and imipenem by Kirby–Bauer and broth microdilution. No susceptibilities were performed for *A ustus*.

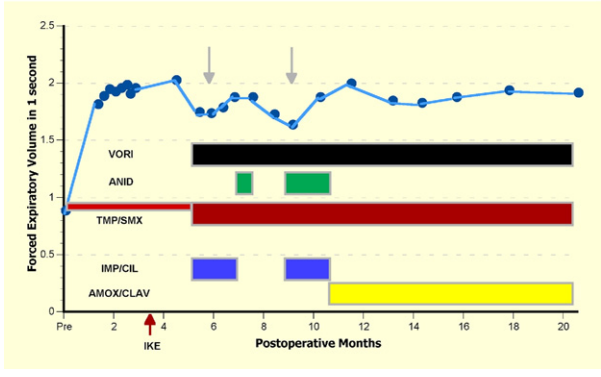

Figure 2 Clinical course after lung transplantation and antibiotic regimens used. Graph depicts the patient's lung function (forced expiratory volume in 1 second) after lung transplantation (blue dots) and the timing of diagnostic bronchoscopies performed (gray arrows). Horizontal bars represent anti-microbial regimens. VORI, voriconazole (black bar); ANID, anidulafungin (green bar); TMX-SMX, trimethoprim–sulfamethixazole (prophylaxis dose: thin red bar; high-dose treatment: thick red bar); IMP, imipenen–cylastatin (blue bar); AMOX/CLAV, amoxicillin/clavulanic acid (yellow bar); IKE, Hurricane Ike (red arrow).

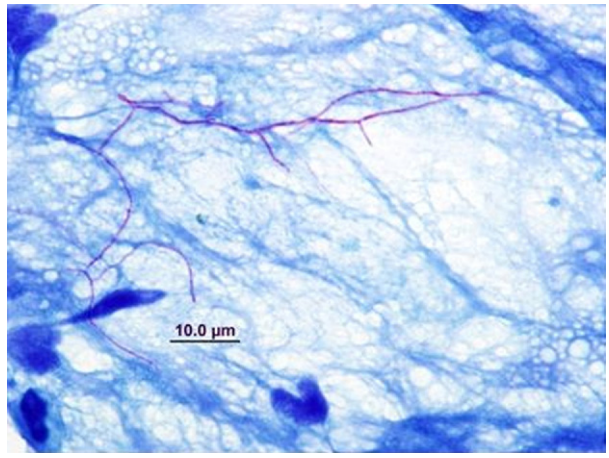

Figure 3 Grocott–Gomori methenamine stain showing filamentous organisms.

The patient's anti-microbial regimen was de-escalated to voriconazole, high-dose TMP-SMX and amoxicillin–clavulanate and this combination was continued for at least 1 year. His current immunosuppressive regimen remained unaltered from the protocol other than adjusting tacrolimus dosing from 3 mg to 2 mg twice daily for voriconazole interaction to maintain target 12-hour trough levels of 10 to 12 ng/ml. His symptoms, lung function and imaging studies have continued to improve (Figure 5).

Discussion

This case illustrates serious concurrent lung infections with rare *Nocardia* and *Aspergillus* spp in a LTR. Both organisms are recovered from organic debris and soil. This patient quite likely had an unusually intense exposure to these pathogens while clearing yard debris after Hurricane Ike.

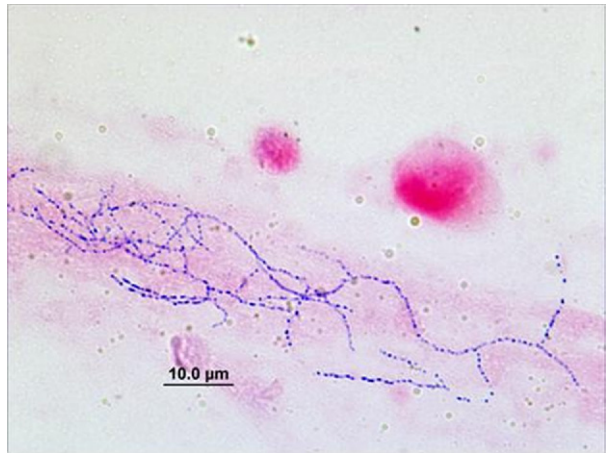

Figure 4 Gram–Weigert stain showing filamentous beaded organisms.