REVERSIBLE PULMONARY FIBROSIS FOLLOWING THE ANTITHYMOCYTE GLOBULIN INJECTION AND CYTOMEGALOVIRUS INFECTION: A CASE REPORT

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ABSTRACT:
Although fibrotic pattern in HRCT is known as incurable injury, but recently reversible fibrosis, after injection of drugs, has been reported. We present a patient with lung fibrosis after Antithymocyte globulin injection and Cytomegalovirus infection. Our case is a 46-year-old man who suffered from acute rejection of renal transplantation and was treated with ATG. He subsequently developed pulmonary infiltration after receiving ATG and also CMV viral load was highly positive in his serum, therefore, ATG therapy was stopped and ganciclovir was prescribed. At first, pulmonary infiltration developed towards fibrosis and volume reduction, but after a month, fibrosis was completely reversed and the patient completely recovered. The key finding of this report is the fact that the appearance of pulmonary fibrosis in HRCT cannot definitively prove that the injury is irreversible.

Keywords: Antithymocyte globulin, Cytomegalovirus, Pulmonary fibrosis.

INTRODUCTION
High Resolution Computerized Tomography (HRCT) is a diagnostic tool which is widely used in the evaluation of lungs diseases. Although fibrotic pattern in HRCT is known as incurable injury, but recently reversible fibrosis, after injection of drugs, has been reported.¹ ² Generally, patients with organ transplantation are more susceptible to lung disease than others. This disease can either be caused by infectious causes such as opportunistic infections or varieties of noninfectious causes such as...
drug side effects depending on the type of organ transplant.³ Cytomegalovirus (CMV) is a viral genus of the viral family known as herpesviridae or herpes viruses. The CMV infection is typically silent in healthy people, but can be life-threatening for the immunocompromised patients including patients with organ transplantation.³ This virus like other herpes viruses is known as the predisposing cause of lung fibrosis rather than having any pathogenic role.⁴,⁵

Antithymocyte globulin (ATG) is used in the prevention and treatment of acute rejection in organ transplantation. There is some evidence to suggest that ATG is responsible for a spectrum of lung injuries varying from transient infiltrates to a full-blown Acute Respiratory Distress Syndrome (ARDS).⁶⁻⁹ ATG has antibodies against human T cells, and is capable to activate the human T cells and cause lung injuries. This mechanism is similar to the mechanism in which lung injury is induced by blood transfusion.¹⁰

In this report, we show that the fibrotic pattern in HRCT can be reversible and also we present one of the pulmonary side effects of ATG as a fibrotic pattern which has not been described before.

**CASE PRESENTATION**

The patient was a 46 years-old male, who had kidney transplantation four years ago due to hypertensive nephropathy. One month before admission, kidney biopsy showed acute rejection; therefore he was hospitalized for ATG therapy. When his vital signs were normal except for the blood pressure of 220/110 mmHg. His oxygen saturation percent was also normal. Bilateral pitting edema was found up to below the knees, his cardiopulmonary status was satisfactory and chest radiograph was normal. In laboratory studies, there was no considerable abnormality except for raised urea and creatinine. The ATG was started in doses of 1.5mg/kg daily and one week after it, he developed fever and chills, when chest X-ray showed infiltration in the left lower lobe (Figure 1). Hospital acquired pneumonia was suspected due to immunodeficiency, therefore the combination of imipenem, ciprofloxacin, and vancomycin was started. Due to the lack of response to the antibiotics after 48 hours (dyspnea and fever), ATG therapy was stopped and CT scan was performed. The advanced ground glass pattern was observed in the lower left lobe and patchy ground glass pattern was seen in other lobes (Figure 2). Because his symptoms continued to the tenth day of hospitalization, bronchoscopy and bronchial lavage was performed. The lavage samples were evaluated for influenza virus, CMV and herpes simplex by molecular technique (PCR). In addition, Pneumocystis carinii staining was done and the results of above were negative, no organism was isolated either, but, CMV viral load was highly positive in his serum, therefore, considering the general condition, intravenous ganciclovir was prescribed. During the next days, fever gradually subsided, but, dyspnea continued and because of improving vital signs and reducing leukocytosis and C-reactive protein (CRP), antibiotic therapy was discontinued after two weeks. Ganciclovir was orally administered for 21 days and discontinued with reducing viral load. At the end of the third week, CT scan was performed again and fibrosis was observed in the left lower lobe (Figure 3). At this stage, as symptoms had disappeared (except for some dyspnea) therefore he was discharged. After one month, symptoms disappeared and CT scan showed no pulmonary fibrosis (Figure 4).
Figure 1. Infiltration is visible in chest X-ray radiograph, seven days after ATG administering.

Figure 2. Ground glass pattern is visible in CT scan, nine days after ATG administering.
DISCUSSION

In our case, HRCT findings were compatible with fibrosis and volume reduction, but after discontinuation of ATG and treatment of CMV infection, this pattern reversed. Recently, the efficacy of HRCT to differentiate the irreversible injury from the reversible one has been negotiable.\(^1\)\(^2\) Patients who receive a kidney transplant, due to immunodeficiency caused by immunosuppressive drugs, are more susceptible to numerous infectious and non-infectious diseases.\(^3\) The CMV is a problem that needs to be taken seriously in immunocompromised patients. Recently, the presence of CMV virus or other herpes viruses are known as one of the predisposing factors for lung fibrosis.\(^4\)

The pathologic changes due to CMV virus were studied on 18 AIDS patients and cellular transformation, pneumonia, alveolitis, granuloma and fibrosis were observed.\(^11\) In another study it was found that activating CMV in mice increased the levels of TNF-\(\alpha\) and caused pulmonary fibrosis, which could have been prevented by administration of ganciclovir.\(^12\)

In this report, increase CMV viral load in the serum, could be a sign of activated virus, and fibrosis might have been due to this activity. Reversible fibrosis after antiviral treatments supports this diagnosis. On the other hand, there are some literature reports that indicate lung injuries due to ATG such as ARDS and fibrosing alveolitis.\(^6\)\(^7\)\(^9\)\(^13\)\(^14\)

Although, in our case CMV was not isolated but its increasing viral load in serum and termination of fever after treatment, can suggest the CMV as a cause of pneumonia. Limitation of our study is its inability to differentiate the effect of virus from the one caused by the drug side effect during the clinical course. Anyway the appearance of fibrosis (confirmed by two radiologists) was reversible after treatment in this case. Therefore two considerable points in this case are; first, that ATG can cause pulmonary complication with fibrotic pattern which is important to be considered in patients taking this drug and secondly the appearance of fibrosis in CT scan (even with volume reduction) does not fully reflect that the damage is irreversible.
CONCLUSION
It can be concluded that CT scan is not completely specific for diagnosing reversible and curable injuries from incurable ones. In cases where the use of ATG causes pulmonary fibrosis, the drug must be discontinued immediately. Finally, it is recommended that if lung involvement is observed after CMV infection, even as fibrosis, treatment should be continued.

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REFERENCES