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IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME MASQUERADING AS A LUNG MASS IN A KIDNEY TRANSPLANT RECIPIENT WITH DISSEMINATED CRYPTOCOCCAL INFECTION

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ABSTRACT
This is a case of a 57-year-old woman with a history of deceased donor kidney transplant, who presented with a headache and nonproductive cough. Cerebrospinal fluid findings were consistent with acute cryptococcal meningitis. Chest computed tomography showed an area of consolidation in the right lung suspected to be cryptococcal pneumonia. The patient was initiated on liposomal amphotericin and 5-flucytosine for disseminated cryptococcal infection, along with reduction of immunosuppression. Approximately 10 days after starting therapy, the patient's cough worsened and repeat chest computed tomography revealed an interval enlargement of the area of consolidation. Bronchoalveolar lavage was negative for any infective etiology but consistent with immune reconstitution inflammatory syndrome. Antifungal therapy was continued with eventual improvement in symptoms afterwards. Early recognition is the key to proper management in patients with immune reconstitution inflammatory syndrome.

INTRODUCTION

Immune reconstitution inflammatory syndrome is an uncommon entity. Until recently, it was mainly described in patients with human immunodeficiency virus. Review of the literature shows that immune reconstitution inflammatory syndrome is now also observed in patients with organ transplant related immunosuppression. The reason for writing this case report is to describe the association of immune reconstitution inflammatory syndrome in patients with kidney transplant after immunosuppression modulation and to promote awareness of this entity. Immune reconstitution inflammatory syndrome is uncommon in solid organ transplant and early recognition is the key to proper management.

CASE PRESENTATION

The patient is a 57-year-old woman, with a history of kidney transplant, presented to the hospital with a 10-day history of headache radiating to the neck. It was associated with photophobia, blurry vision, nausea and vomiting. She also reported low grade fevers and a dry cough. She denied any shortness of breath, chest pain, head trauma, weakness and loss of consciousness or confusion. There were no sick contacts or recent travel. Her past medical history was significant for type 2 diabetes mellitus and hypertension resulting in a deceased donor kidney transplant 10 years ago. Immunosuppression was stable with mycophenolate mofetil, tacrolimus, and prednisone and there was no recent rejection.

On examination she was afebrile and hemodynamically stable. She had photophobia to bright light. Complete neurological examination was unremarkable. Auscultation of the chest revealed a few crackles in the right upper chest. Cardiac auscultation revealed normal heart sounds without any added sounds.

The abdomen was benign with normal bowel sounds. There were no obvious skin lesions.

The patient was started on induction therapy with liposomal amphotericin and 5-flucytosine. As cryptococcal infection is opportunistic, the patient's immunosuppression was reduced; namely mycophenolate mofetil was stopped, tacrolimus was reduced and prednisone was continued. Due to the patient's mild nonproductive cough, computed tomography of the thorax was done and revealed mass like consolidation in the right upper lobe, which was suspicious for cryptococcal pneumonia.

Ten days after starting induction therapy, the patient's cough worsened. A repeat computed tomography of the chest showed an interval increase in opacity in the right upper lung. The patient subsequently underwent bronchoscopy with a bronchoalveolar lavage, which was negative for any pathogen including cryptococcus. The bronchoalveolar lavage did reveal an elevated white blood cell count with predominantly macrophages suspicious for immune reconstitution inflammatory syndrome. Antifungal therapy was continued (due to presumed immune reconstitution inflammatory syndrome) and was later switched to consolidation therapy with oral fluconazole. Her symptoms including headache and cough resolved gradually. Follow-up computed tomography of the chest, 4 weeks after antifungal therapy, showed improvement in right upper lung consolidation.

INVESTIGATIONS

Relevant Imaging Results

Initial computed tomography of the head showed patchy hypodensities in bilateral basal ganglia with no acute intracranial ischemia, hemorrhage or mass effect.

Initial computed tomography of the thorax showed an area of mass like consolidation in the right upper lobe (figure 1). Repeat computed tomography of the thorax was performed approximately 10 days after starting antifungal therapy (due to worsening cough and intermittent fevers) and showed interval enlargement of the mass like, right upper lobe consolidation (figure 2). This was believed to be secondary to immune reconstitution inflammatory syndrome. As a result, anti-fungal therapy was continued.

Follow-up computed tomography of the thorax was performed 4 weeks after starting antifungal therapy and showed a resolving right upper lobe consolidation and ground glass opacity (figure 3).

Relevant Laboratory Investigations

Initial laboratory tests, including complete blood count with differential and metabolic panel, were within normal limits. Cerebrospinal fluid analysis was consistent with acute cryptococcal meningitis. Additional cerebrospinal fluid analysis showed positive cryptococcal antigen and culture. Cultures were negative for bacterial and viral pathogens. Cerebrospinal fluid pressure was 28 cm H2O at the time of the initial lumbar puncture. It was clear, colorless, had a red blood cell count of 27 cells/μL, and a white blood cell count of 23 cells/μL (with 90% lymphocytes, 7% neutrophils and 3% macropahages). Gram stain and bacterial cultures were negative. Herpes Simplex Virus DNA (by polymerase chain reaction) and Histoplasma antigen were negative.

Bronchoalveolar lavage was clear, colorless, and had a white blood cell count of 160 cells/μL (with 89% macrophages, 6% neutrophils, 3% lymphocytes and 2% monocytes). Bacterial, viral and fungal cultures were negative.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in an immunocompromised patient with a right lung mass includes infection, inflammation or malignancy. Infection is the most important differential to consider in immunocompromised patients including bacterial, viral, mycobacterial, and fungal etiologies. Pulmonary nocardiosis can present as a lung mass with additional skin or brain lesions. In our case, the bronchoalveolar lavage modified acid fast stain was negative. Fungal infections including histoplasmosis, aspergillosis can present as lung mass. The bronchoalveolar lavage was negative for other fungal etiologies. Wegener granulomatosis is an inflammatory cause which can be considered, but given the acute presentation with resolution of symptoms with antifungal therapy, it was ruled out. Malignancy is important to rule out as the cause of the lung mass, but was unlikely in our case given the acute presentation and improvement with treatment.

TREATMENT

Induction therapy for disseminated cryptococcal infection was started with intravenous liposomal amphotericin and 5-flucytosine for 2 weeks followed by oral fluconazole as consolidation therapy. Multiple therapeutic lumbar punctures were done to reduce cerebrospinal fluid pressure. Overall immunosuppression was reduced due to cryptococcal infection.

OUTCOME AND FOLLOW-UP

After 4 weeks of antifungal therapy, symptoms of cough and headache were completely resolved. Follow-up computed tomography of the thorax (four weeks after starting therapy) showed a significant decrease in right lung opacity. His immunosupressants were continued without any further complications. The patient continues to follow-up with the infectious disease clinic on an outpatient basis and is enjoying good health.

DISCUSSION

Immune reconstitution inflammatory syndrome is an overwhelming response of the immune system against opportunistic infections in immunosuppressed individuals. A paradoxical worsening of symptoms and imaging studies is typically seen after starting appropriate antimicrobial

therapy. The proposed mechanism of immune reconstitution inflammatory syndrome is described as a rise in pro-inflammatory cells and a decrease in anti-inflammatory cells. In immune reconstitution inflammatory syndrome, there is an imbalance of pro- and anti-inflammatory responses. [1] Another mechanism is immunomodulatory response of antimicrobials. Amphotericin B increase T helper 1 response by its interaction with Toll-like receptors.[2 3]

Immune reconstitution inflammatory syndrome has been commonly described in human immunodeficiency virus patients, but it is uncommonly seen in solid organ transplant recipients. There have been only a few case reports of immune reconstitution inflammatory syndrome in liver and kidney transplant recipients. Cryptococcus is the most common fungal infection causing immune reconstitution inflammatory syndrome in solid organ transplant recipients due to its unique characteristic of mitogenic responses.[4] In transplant recipients, immune reconstitution inflammatory syndrome can be explained by escalation of the pro-inflammatory pathway by reducing and/or stopping immunosuppressive drugs during an acute infection. In our patient, immunosuppression was reduced on presentation concomitant with initiation of antifungal therapy. This resulted in the worsening of symptoms after 10 days of appropriate therapy, which is consistent with immune reconstitution inflammatory syndrome.

Literature review shows that 5%-11% of cryptococcal infection in solid organ transplants develop immune reconstitution inflammatory syndrome following antifungal treatment. In renal transplant patients with cryptococcus related immune reconstitution inflammatory syndrome, 66% developed allograft rejection as compared to 5.5% who had cryptococcal infection without immune reconstitution inflammatory syndrome ($p = 0.012$). [5] Rapid discontinuation of calcineurin inhibitors has also been described as an independent predictor of immune reconstitution inflammatory syndrome.[6] In fact, calcineurin inhibitors have antifungal activity and offer synergistic advantage in the management of cryptococcal infection. [7]

Diagnosis of immune reconstitution inflammatory syndrome is challenging due to a lack of specific biomarkers to differentiate immune reconstitution inflammatory syndrome from disease worsening/ progression. No specific guidelines are available to treat immune reconstitution inflammatory syndrome, but steroids have been the mainstay of management in severe cases. In our case, the symptoms resolved without any increase in the dose of steroids. Sudden reduction/withdrawal of immunosuppressive drugs can potentiate immune reconstitution inflammatory syndrome.

LEARNING POINTS/TAKE HOME MESSAGES

- Immune reconstitution inflammatory syndrome is an entity which occurs secondary to immunomodulation in immunocompromised patients, such as those with human immunodeficiency virus and solid organ transplant recipients, with concomitant opportunistic infection.
- Sudden withdrawal/reduction of immunosuppressant is related to the development of immune reconstitution inflammatory syndrome in organ transplant recipients due to an incremental response from pro-inflammatory cells.
- In the setting of infection, diagnosis of immune reconstitution inflammatory syndrome is very challenging as it is difficult to differentiate it from failure of therapy and/or new infection
- Early recognition and appropriate continuation of antifungal therapy along with anti-inflammatory drugs is the mainstay of treatment of immune reconstitution inflammatory syndrome.

Figure 1. Initial computed tomography of the thorax showing mass like consolidation in the right upper lobe.

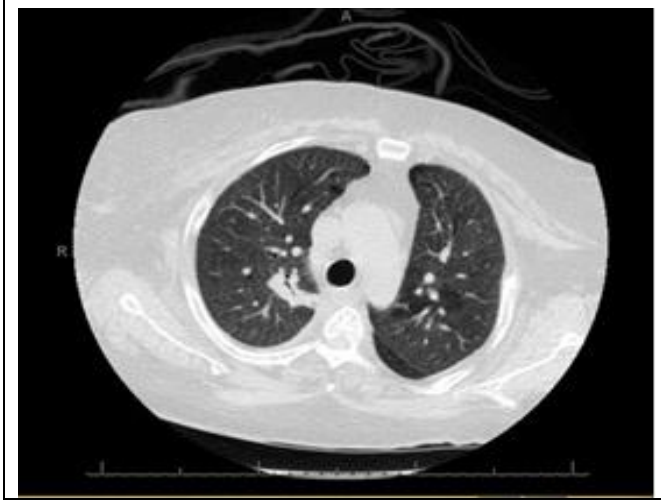
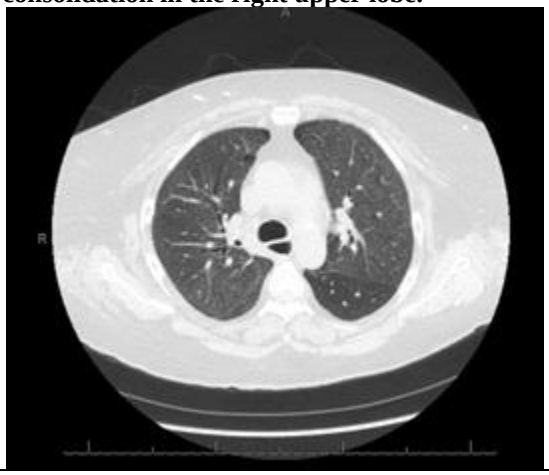


Figure 2. Repeat computed tomography of the thorax, 10 days after starting induction therapy and reducing immunosuppression. Interval increase in the mass like consolidation is seen in the right upper lobe.

Figure 3. Follow-up computed tomography of the thorax in the outpatient setting (4 weeks from onset of therapy). Interval improvement of mass like consolidation in the right upper lobe.



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