CASE REPORT

NOCARDIOSIS REVEALED BY THYROID ABSCESS AND PNEUMONIA IN A LIVER TRANSPLANT RECIPIENT

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Abstract. Nocardia thyroid abscess with pneumonia is a rare clinical presentation. We reported a liver transplant recipient with *Nocardia* thyroiditis and pneumonia after receiving high dose immunosuppressants to preserve his graft. The patient is a 50-year-old male who developed hepatitis C virus-related liver cirrhosis and received a liver transplant. Seven months post-transplantation the patient developed graft rejection, which was treated with 3 days pulse dose methyl-prednisolone followed by an increased dose of his tracolimus, mycophenolate and prednisolone. He presented to the hospital with a 2 week history of fever, tenderness in his anterior neck and dry cough. On admission his temperature was 39.5^{o}C. The right wing of his thyroid gland was swollen to 3 cm in size, fluctuant and tender. On auscultation of his lungs there were fine crepitations and increased vocal resonance in the right middle lung field. On laboratory testing, a complete blood count (CBC) revealed leukocytosis (19,900/mm^3) with neutrophils (97%). A chest X-ray showed an patchy infiltrates and round circumscribed densities in the superior segment of the right lower lobe of his lung. A CT scan of his neck revealed a diffusely enlarged right wing of the thyroid gland, 3.8 cm in diameter that had an abnormal hyposignal area. A CT of his chest revealed consolidation of the superior segment of the right lower lobe and necrotic right paratracheal lymph nodes with inflamed strap muscles. Fine needle aspiration of the right lobe of thyroid gland was performed. Modified acid-fast bacilli (MAFB) staining showed partially acid-fast beaded branching filamentous organisms and a culture grew out *Nocardia asteroides*. He was treated with trimethoprim-sulfamethoxazole for 6 months. He improved clinically and his chest X-ray also cleared.

Keywords: nocardia thyroid abscess, disseminated nocardiosis, liver transplant recipient

INTRODUCTION

Organ transplant patients need immunosuppressive drugs to prevent graft rejection, but these increase susceptibility to infections (Duncan and Wilkes, 2005; Mehrabi *et al*, 2008). Pulmonary infections are the leading cause of morbidity and mortality among transplant patients

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(Duncan and Wilkes, 2005; Mehrabi *et al*, 2008). Immunosuppression for liver transplant receipients includes induction, maintenance, and anti-rejection phases. The standard for anti-rejection protocol is triple therapy consisting of 1) cyclosporine, methylprednisolone and mycophenolate mofetil (MMF) or 2) tacrolimus, methylprednisolone, and MMF (McGuire *et al*, 2009). Cyclosporine A and tacrolimus are the cornerstones of immunosuppression in most liver transplant patients.

During the past decade, post-liver transplant survival rates have improved. The current one-year survival rate exceeds 90% and is 70% by 8 years (Roberts *et al*, 2004). Immunosuppression that affects T-cell function makes patients more susceptible to opportunistic infections due to *Nocardia* spp, *Legionella* spp, *Listeria monocytogenes*, *Mycoplasma* spp, *Salmonella* spp and *Rhodococcus equi* (Fishman, 2007; del Pozo, 2008). Opportunistic bacterial infections, however, are uncommonly occur after 6 months post-transplant due to receiving stable and lower maintenance doses of immunosuppressive drugs if there is good graft function.

Nocardia infection is a life-threatening, particularly in immunocompromised patients; it usually affects the lungs, skin and central nervous system (Mari *et al*, 2001). The thyroid gland is an uncommon site of infection for this pathogen (Carriere *et al*, 1999). We report here a rare case of nocardia thyroid abscess and pneumonia in a liver transplant recipient. This report was approved by the Research Ethics Committee (HE561295) of Khon Kaen University.

CASE REPORT

A 50-year-old male employee living in Khon Kaen Province, Thailand, presented to the hospital with a 4 day history of fever and chills preceded by 2 weeks of low grade fever, swelling on his anterior neck and pain with swallowing. He was diagnosed with having acute bacterial pharyngitis and treated with 3 days of intravenous amoxicillin/clavulanate and then switched to the oral form. His fever subsided, but then recurred 2 days later with the same symptoms. Four days prior to admission, he developed high grade fever and chills, then a dry cough and right chest pain. He complained of a swollen painful right anterior neck. He was then admitted to Srinagarind Hospital.

The patient had a past medical history of Child class B liver cirrhosis due to hepatitis C diagosed 7 years previously. He also had a history of type 2 diabetes mellitus diagnosed 7 years previously. The patient had undergone liver transplantation 9 months previously for Child class C liver cirrhosis with portal hypertension. On admission medications included tracolimus (1 mg) 4 tablets twice daily, mycophenolate (180 mg) 2 tablets twice daily, to prevent graft rejection. He also received Mixtard insulin for his diabetes mellitus and amlodipine 5 mg daily for his hypertension.

Five months previously, the patient developed an inferior vena cava (IVC) thrombosis treated with an IVC stent. Two months previously, the patient developed progressive jaundice and was diagnosed with acute graft rejection confirmed by liver biopsy. He was treated for 3 days with methylprednisolone 1 g pulse dosing and an increased dose of tracolimus, mycophenolate and prednisolone for 2 weeks followed by a gradually tapering dose.

Physical examination on admission revealed an elderly febrile fully conscious male. His initial vital signs were a temperature of 39.5°C, a blood pressure of 150/90 mmHg, a pulse of 120/minute and

a respiratory rate of 24/minute. He was not pale and had no icteric sclera. The right wing of his thyroid gland was swollen to 3 centimeters in diameter, fluctuant in consistency and tender to palpation (Fig 1). His cervical lymph nodes were not palpable. His trachea was in midline position. His heart sounds were normal. He had occasional fine rales in the lungs with increased vocal resonance heard in the right middle lung field. His abdomen was soft and nontender. His spleen was not palpable and his liver span was 10 centimeters. He had palmar erythrema of both hands and spider nevi on his chest wall. He had no pedal edema or finger clubbing.

His initial hemoglobin concentration was 10.5 g/dl, his hematocrit was 33.3%, and his white blood cell count was 19,900/mm^3, with 97% neutrophils and 3% monocytes. His platelet count was 193,000/mm^3. The liver function testing revealed a reverse albumin and globulin ratio and an elevated alkaline phosphatase. His cholesterol was 124 mg/dl, his albumin was 2.6 g/dl, his globulin was 4.2 g/dl, his total bilirubin was 1.7 mg/dl, his direct birilubin was 1.4 mg/dl, his ALT was 37 U/l, his AST was 22 U/l and his alkaline phosphatase was 374 U/l. His BUN was 19.3 mg/dl and his creatinine was 0.7 mg/dl. His electrolytes were mildly abnormal: sodium was 121, potassium was 4, bicarbonte was 25.7, and chloride was 87 mEq/l. His calcium was 9.4 mg/dl and his phosphate was 2.4 mg/dl. A chest X-ray show ill-defined infiltration in the right perihilar area (Fig 2).

He was diagnosed with having acute pharyngitis and aspiration pneumonia and treated with intravenous amoxicillin/clavulanate. He continued to have a fever of 38ºC - 39ºC. Two blood culture specimens showed no growth. A sputum culture showed normal flora with a few *Klebsiella pneumoniae* and *Enterobacter* spp. A chest radiograph repeated on day 3 of hospitalization showed a progressive infiltration (Fig 3).

Bronchoscopy was planned to biopsy the opacity in his right lung. Diagnoses

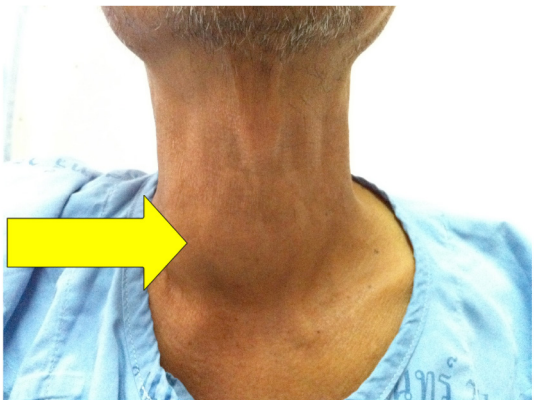

Fig 1–Swelling of the right wing of the thyroid gland.

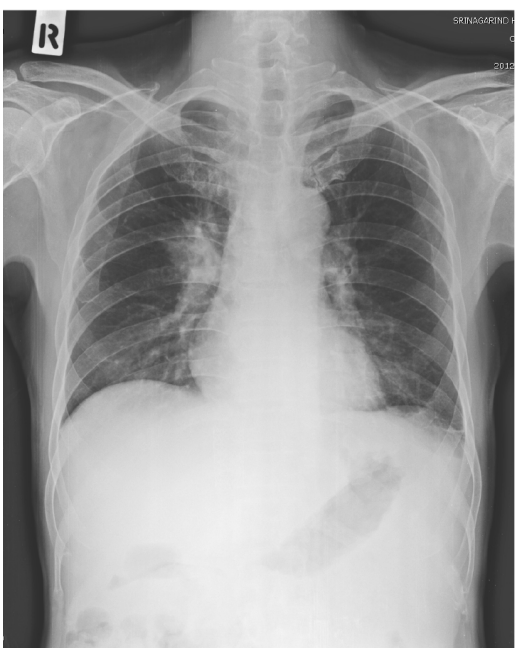

Fig 2–Chest radiograph on the day of admission showing a right perihilar infiltration.

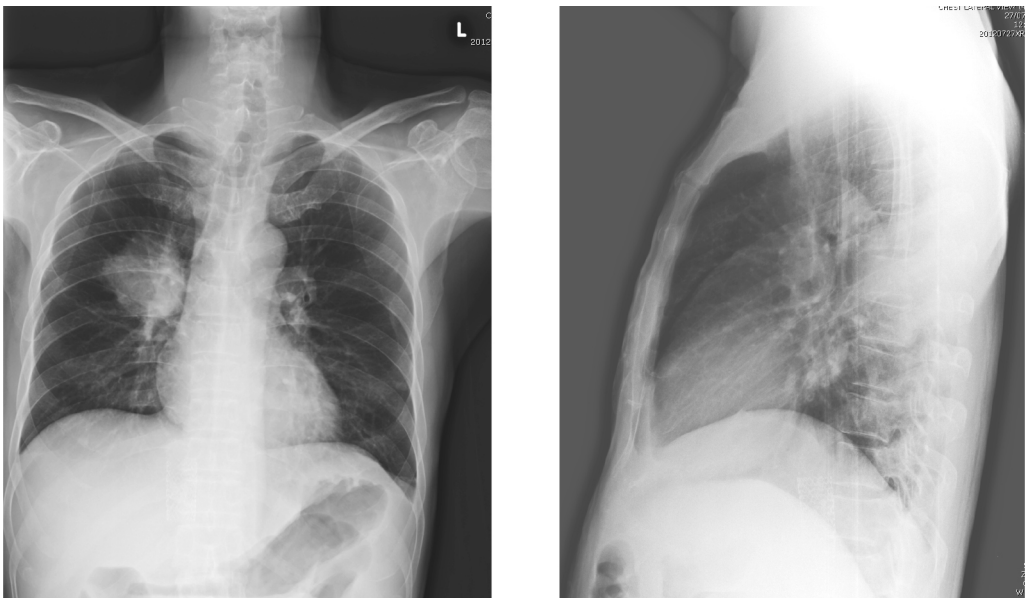

Fig 3–Chest radiograph on day 3 of hospitalization showing a round circumscribed opacity in the superior segment of right lower lobe.

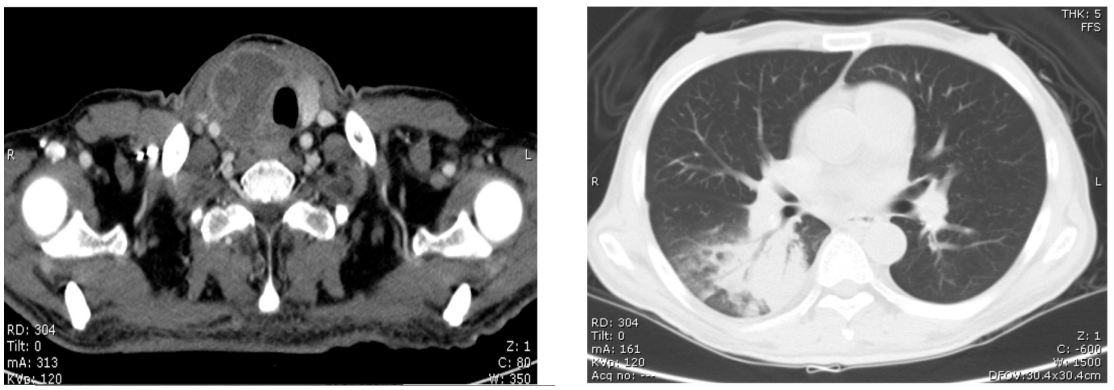

Fig 4–Computed tomography of the neck and chest revealed an enlarged right wing of the thyroid gland with abscess formation and consolidation in the superior segment of the right lower lung.

entertained given his recent change in immunosuppressive therapy included intracellular organisms, such as tuberculosis, *Cryptococcus, Pneumocystis jirovecii, Nocardia, Strongyloides,* and *Cytomegalovirus*. Needle aspiration of the thyroid gland was also performed along with computed tomography of the neck and chest (Fig 4) which revealed a diffusely enlarged right wing of the thyroid gland of 3.8 cm, with a hyposignal area. The scan also showed irregular enhancement with inflammation of the anterior fat plane and strap muscles. The scan of the chest revealed consolidation of the lungs with an air bronchogram in the superior segment of right lower

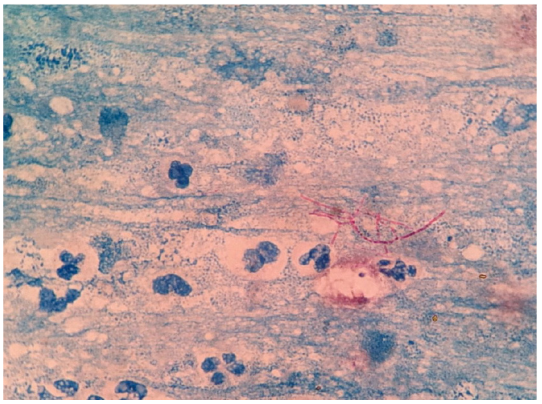

Fig 5–Modified acid-fast bacilli (MAFB) staining of the thyroid gland aspirate showed partially acid-fast staining beaded branching filamentous organisms.

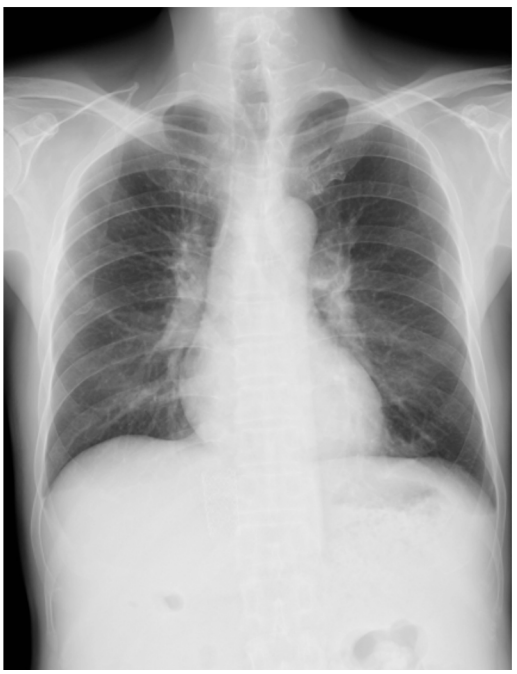

Fig 6–Chest radiograph post-treatment with no infiltration.

lobe. Necrotic lymph nodes were apparent in the right paratracheal region with possible precarinal and subcarinal lymph nodes enlargement. Modified acid-fast bacilli (MAFB) staining of the thyroid aspirate revealed partially acid-fast staining beaded, branching, filamentous organisms (Fig 5) and a culture of the aspirate grew out *Nocardia asteroides*.

The patient was then diagnosed as having disseminated nocardiosis affecting the thyroid and lung. He was started on trimethoprim-sulfamethoxazole (80/400) 3 ampules intravenous every 8 hours. One week later the fever had resolved, the thyroid was no longer tender and the patient had no more cough. The antibiotic was changed to oral trimethoprim-sulfamethoxazole (80/400) 3 tablets thrice daily for 6 months. A chest radiograph at the end of treatment had returned to normal (Fig 6).

DISCUSSION

Despite the revolution in organ and stem cell transplantation in modern medicine, infections are still an important problem post-transplantation due to immunosuppressive therapy given to prevent graft rejection (Duncan and Wilkes, 2005; Mehrabi *et al*, 2008). Even with measures such as use of protective barriers, antimicrobial prophylaxis and vaccination, up to 80% of liver transplant recipients develop at least one infection during the first year post-transplantation (Romero and Razonable, 2011).

Infection risk is influenced by surgical factors, levels of immunosuppression, environmental exposure, and types of prophylaxis (Fishman, 2007; Grim and Clark, 2011). Infections during the first month post-transplantation are usually associated with complications of surgery; nosocomial infections occur through prolonged hospitalization prior to transplantation and post-operative and can consist of bacterial and candidal wound infections, urinary tract infections, catheter-

related infections, and hospital-acquired bacterial pneumonia (Grim and Clark, 2011).

During the 6 months post- transplantation there is usually maximal immunosuppression. Infections that can occur during this time include viral infections, specially cytomegalovirus, varicalla zoster and hepatitis B and C and fungal infections, such as those caused by *Aspergillus*, *Cryptococcus*, *Histoplasma*, and *Coccidioides*. Some rare bacterial infections can occur caused by *Nocardia, Listeria* and *Mycobacterium tuberculosis* (Grim and Clark, 2011).

Seven to 12 months post-transplantation and beyond, common infections include influenza, urinary tract infections, and community-acquired pneumonia, similar to the general population. Opportunistic infections can occur if it is necessary to increase immunosuppressive therapy due to graft rejection and poor graft function (Grim and Clark, 2011). This is what happened in our reported case. These infections include *Nocardia* species, *Aspergillosis, Cytomegalovirus, Pneumocystis jirovecii* and *Mycobacterium tuberculosis* (Grim and Clark, 2011). Infectious complications occurring greater than 1 year post-transplantation are less common, but include cholangitis and pneumonia (Aberg *et al*, 2011).

The peak incidence of nocardial infection occurs 2 to 6 months post-transplantation, but may occur later as well if the patient needs high dose immunosuppression to preserve their graft (Chapman and Wilson, 1990; Wiesmayr *et al*, 2005). A randomized controlled trial comparing the use of mycophenolate mofetil with cyclosporine or tacrolimus and an identical corticosteroid dose taper following liver transplantation showed the same long-term incidence of rejection and infection (Fisher *et al*, 2004). Tacrolimus, mycophenolate and cyclosporine inhibit T-lymphocyte activity that causes graft rejection (McGuire *et al*, 2009). Corticosteroids are generally given in large doses during the first week after liver transplantation and are tapered rapidly to low levels or completely eliminated within weeks to months. In patients with graft rejection, high dose corticosteroids are often used to prevent rejection (McGuire *et al*, 2009). The high dose pulse methylprednisolone is an important risk factor associated with opportunistic infections (Volpin *et al*, 2002), including *Nocardia* infection, even though it is not a common pathogen in liver transplant recipients (Peleg *et al*, 2007; Jimenez-Galanes Marchan *et al*, 2009). A study of 1,840 liver transplant patients found only 2 (0.1%) developed *Nocardia* infection and only one developed disseminated *Nocardia* infection (Peleg *et al*, 2007). High dose corticosteroids and high dose calcineurin inhibitors, such as cyclosporine and tacrolimus, increase the risk for developing *Nocardia* infection in organ transplant recipients (Peleg *et al*, 2007). Our reported case received high dose corticosteroids and an increase in the dose of tracolimus.

Nocardia infection in liver transplant recipients has a bad prognosis if there is a delay in treatment. Common sites of *Nocardia* infection include lungs, skin and the central nervous system (Chapman and Wilson, 1990; Lerner, 1996; Mari *et al*, 2001; Wiesmayr *et al*, 2005). The thyroid location of *Nocardia* infection is unusual (Carriere *et al*, 1999; Vandĵme *et al*, 2001; Su *et al*, 2011). Many reported cases have other organ involvement, especially the lungs (Carriere *et al*, 1999; Vandĵme *et al*, 2001; Su *et al*, 2011). Ultrasonography of *Nocardia* infected thyroid glands usually shows heterogeneous nodules and abscess formation (Carriere *et al*, 1999; Vandĵme

et al, 2001; Su *et al*, 2011). Chest X-rays usually show a patchy alveolar infiltration, dense infiltrate with cavitation, multi-lobar consolidation, and pleural effusion (Mari *et al*, 2001). A chest computed tomography of a *Nocardia* infected lung usually shows a lobulated mass with central necrosis, multiple consolidations with cavitations, or pleural effusions (Carriere *et al*, 1999; Vandĵme *et al*, 2001; Su *et al*, 2011). Our reported case probably had a primary infection in the thyroid gland followed by a pulmonary infection. Since this is a rare clinical presentation, a delay in diagnosis and treatment occurred in this patient. If *Nocardia* infection was considered immediately, and if a Gram stain and modified acid-fast stain had been performed initially the diagnosis would have been made earlier (Saubolle and Sussland, 2003). The definitive diagnosis was made by identifying *Nocardia* on culture, which took 5 days to isolate (Saubolle and Sussland, 2003). The diagnosis in this patient was made by staining and culture of the thyroil abscess aspirate. The treatment of choice for nocardiosis is trimethoprim/sulfamethoxazole (Lerner, 1996; Welsh *et al*, 2013). This patient responded well to this antimicrobial therapy.

In conclusion, *Nocardia* infection is uncommon but does occur in transpant recipients on immunosuppressant therapy. *Nocardia asteroides* infection can disseminate. *Nocardia* infection can occur in the thyroid gland. The diagnosis of nocadiosis may be delayed. However, timely treatment can successfully eradicate this organism.

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