Case Report

Diffuse Alveolar Hemorrhage (DAH) in the Immediate Post-transplant Setting: An Unusual Case and a Review of Literature

Abstract

Diffuse alveolar hemorrhage is known to be a devastating clinical condition with myriad etiologies. The immediate post-transplant period is plagued by immunosuppression, surgical complications, and nosocomial sources of infection. Diffuse alveolar hemorrhage in this setting is usually attributed to infection. In this case report, an unusual cause of diffuse alveolar hemorrhage due to anti-thymocyte globulin used as an induction agent is described, and an approach to DAH in the immediate post-transplant setting is discussed.

Keywords: *Anti-thymocyte globulin, diffuse alveolar hemorrhage, renal transplant*

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Introduction

Diffuse alveolar hemorrhage (DAH) is a life-threatening disease entity that may occur post kidney transplantation. Due to the immediate post-transplant period being associated with intense immunosuppression and nosocomial sources of infection, DAH in this setting is usually attributed to infection. In this case report, an unusual cause of DAH possibly due to anti-thymocyte globulin (ATG) is described.

The case

A 36-year-old male was referred to our center for kidney transplantation. The patient had a history of chronic kidney disease on dialysis since the past 8 months. The cause of ESRD was not known, and pretransplant evaluation showed bilateral shrunken kidneys and bland urine sediment. Other investigations were within normal limits, and he was planned for transplant with his mother as a donor. CDC crossmatch was negative and ATG was the induction agent as per our unit protocol. Nasopharyngeal swab testing for COVID RT-PCR and CT Chest were done both for the donor and the recipient 2 days prior to transplantation and were within normal limits.

On the day of kidney transplantation, 100 mg of ATG (1.5 mg/kg) was administered over a period of 4 h. The patient developed hypotension intraoperatively during administration of ATG, with a drop in the systolic blood pressure from 140 mm Hg systolic to 90 mm Hg systolic. However, blood pressure improved with IV fluid administration, and ATG infusion was completed prior to graft anastomosis. The rest of the surgery was uneventful with a steady decline in creatinine in the post-operative period. He was maintained on triple immunosuppression with steroids, tacrolimus, and MMF.

On the 2nd post-operative day (POD), he developed breathlessness with mild hemoptysis. There was a drop in SpO_2 to 90% on room air and he required oxygen @5 L/min to maintain a target saturation of 93%–95%. There was no fever or bleeding from any other site or chest pain. His jugular venous pressure (JVP) was normal, and he had no edema. Heart sounds were normal. Investigations showed a drop in hemoglobin with normal coagulation parameters [Table 1]. He also had mild lymphopenia and thrombocytopenia, likely due to ATG. Peripheral smear did not show any evidence of hemolysis and serum LDH was 223 IU/L. Urine output was 5 L, and drain output was less than 100 ml. USG did not show any collection at the graft site. Both ECG and echocardiography were normal. His chest X-ray showed bilateral inhomogeneous fluffy infiltrates [Figure 1]. CT of the chest was done, which showed bilateral

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diffuse ground-glass opacities along with bilateral pleural effusion [Figure 2]. Sputum gram stain was negative; blood cultures and a repeat nasopharyngeal swab for COVID RTPCR were also negative. Antibiotics were upgraded to cover gram-negative and gram-positive organisms.

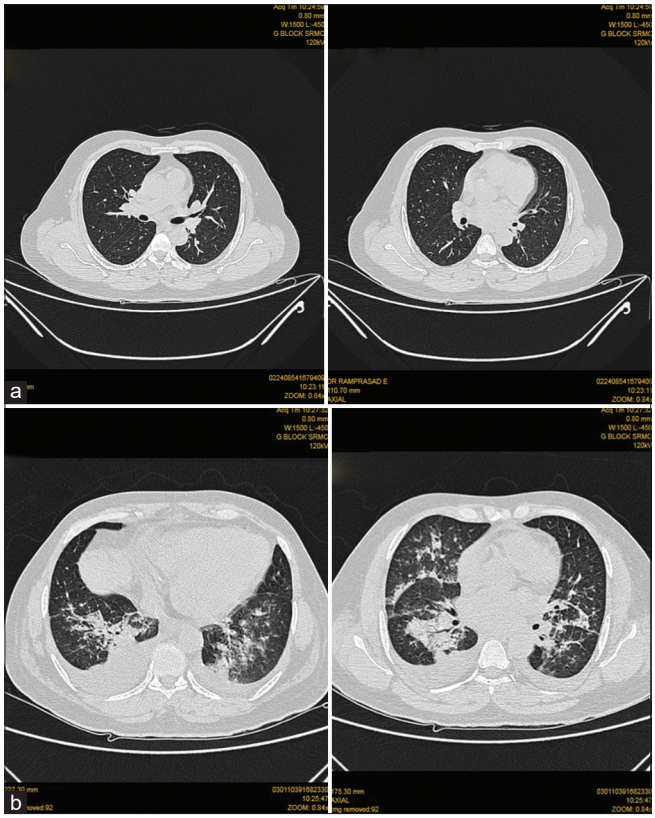

Figure 1: (a) CT scan of the chest prior to kidney transplantation: normal lung fields. (b) CT scan of the chest on day 3 post-transplantation- bilateral mild pleural effusion and homogenous opacites in bilateral lung fields

The patient continued to have hemoptysis despite antibiotics and persistent high-flow-oxygen requirement. A bronchoscopy with bronchoalveolar lavage was done on POD 4. Bronchoscopy revealed active hemorrhage in all lung segments with increasingly hemorrhagic fluid on subsequent washes. BAL fluid demonstrated 30% macrophages, of which 33.3% were hemosiderin-laden, consistent with a diagnosis of DAH. [Table 2]. Immune and infectious causes were ruled out as summarized in Table 2. Graft function remained stable with creatinine at 1.1 mg/dL and there was no hematuria or proteinuria. Due to the absence of other causes of DAH, a diagnosis of drug-induced DAH due to ATG was considered. The patient was managed conservatively with oxygen support

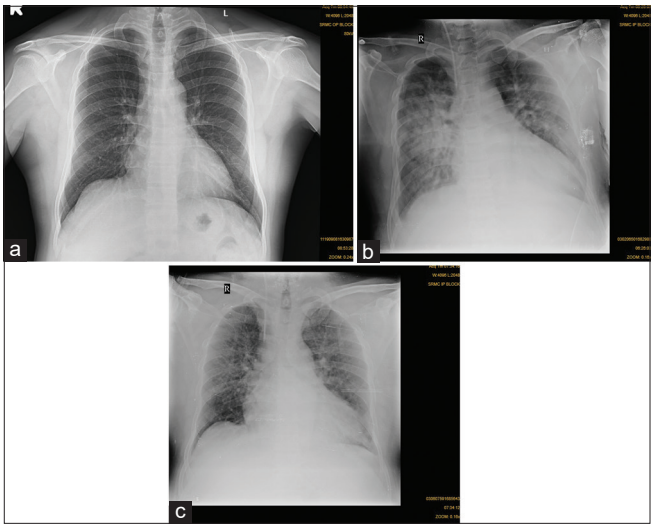

Figure 2: (a) Chest X-ray pre-operative: normal PA film prior to transplantation. (b) Chest X-ray Day 4 post-transplantation: AP view showing bilateral diffuse infiltrates with perihilar prominence. (c) Chest x-ray post-operative day 6 with the resolution of infiltrates

Table 1: Laboratory values according to postoperative days

Test	Pre-transplant	Day 1 post-transplant	Day 3 post-transplant	Day 6 post-transplant
Hemoglobin	11 gm/dL	9.2 gm/dL	8.3 gm/dL	8.3 gm/dL
Total counts	9900/mm^3	11,000/mm^3		7900/mm^3
Platelet counts	2.3 l/mm^3	0.88 l/mm^3		1.5 l/mm^3
Creatinine	6.3 mg/dL	3.1 mg/dL	1.4 mg/dL	1.2 mg/dL

Table 2: Etiology work up for DAH

cANCA ELISA	<2 R U/mL
pANCA ELISA	<2 RU/mL
Anti-GBM ELISA	1.4 RU/mL
Quantitative CMV PCR	604 copies/mL
Blood culture bacterial and fungal	No growth
Sputum culture, bacterial	No growth
Cytology BAL fluid	Bronchial epithelial cells 40%, alveolar macrophages 30% (of these 1/3 are hemosiderin-laden), lymphocytes 10%, neutrophils 10%, squamous cells 10%
BAL fluid culture bacterial and fungal	Negative
BAL staining for bacteria, nocardia FA for PCP staining	No smear positivity, nocardia negative, FA for PCP negative
Serum LDH	223 U/L

and antibiotics. No further doses of ATG were given. Methylprednisolone was given at 125 mg/day on POD 1 and 2 followed by prednisolone at 1 mg/kg till the tenth POD after which tapering was started. Gradually, hemoptysis settled by POD 7 and he was gradually weaned off oxygen support. Repeat chest X-ray showed a significant clearing of the lung fields. The patient was discharged on POD 14 with a stable hemoglobin of 8.3 gm/dL, serum creatinine of 1.1 mg/dL, and no respiratory complaints.

Discussion

Diffuse alveolar hemorrhage is a life-threatening entity with multiple potential etiologies. This catastrophic disease in an immunocompetent host is often brought about by vasculitic events. In the post-transplant setting, that is, the immunocompromised host, the circumstances are vastly different.[1] Although the potential for hitherto underdiagnosed vasculitic events persists, the likelihood of an infective etiology is higher than other causes of DAH.

The evaluation of DAH requires a two-step approach.[2] One is the establishment of the diagnosis of DAH, which is done by a history of hemoptysis, lung infiltrates on CT, and evidence of hemorrhage on bronchoscopy. The classical diagnosis of DAH is made when repeated aliquots of bronchoalveolar lavage fluid show increasingly hemorrhagic fluid. In this patient, the BAL fluid showed persistently hemorrhagic fluid with the presence of 30% alveolar macrophages, with 33.3% of them being hemosiderin-laden. A value of 20% hemosiderophages is considered consistent with alveolar hemorrhage[3] and is considered to be associated with increased mortality in patients with acute lung injury.[4]

The second step in the evaluation is that of identifying the etiology of DAH. In the recipient of a solid organ transplant who is on multiple immunosuppressive medications, the infection needs to be rigorously ruled out. The common infections in the Indian setting, within the first month of transplant in keeping, are usually bacterial and nosocomial in origin.[5] Among the opportunistic infections, CMV pneumonitis and invasive pulmonary aspergillosis have both been linked in the past to DAH.[6] However, these infections are less common in the early post-transplant period. In the patient described in this report, these infections were actively sought out and ruled out with meticulous microbiological testing. Immune-mediated causes were ruled out in our case by doing anti-GBM, C-ANCA, and P-ANCA antibodies, which were negative.

Drug-induced DAH in transplantation has been described earlier with sirolimus, mycophenolate mofetil, and alemtuzumab.[7-9] ATG has been known to induce acute lung injury or non-cardiogenic pulmonary edema,[10] but DAH with ATG has not been reported earlier. In our case, the patient was continued on other immunosuppressives, but further doses of ATG were not given. The temporal association of the drop in blood pressure post ATG followed by the development of a DAH in which immunological and other infectious causes were ruled out and other immunosuppressive drugs continued led us to believe that ATG was the cause of DAH in our patient.

Several potential mechanisms for ATG related acute lung injury have been postulated.[11] One mechanism described is akin to transfusion-associated acute lung injury (TRALI), where anti-leucocyte antibodies in ATG may bind to recipient neutrophils, causing cellular activation leading to local endothelial injury to microcirculation. The second theory that has been postulated is that due to a cytokine storm, high levels of cytokines such as IL-1 and IL-6 have been demonstrated in patients who have received ATG.[12] Cytokines such as TNF-alpha, IL-1, IL-6, and IL-8 have been associated with increased pulmonary capillary permeability.[11,13] A third theory is direct injury to the lungs by ATG or complement-mediated acute hemorrhagic pulmonary lesions described in animal models.[14]

Treatment of DAH depends on the etiology. In drug-induced causes, this mandates stopping the implicating drug. Supportive therapy in the form of mechanical ventilation may often be needed. High-dose corticosteroids have been tried in acute lung injury secondary to ATG.[11] Our patient required high-flow oxygen inhalation, which was gradually weaned over 5 days. Prednisolone was given at 1 mg/kg till POD 10, after which tapering was started and other transplant maintenance immunosuppressives were continued.

Conclusion

DAH in the post-transplant setting is a rare event with potentially disastrous outcomes. Although causality cannot be conclusively proven, through a systematic method of ruling out other etiologies, DAH was considered most likely due to ATG in this setting.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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