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Case Report

Immune function in a patient with aspergillosis after lung transplantation: Case Report

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We report a case that was successfully treated invasive pulmonary aspergillosis after living donor lobar lung transplantation and monitored patients' immune function with ImmuKnow® assay. A 43-year-old woman underwent living donor lobar lung transplantation for pulmonary alveolar proteinosis. Two healthy her relatives donated each lower lobe. Six months after transplantation, she was diagnosed as invasive pulmonary aspergillosis (IPA). During the anti-fungal treatment, one immunosuppressant was withdrawn and the trough level of calcineurin inhibitor was reduced to the minimum. Despite of such a low immunosuppressive status, Immuknow® assay showed that immune function was maintained in the moderate range, which encouraged us to keep this strategy for IPA. Immune evaluation by Immuknow® is useful method for monitoring and controlling patients' immune status especially in the infected condition, which revealed moderate immune level could be maintained with only two immunosuppressant drugs in the patient after recovery from IPA.

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Introduction

Lung transplant recipients are susceptible to infection due to aggressive triple immunosuppressant regimens. To prevent rejection, many laboratory studies are needed, including monitoring of immunosuppressant levels and lung function test. However, serum immunosuppressant levels alone may not accurately reflect the patient's immune status. Immuknow® (Cylex, Columbia, MD) is a novel in vitro assay for measuring cell function of stimulated T cells[1]. We report a case of invasive pulmonary aspergillosis (IPA) after living donor lobar lung transplantation by monitoring and controlling patients' immune status.

Case

A 43-year-old woman underwent living donor lobar lung transplantation for pulmonary alveolar proteinosis. One donor was her old brother, whose left lower lobe was donated. The other donor was her husband for right lower lobe. Both donors were apparently healthy. Her postoperative course was uneventful, and she was discharged without oxygen support. She had been receiving a standard triple immunosuppressant

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regimen, including tacrolimus, mycophenolate mofetil (1500 mg / body), and prednisolone (0.4mg / kg for the first six months, following 0.2 mg / kg). The prophylaxis for fungal infection was oral itraconazole 100 mg daily. Six months after transplantation, she developed a nonproductive cough, and chest CT showed multiple nodular shadows, mainly involving the right lung (Fig. 1). CT-guided lung biopsy was done, and these nodules were found to be *Aspergillus fumigatus*. Thus, she was diagnosed as having IPA. Mycophenolate mofetil was withdrawn immediately, and the trough level of tacrolimus was reduced to around 5 - 8 ng/ml to allow the patient's immune status to recover to battle the infection. The patient was treated with oral voricocazole 300 mg twice daily, inhalation of amphotericin B 10 mg 5 times daily, and intravenous micafungin 300 mg daily. Fortunately, her condition improved over 3 months of hospitalization, and she was discharged without any symptoms. Oral voriconazole and inhaled amphotericin B were continued as prophylaxis for 9 months. A follow-up chest CT showed complete resolution of the multiple nodular shadows (Fig. 2). The details of this case were reported previously[2].

The patient's immune function was measured using the Immuknow® assay during the convalescent period (from 14 to 19 months after transplantation) (Fig. 3). Local ethics committee approval was obtained prior to commencement of this study. The patient gave her written, informed consent. During this period, T-cell immune function was moderate. After recovery from IPA, the patient's immune function still remained within the moderate range despite the discontinuation of one immunosuppressant. No rejection or other infection was seen during this period. Also, her FEV1.0 (forced expiratory volume in one second) remained stable during the treatment (Fig. 4).

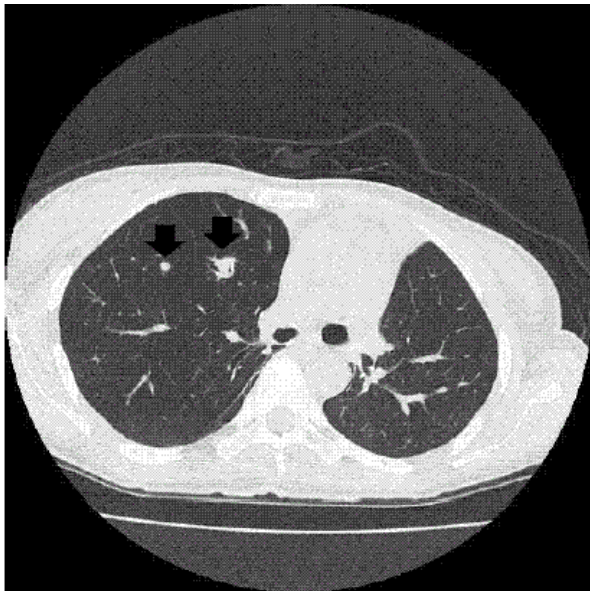

Figure 1. Chest CT shows multiple nodular shadows (arrows). CT-guided lung biopsy found that these shadows were sites of *Aspergillus fumigatus* infection.

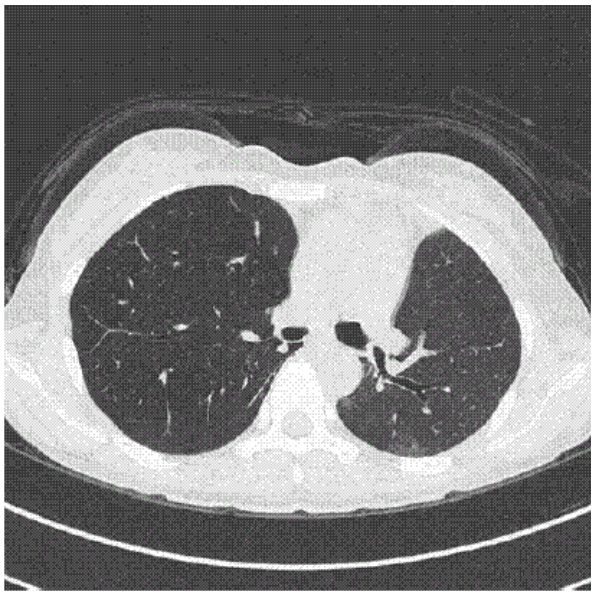

Figure 2. Invasive pulmonary aspergillosis can be seen to have been successfully treated by oral voriconazole, micafungin injection, amphotericin B inhalation, and reducing immunosuppressant therapy under monitoring with the ImmuKnow® function test.

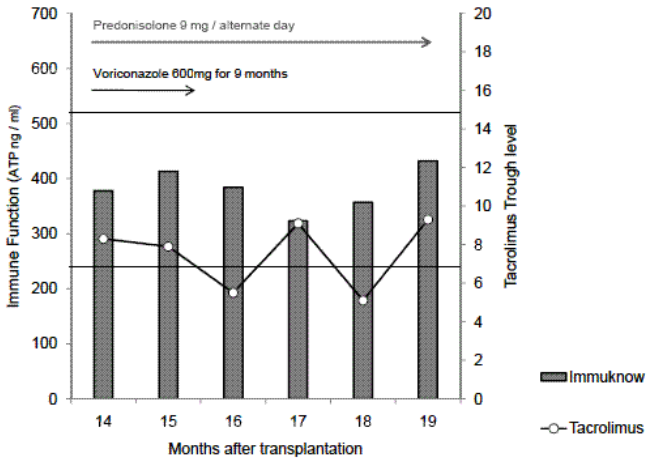

Figure 3. The gray bar shows the immune function level from 14 month to 19 months after transplantation during the recovery phase from invasive pulmonary aspergillosis (IPA). During this period, T-cell immune function was moderate. Immune function remained within the moderate range after recovery from IPA 14 months after the infection. The line plot shows tacrolimus trough levels, which were controlled at a low level (around 5 - 8 ng/ml). The horizontal lines represent cutoffs for strong (525 ng/ml ATP), moderate (524 - 226 ng/ml ATP), and low immune function (225 ng/ml ATP).

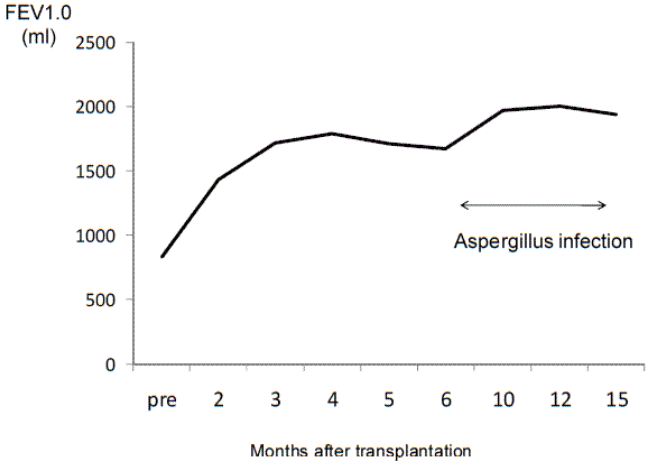

Figure 4. There was no decline of the forced expiratory volume in one second after transplantation despite in the period of aspergillus infection (arrows). FEV1.0 = Forced expiratory volume in one second, pre = pre operation

Discussion

This is a report of immune function monitoring during the treatment of IPA after living donor lobar lung transplantation. Our report highlights two important facts: monitoring of immune function is effective and reliable during treatment for IPA after lung transplantation; and just two immunosuppressant drugs, a calcineurin inhibitor and a steroid, can maintain moderate immune function after living donor lobar lung transplantation.

Lung transplant recipients have the highest rate of infection among solid organ transplant recipients[3]. Moreover, rejection, both acute and chronic, remains a major problem. Long-term survival after lung transplantation is hindered by infection and lung allograft rejection[4]. Therefore, a number of parameters are monitored after transplantation to prevent or identify early complications related to lung transplantation in the hope of reducing morbidity and mortality. These include routine laboratory studies, imaging, surveillance lung biopsy, and monitoring of immunosuppressant levels and lung function. Monitoring of serum immunosuppressant levels allows individualization of patients' immunosuppressant therapy. However, immunosuppressant levels alone may not reflect the patient's immune status[5]. Immuknow® (Cylex, Columbia, MD) is a novel in vitro assay for measuring cell function of stimulated T cells, which has been licensed by the Food and Drug Administration for monitoring the immune system of transplant patients[1]. It functions on the principle of incubating target T cells with phytohemagglutinin and measuring the production of intracellular ATP as a reflection of cell metabolism[6]. Immune status is expressed as strong (525 ng / ml ATP), moderate (524 - 226 ng / ml ATP), and low immune function (225 ng / ml ATP). Recently, there have been some reports of the use of this assay in clinical lung transplantation[2-4, 7]. These reports indicate that knowing the immune function could help determine who may be at risk for infection or rejection. Bhorade et al[5] assessed the functional immune response by the ImmuKnow® assay in 143 sequential blood samples from 57 lung transplant recipients and reported that the ImmuKnow® assay levels were lower in infected lung transplant recipients compared with non-infected recipients.

In the present case, the patient had received standard triple immunosuppressant therapy (calcineurin inhibitor, mycophenolate mofetil, and steroid). However, 6 months after transplantation, the patient developed IPA, which has been believed to be a fatal disease after lung transplantation[8]. At first, she was started on voriconazole 600 mg and micafungin injections for IPA. Simultaneously, mycophenolate mofetil was stopped, and reduction of the trough level of calcineurin inhibitor was started to recover from the immunosuppressed status. On the other hand, during treatment, we became very concerned that the patient may develop chronic rejection due to reduced immunosuppression. Thus, we started to measure immune function using the ImmuKnow® assay. This assay showed that immune function was maintained in the moderate range, which encouraged us to reduce the immunosuppressant to the lowest possible level though most of the monitoring was undertaken after the disease was almost under control.

Optimization of the dosages of immunosuppressants is a constant dilemma. Patients suffer rejection for a long period during their lives, possibly because of fluctuations in immune status with low-level immunosuppression. On the other hand, patients are susceptible to infection because of frequent exposure to infectious air-borne microorganisms (bacterial, viral, fungal, and protozoal) with high level immunosuppression. In addition, triple immunosuppressant regimens result in a number of morbidities, including hypertension, renal dysfunction, diabetes, and post-transplant lymphoproliferative disease. To date, there is no clinical evidence to support maintaining lung transplant patients on less than three immunosuppressant drugs. Based on the present data, the patient's immune function remained within the moderate range despite use of only two immunosuppressant drugs, tacrolimus and prednisolone, after recovery from IPA. When monitoring the immune status using ImmuKnow® is possible, an immunosuppressant regimen that consists of only tacrolimus and prednisolone might be better to

maintain immune function and reduce the side effects of mycophenolate mofetil when chronic infection develops. In general, most living donor lobar lung transplantations are undertaken between relatives and extensive immunologic matching may take place beforehand, to select the appropriate donor. Also it can be expected, under these circumstances, that the likelihood of rejection and need for immunosuppressant drugs may be less.

Conclusion

Though this is just a case report, immune evaluation by Immuknow® might be a useful method for monitoring patients' immune status. This method showed that a moderate immune status could be maintained with only two immunosuppressants in a patient with chronic IPA infection. Further study is needed to determine the role of Immuknow® in optimizing the immune status of lung transplant patients.

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Disclosures and Freedom of Investigation

We have no personal conflict of interest and no outside support for this research.

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