Acute lung injury during antithymocyte globulin therapy for aplastic anemia

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The case of a 33-year-old man with aplastic anemia who experienced recurrent episodes of hypoxemia and pulmonary infiltrates during infusions of antithymocyte globulin (ATG) is described. With the use of high-dose corticosteroids, the patient's original episode resolved, and were subsequently prevented before additional administrations of ATG. Rare reports of an association between ATG and acute lung injury are found in the literature, but this is the first report of successful steroid-supported re-exposure. Although the mechanism of ATG-related acute lung injury remains uncertain, it may be parallel to the mechanism of transfusion-related acute lung injury because the pathogenesis of the latter relies, in part, on antileukocyte antibodies. ATG-related toxicity should be included in the differential diagnosis of new, infusion-associated pulmonary infiltrates, and corticosteroids may be a useful therapeutic consideration in the management.

Key Words: Acute lung injury; Antithymocyte globulin; Aplastic anemia; Transfusion-related acute lung injury

Antithymocyte globulin (ATG) is an immunosuppressant drug used in treating aplastic anemia and solid organ transplant rejection. Adverse effects commonly include infusional fever, chills, urticaria and less often, a serum sickness reaction one to two weeks later (1,2). Anaphylactic or anaphylactoid reactions may occur idiosyncratically, sometimes presenting with bronchoconstrictive respiratory distress. However, case reports on isolated acute lung injury have also been published over the past two decades (3-7). We describe a case of successfully treated ATG-induced acute lung injury and review the speculated pathogenesis, offering a new perspective on parallels with transfusion-related acute lung injury (TRALI).

CASE PRESENTATION

A 33-year-old African-Canadian man presented in March 2007 with jaundice (bilirubin 252 µmol/L) and elevatedaminotransferases (aspartate aminotransferase 1667 U/L, alanine aminotransferase 2203 U/L). Liver biopsy demonstrated cholestatic hepatitis – serology-negative for hepatitis A, B and C. Over the ensuing two months, he developed progressively worsening pancytopenia (hemoglobin 85 g/L, white blood cell count 1.9×109/L, neutrophils 0.9×109/L, platelets 2×109/L, reticulocytes 13×109/L). Bone marrow biopsy showed hypo-cellularity without dysplasia or infiltrates; paroxysmal nocturnal hemoglobinuria screen was negative. There was no cardiorespiratory history. Baseline computed tomography (CT) scan of the chest was normal.

Hepatitis-associated aplastic anemia was diagnosed and equine ATG initiated (Atgam, Pharmacia & Upjohn, USA) – 40 mg/kg intravenously daily for four days. Before each ATG infusion (total volume 1.2 L), he was premedicated with hydrocortisone 100 mg and diphenhydramine 40 mg/kg intravenously. The first infusion was uneventful. Near to the end of the second ATG infusion (day 2), he complained of chest tightness, chills and rigors. His temperature rose to 38.5°C and over several hours the O2 saturation dropped to 91% while breathing ambient air, corrected with O2 at 3 L/min by nasal prongs. Blood pressure was 120/60 mmHg and jugular venous pulsations were not elevated. Blood, sputum and urine cultures were negative. Piperacillin/tazobactam and ciprofloxacin were started for febrile neutropenia. He was empirically given intravenous furosamide without clinical improvement.

The third infusion of ATG (day 3) was administered on schedule, but the infusion rate was slowed from 100 mL/h to
of antithymocyte globulin demonstrates bilateral pleural effusions continuing the supplemental O2. CT scan of the chest revealed improved over the next several hours, defervescing and discontinuing intravenously before and during the fourth infusion (day 4). Two hours into the infusion of ATG, the patient’s dysnea and hypoxemia worsened (O2 saturation 81% on room air). He became increasingly dyspneic, requiring face mask O2 (fraction of inspired O2 32%) to maintain saturations above 95%. He denied cough, chest pain or hemoptysis, but reported mild diffuse myalgias and arthralgias. An additional dose of hydrocortisone 100 mg was administered intravenously and he improved over the next several hours, defervescing and discontinuing. CT scan of the chest revealed diffuse bilateral patchy areas of consolidation with ground glass opacities (Figure 1). Because of the rapid improvement, bronchoscopy was not performed.

Pre-emptive doses of hydrocortisone 100 mg were administered intravenously before and during the fourth infusion. Two hours into infusion, his temperature rose to 39°C and his hypoxemia worsened (O2 saturation 81% on room air). He became increasingly dyspneic, requiring face mask O2 (fraction of inspired O2 32%) to maintain saturations above 95%. He denied cough, chest pain or hemoptysis, but reported mild diffuse myalgias and arthralgias. An additional dose of hydrocortisone 100 mg was administered intravenously and he improved over the next several hours, defervescing and discontinuing the supplemental O2. CT scan of the chest revealed diffuse bilateral patchy areas of consolidation with ground glass opacities (Figure 1). Because of the rapid improvement, bronchoscopy was not performed.

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neutrophil-specific, more recently, monocytes (12) and lymphocytes (13) have also been implicated. Whether antileukocyte antibodies of animal origin can recapitulate these observations is not yet known. It is possible that the pathophysiology of lung injury induced by ATG is congruent with and supportive of the antigen-antibody hypothesis of TRALI. ATG-induced lung injury, such as TRALI, does not occur in all cases in which a cognate immune interaction is present (14). TRALI seems to require either a patient predisposition and/or a 'second-hit' priming event (15), and the infrequency of acute lung injury secondary to ATG may similarly be multifactorial.

There are other possible mechanisms to explain acute lung injury. A cytokine release syndrome, well appreciated in the use of ATG and OKT3, may also play a role in the development of pulmonary edema (16). Pulmonary capillary endothelial permeability increases in response to tumour necrosis factor-alpha, interleukin-1 and interleukin-8 released from damaged or activated lymphocytes, similar to the pathogenesis of ARDS in sepsis (17). Alternatively, ATG may cause direct pulmonary cytotoxicity. ATG has been observed to bind nuclear and cytoplasmic components of lung in vitro (18). A complement-mediated acute hemorrhagic pulmonary lung lesion in an animal model was reported by Haefen et al (9); interestingly, this lesion was prevented by absorption of serum with homogenie suspensions of lung and thymus, suggesting that the reaction was due to direct antibody-mediated cytotoxicity. The literature on this subject is very limited and further basic and clinical investigations are required to clarify the mechanism of acute lung injury associated with ATG.

It is unclear why the acute lung injury episodes in the present case were more transient and less severe than those of the previous reported cases. After the first episode of hypoxemia (with the second ATG infusion), we elected to continue ATG, believing initially that an infectious process was the likely cause. The infusion protocol was slowed and an extra dose of Solu-Cortef (Pfizer, Canada) was administered during the next episode of dyspnea and hypoxemia (with the third ATG infusion). As such, the hypoxemia resolved over the subsequent 12 h. Extra doses of hydrocortisone were given in anticipation of the fourth ATG infusion, and the subsequent episode of dyspnea and hypoxemia was even shorter than the previous. These regimen responses may have ameliorated the severity of the lung injury.

The present case and the mechanisms behind ATG-mediated acute lung injury raise important considerations for the diagnosis and management of this severe adverse effect. ATG should be considered a potential cause of acute hypoxemia or pulmonary infiltrates, and lists of medications known to cause respiratory disorders should be updated to include ATG (19,20). In cases of suspected acute lung injury during an ATG infusion, there may be value or interest in submitting serum for lymphocytotoxicity assays used in the serological workup of suspected TRALI reactions to compare T cell-specific reactivities with other cases.

The management of these cases must be based on sound clinical judgment. Deciding whether to continue ATG is difficult, and should be based on the severity and progression of the lung injury. Slowing the infusion and administering additional doses of corticosteroids may limit progression of lung injury and facilitate regimen completion.

CONFLICTS OF INTEREST: None of the authors have any potential or actual financial conflicts of interest to disclose.

REFERENCES