LUPINE PUBLISHERS

Journal of Clinical & Community Medicine

DOI: 10.32474/JCCM.2023.05.000214

ISSN: 2690-5760

Case Report

Hypersensitivity Reaction to Anti-Thymocyte Globulin (Equine) Resulting in Hypotension, Cerebrovascular Accident, Intravascular Hemolysis, Thrombocytopenia, Acute Liver Injury, Delayed Graft Function, Acute Lung Injury, Followed By Fatal Anaphylaxis to Second Dose of Basiliximab in A Living Unrelated Kidney Transplant Recipient: A Case Report

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Received: October 02, 2023 **Published:** October 26, 2023

Case Summary

Anti-thymocyte globulin (ATG) (Equine) and Basiliximab are widely used as anti-rejection therapy in renal transplant recipients with high immunological risks. They are effective and generally well tolerated; however, fatal reactions are rarely reported. We report hypotension 10 hours after injection ATG with resultant right hemiparesis and motor aphasia due to cerebrovascular accident (cerebral infarct), transaminitis, intravascular hemolysis, thrombocytopenia, delayed graft function and acute lung injury due to hypersensitivity reaction to ATG in a living unrelated kidney transplant recipient, 58-years old male with high vascular risks. He did not show features of hypersensitivity with ATG test infusion. We switched to Basiliximab to reduce immunological risks after explaining risks and benefits to the patient and his family. The blood pressure dropped suddenly five minutes after initiation of second dose of Basiliximab; it was resuscitated successfully and infusion was stopped. Ninety minutes later, he had sudden death. Clinicians should aware of fatal hypersensitivity reaction and multi-organ failure although there is no reaction to test dose infusion or first dose.

Keywords: Anti-thymocyte globulin (Equine); Basiliximab; hypersensitivity reaction; multi-organ failure; sudden death; kidney transplant

Introduction

The aim of renal transplant is to gain normal renal function with longest duration as well as lowest risks to recipient. Currently available agents for induction therapy in Myanmar are anti-thymocyte globulin (ATG) and Basiliximab; and they are

used for patients with high immunological risks. Anti-thymocyte globulin (ATG) (Equine) is an equine-derived purified polyclonal immunoglobulin directed against human T-lymphocytes. Basiliximab is a recombinant monoclonal antibody (75% human 25% murine); it prevents T-lymphocyte proliferation induced by IL-2. The choice of immunosuppressants depends on immunological risks. Though both ATG and Basiliximab had higher potency in prevention of acute rejection [1–7], the efficacy of ATG was stronger than Basiliximab in majority of studies [8]. They were found to have fewer adverse events than other T cell depleting agents [9,10]. Regarding the comparison of ATG and Basiliximab in the immuno-induction therapy in kidney transplant recipients, some studies were positive on Basiliximab; it was effective and safe with less complication compared with the ATG [9,11-13]. Nonetheless, Yang et al supported ATG 'though both single bolus ATG and basiliximab induction therapy achieved similar one-year graft/patient survival, single bolus ATG yielded much lower AR rate than basiliximab without increase in infection episodes and severe adverse events' [14].

ATG was recommended for induction therapy in high-risk patients; high levels of panel reactive antibodies and retransplantation [15]. On the other hand, some findings did not make statistically significant differences regarding long-term graft and patient survival, cancer, or total infection rate between ATG group and Basiliximab group [16,17]. In comparison of side effects such as incidences of Cytomegalovirus infection, leucopenia, and thrombocytopenia, the events were significantly higher in ATG group than Basiliximab group; therefore, ATG should be use in patients who are at high risk for acute rejection and delayed graft function [16,18-20]. Because of the serious risk of anaphylaxis with ATG, premedication therapy was strongly recommended [21]. Therefore, ATG infusion by increasing premedication or modifying infusion protocol with systemic steroids was suggested [22]. Hypersensitivity reactions causing multi-organ failure were rarely reported; severe reactions amounting to death were rarely seen [9,23,24]. We report a case of multi-organ failure and sudden death as a result of hypersensitivity reaction to ATG and Basiliximab.

Case Presentation

A 58-year-old ex-smoker with end-stage kidney disease (ESKD) on maintenance hemodialysis underwent a living unrelated donor kidney transplantation on July 28th, 2023. The patient's underlying kidney disease was suspected to be diabetic kidney disease, although no history of renal biopsy was available. The patient had a hemodialysis [HD] vintage of two times per week for two years (total of 288 sessions) utilizing a left brachiocephalic fistula. The residual urine production was approximately 700 ml/day. Previously, the patient had received three units of blood transfusion, with the most recent one administered in September 2021. The donor was a 27-year-old living unrelated female who displayed no prior evidence of renal issues.

The patient had a standard immunological risk:

a) Positive blood transfusion history.

b) Normal CDC crossmatch with positive B cell.

c) Weakly positive class I donor-specific antibodies (B*57:01 - MFI 1609, B*57:03 - MFI 753)

Additionally, the patient carried a high surgical/cardiovascular risk according to carotid doppler, abdominal contrast-enhanced CT (CECT) scan and coronary angiogram. There were extensive calcified plaques in the left carotid bulb in the internal carotid artery (ICA), luminal narrowing, and the presence of small calcified plaques in the right carotid bulb. Abdominal contrast-enhanced CT (CECT) scan showed atherosclerotic changes in the abdominal aorta, renal arteries, and both common iliac arteries, with preservation of the right external iliac arteries. A coronary angiogram (August 25th 2022) demonstrated minor coronary artery disease (CAD). The patient's infection risk was low, with both donor and recipient being free from viral markers and latent tuberculosis (TB), although CMV IgG was positive. The induction immunosuppressive regimen included ATG (Equine) (Thymogam) at a planned dose of (10 mg/Kg) 750 mg OD from Day 0 to Day 4 as transplant protocol. Notably, the patient exhibited no significant anaphylactic reaction during the ATG (Thymogam) test dose administered one day before the operation. The immune-suppressants were steroids, tacrolimus and mycophenolate mofetil.

The transplant operation was conducted on July 28th, 2023; it lasted approximately three hours. The donor's right kidney weighed around 119 g, with a total ischemic time of 70 minutes (1st warm ischemic time: 3 min, 2nd warm ischemic time: 44 min, cold ischemic time: 23 min). The allograft renal artery was anastomosed to the right external iliac artery using an end-to-side technique, and two allograft renal veins were similarly connected. Induction immunosuppressive therapy with ATG (750 mg) commenced three hours prior to the operation and continued throughout the procedure, totaling six hours. The blood pressure, pulse rate, and oxygen saturation were stable through-out surgery. Following surgery, the patient's blood pressure initially measured around 130/60 mmHg (MAP 80-90); however, three hours post-operation period (i.e., 10 hours after therapeutic dose; 22:00 hour July 28th, 2023), it dropped to 110/60 mmHg (MAP 60 mmHg). To maintain a MAP of 90-100 mmHg, inotropic support with noradrenaline was initiated. However, the desired blood pressure range was challenging to achieve. He was drowsy at the same time; and it was thought to be related with opioids analgesics initially.

At 4:00 am (04:00 hour July 29th, 2023), he was uncommunicable; reduced movement on right side; equivocal planter response on both sides; Glasgow Coma Scale 8/15 (E4, M3, V1). An urgent NECT (head) (Photos 7 & 8) revealed a cerebral infarction in the left frontoparietal region. (Photos 1 & 2) Therefore, the patient developed CVA (cerebrovascular accident) secondary to hypotension in previously hypertensive case with severe carotid atherosclerosis, probably water-shed infarct. When the blood pressure was stable at 120/90 mmHg, dysphagia and

motor aphasia were marked with right facial palsy (UMNL) and right sided hemiparesis. As of thrombolytic therapy for timely revascularization, it was contraindicated at present. Moreover, anti-platelet therapy was withheld because his platelet count decreased dramatically to 30x109/L; pre-transplant count done 24 hours before surgery was 165x109/L. (Figure 1).

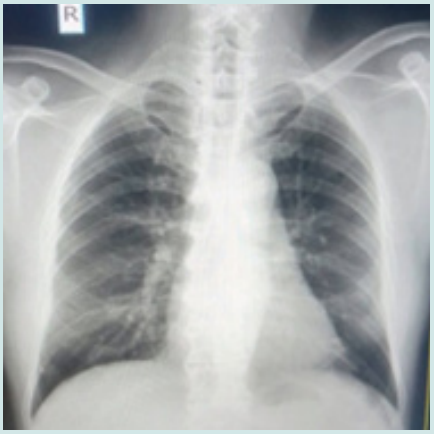

Photo 1: Chest radiograph prior to transplant.

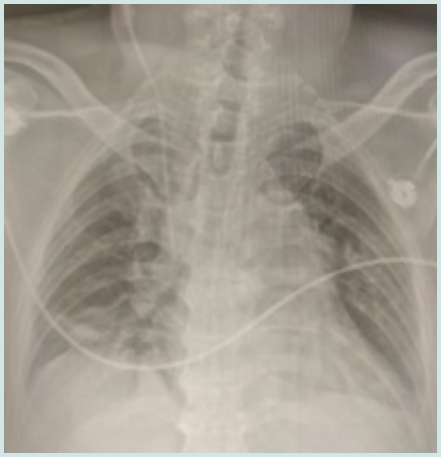

Photo 2: Chest radiograph Day '1' showing alveolar shadows in right lower zone.

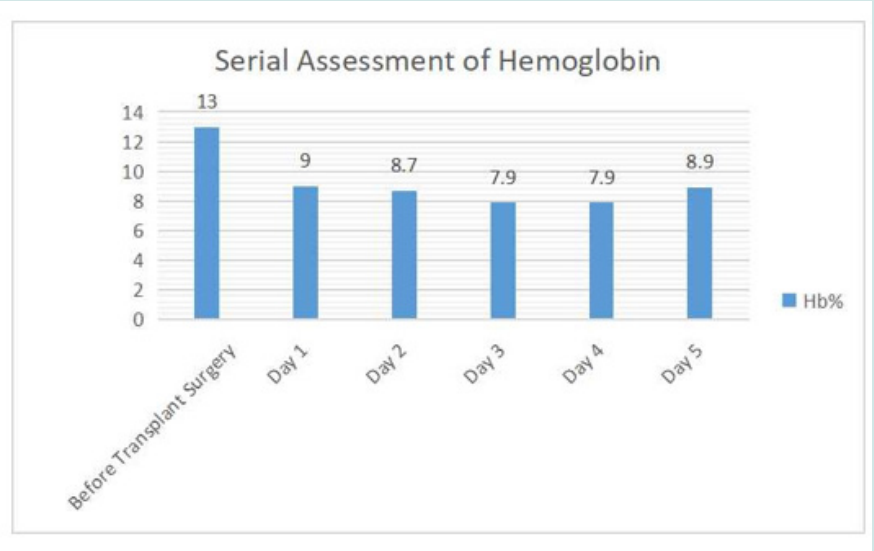

Photo 2: Chest radiograph Day '1' showing alveolar shadows in right lower zone.

At the same time, hemoglobin dropped to 9 gm% [pretransplant value 13 gm%] with neutrophil leukocytosis [TWBC 20.4x109/L]. (Figures 2 & 3) Total bilirubin was raised suddenly to 2.5 mg/dl with severe transaminitis; ALT was 2415 IU/L; AST was 2249 IU/L; and alkaline phosphatase was normal [35 IU/L]. LDH was 2511 IU/L. (Figure 4) The clinical event, undue hypotension [appropriate rehydration with fluids and electrolytes therapy without blood loss] and drastic changes in blood parameters [sudden dropped in hemoglobin, severe thrombocytopenia, very high liver parenchymal enzymes, slow fall in serum creatinine] pointed that the patient was having an anaphylactic severe hypersensitivity reaction to ATG. Therefore, intramuscular adrenaline [0.5 ml] was administered, the subsequent ATG dose was discontinued. In view of salvaging transplanted grafted kidney, giving Basiliximab infusion was initiated, along with extended IV methylprednisolone administration. Blood pressure dramatically rose after injection of adrenalin; and inotropic support was tapered. The patient had a urine output of 100-380 ml/hour on the first postoperative day with a total output of 4110 ml against an intake of 5061 ml.

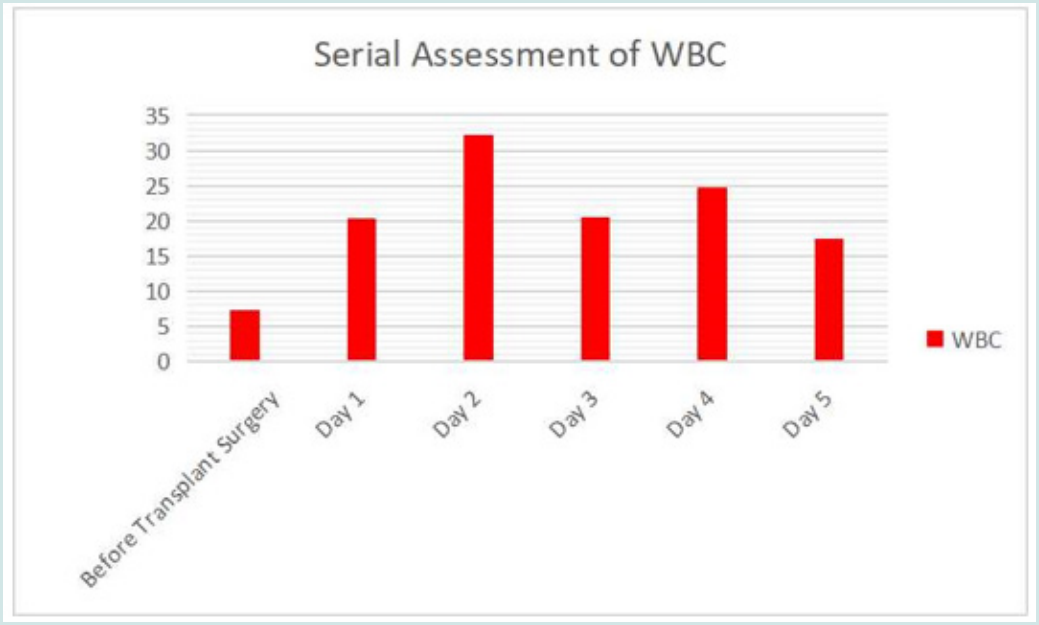

Figure 2: Serial changes in Total WBC count.

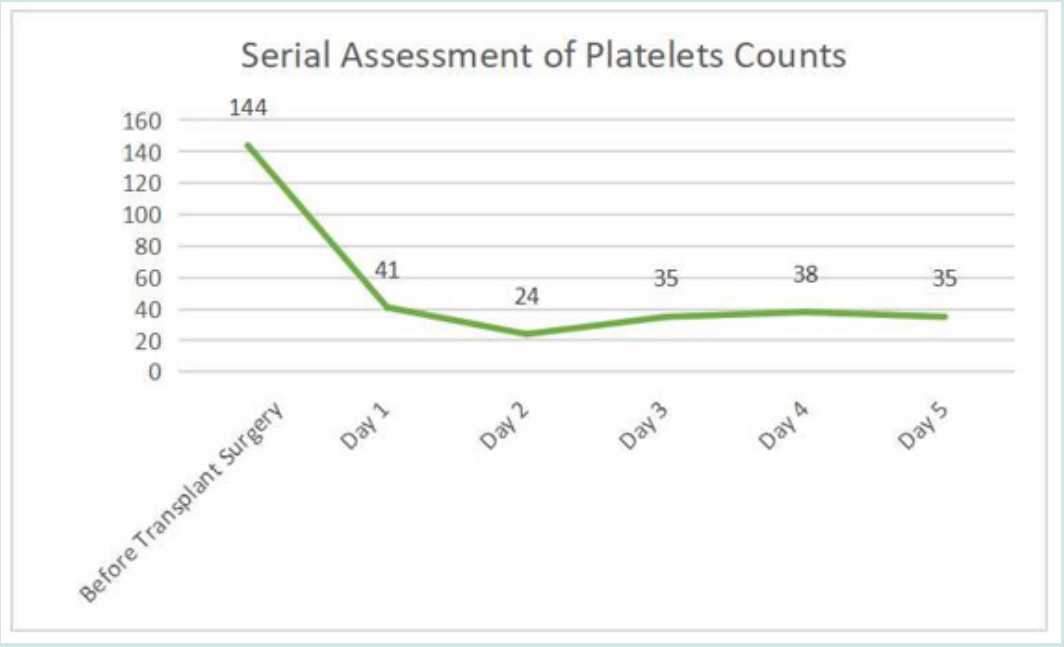

Figure 3: Serial changes in platelet count.

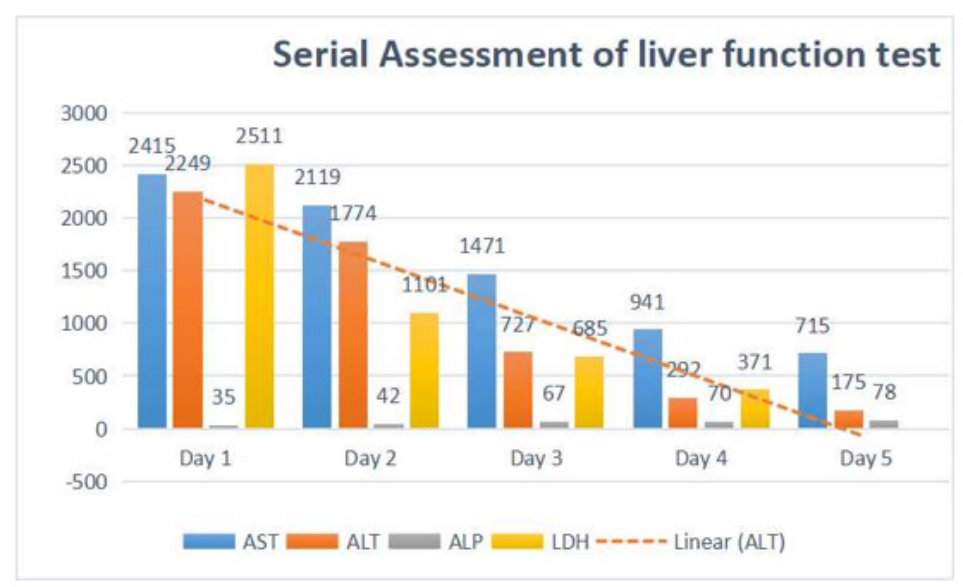

Figure 4: Serial changes in AST, ALT, ALP and LDH.

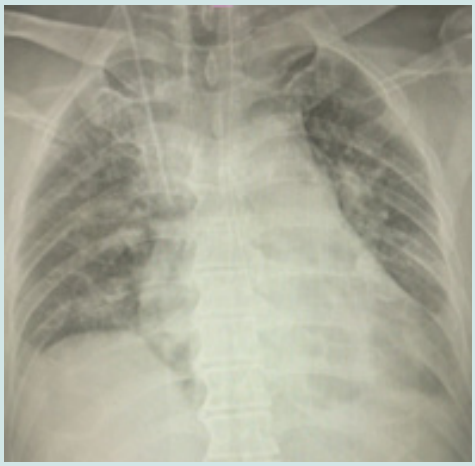

Photo 3: Chest radiograph Day '2' revealing extension of alveolar shadows to middle zones.

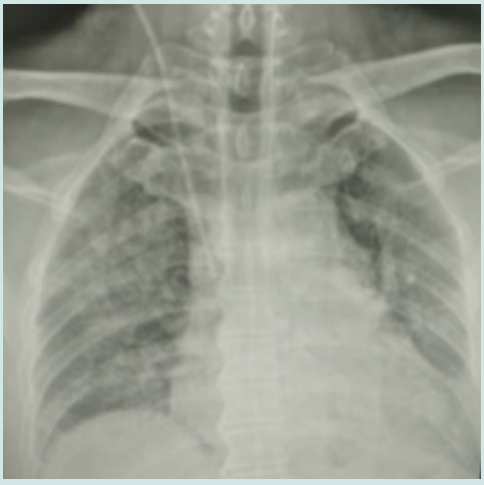

Photo 4: Chest radiograph Day '3' showing more opacities in middle and upper zones.

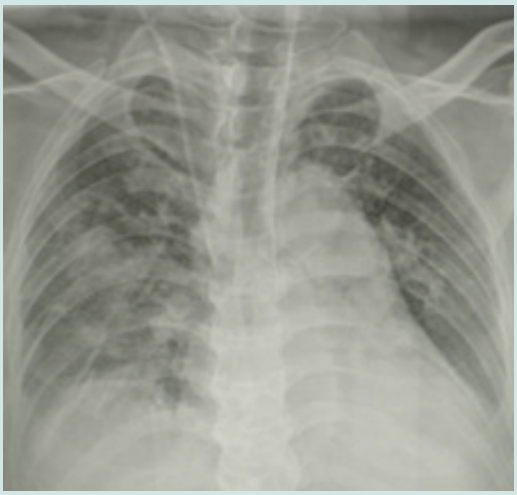

Photo 5: Chest radiograph Day '4' revealing more prominent alveolar shadows.

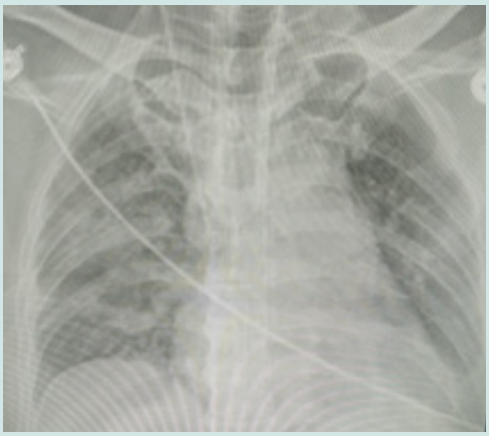

Photo 6: Chest radiograph Day '5' having expension of alveolar shadows.

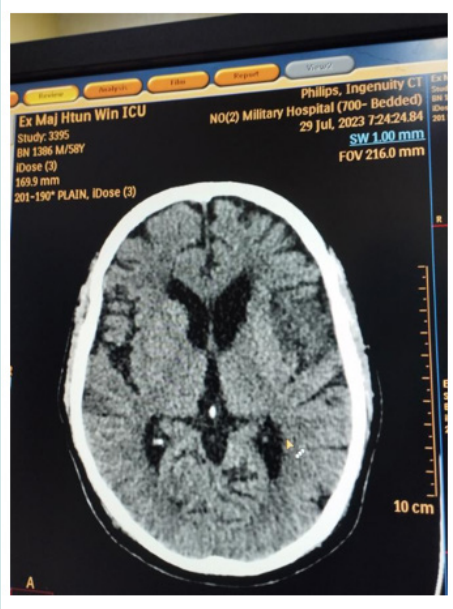

Photo 7: NECT Head showing infarct area at left fronto-parietal zone.

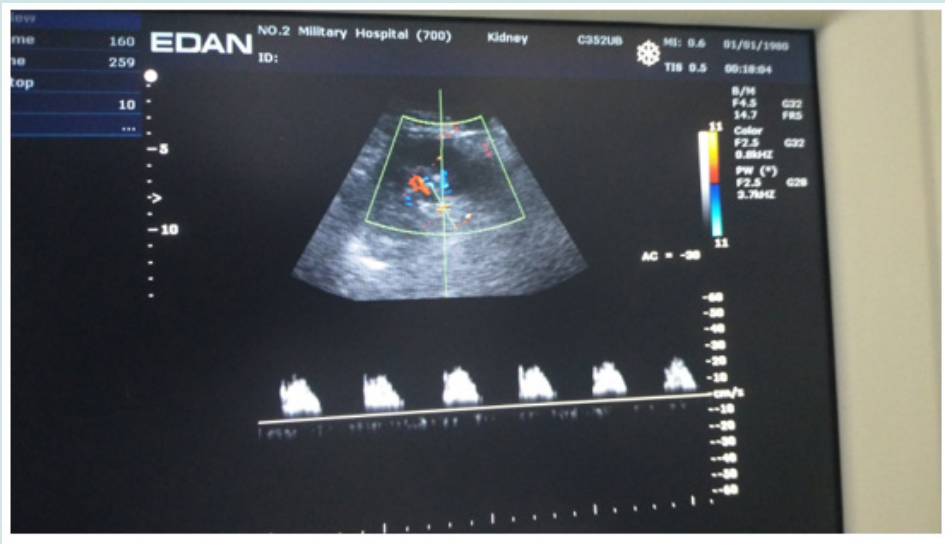

Photo 8: Allograft Doppler Ultrasound showing 'absent of diastolic flow' in segmental renal artery.

Due to impaired swallowing function, suction was performed every 2-4 hours, and chest physiotherapy was conducted every 4 hours. Oral drugs (Tacrolimus and mycophenolate mofetil) were given through Ryle's tube. Because the platelet count was too low, two units of platelet-rich plasma (PRP) were administered on the second postoperative day. Compared to pre-transplant film, chest radiograph on 'Day 1' showed faint alveolar shadows in middle zone as seen in 'photos 1 & 2'. On second post-operative day (after 24 hours), urine output decreased to 30 ml/hour; therefore, IV frusemide infusion initiated. The urine output ranged from 30-160 ml/hour; total urine output decreased to 1940 cc/24 hour with an intake of 1521 ml/24 hour. Considering reduced urine output and elevated renal function tests, hemodialysis (HD) was performed with a Heparin-free, Low Flow technique, utilizing ultrafiltration (UF) at 300 ml for two hours. For delayed allograft function, a second HD session was performed on the third postoperative day, lasting three hours. Fluid replacement was guided by central venous pressure (CVP), inferior vena cava (IVC) measurements, and lung ultrasound [USG]. The cumulative intake/output was 2892 ml/2150ml respectively. Oxygen therapy was given via face mask; SaO2 was maintained at 98%. Serial chest radiograph (Photos 3-6) reveals increasing alveolar shadows in both lungs.

On the fourth postoperative day, the patient was tachypneic, respiratory rate of 48 breaths per minute; intermittent non-invasive ventilation (NIV) support was given with FiO2 (60-80L). Possible aspiration pneumonia with ARDS was suspected. Moreover, the level of consciousness deteriorated; blood sugar levels rose to 423 mg/dl and soluble insulin infusion was initiated according to blood sugar . On the other hand, blood pressure remained stable [ranging from 150/70 to 180/80 mmHg] with a heart rate of 80-120/min without the support of inotropes. Although CBC, LFT, PT/INR, and CRP results showed improvement, renal function tests remained compromised. Consequently, a third HD session was performed for four hours, incorporating an ultrafiltration volume of approximately 1420 ml.

As per the induction protocol, the second dose of Basiliximab infusion commenced at 13:00 hour 5th post-operative day (13:00 hour August 2nd, 2023). Five minutes after initiating Basiliximab infusion, the patient's blood pressure rapidly declined from 150/70 mmHg to 70/30 mmHg; severe hypersensitivity reaction to Basiliximab (second dose). The drug infusion was stopped; IM adrenaline (0.5 ml) was administered. It was accompanied by fluid resuscitation and inotropic support. The shock resolved after a brief period, and subsequent weaning of IV noradrenaline and dobutamine infusions were done within 30 minutes. The patient's level of consciousness remained impaired; NIV support with FiO2 of 80 was maintained. Invasive ventilation was considered due for several reasons: rapid respiratory rate; increased oxygen requirements; diminished level of consciousness and the risk of biphasic anaphylactic shock. Tragically, while attempting endotracheal tube insertion, the patient had a cardiac arrest at 14:40 hour i.e., 90 minutes after cessation of Basiliximab. Despite immediate Advanced Cardiac Life Support intervention under the supervision of an ICU team, including anesthetists, nephrologists and cardiologists, it was unsuccessful. Regrettably, the patient's demise was declared at 15:45hr on August 2nd, 2023.

Discussion

Because of the serious risk of anaphylaxis with ATG, premedication was strongly recommended [21]. Therefore, ATG infusion by increasing premedication or modifying infusion protocol with systemic steroids was suggested [22]. However, hypersensitivity reactions causing multi-organ failure were not commonly reported; extremely severe reactions amounting to death was very rare [9,23,24]. We report a case of multi-organ failure and sudden death as a result of hypersensitivity reaction to

ATG and Basiliximab. ATG infusion did not give rise to significant complications if patient did well with test dose infusion. ATG was reported as effective and it did not produce serious adverse effects in various transplant [14]: liver, kidney, lung, bone marrow, heart [25] and islet cell transplant. However, because of the serious risk of anaphylaxis with ATG, premedication was strongly recommended [21,26]. Therefore, ATG infusion by increasing premedication or modifying infusion protocol with systemic steroids was suggested [22]. Saeed et al. (2020) highlighted the awareness of intra-operative shock due to ATG [27].

The patient did not have flu-like symptoms such as fever, chills, dyspnea, nausea, vomiting and diarrhea with test dose; he developed undue hypotension only 10 hours after therapeutic infusion. Generally, features of anaphylaxis can occur within minutes of exposure to an offending agent; nevertheless, it may develop more than 30 min later. Furthermore, late-phase or biphasic reactions can occur 8–12 hour after initial exposure; and severe anaphylaxis might last up to 32 hours even with de-sensitization [28]. Therefore, awareness of severe anaphylaxis is very important though the incidence is less than 1/1,000. ATG induced cardiac arrest during intra-operative period was reported by Navas-Blanco et al [29]. The patient had CVA (cerebrovascular accident) secondary to hypotension because cerebral auto-regulation was impaired in old age, hypertensive case with atherosclerosis. CT head showed a cerebral infarction in the left frontoparietal region. It was strongly related with significant narrowing in left carotid artery. In fact, the patient should have undergone carotid end atherectomy first. It was a delicate dilemma of balancing severe thrombocytopenia and anti-platelete therapy/anti-thrombolytic therapy for cerebral infarction. Early anti-platelet therapy/anti-thrombolytic therapy could prevent further extension of infarct and it could salvage infarct area. On the other hand, severe thrombocytopenia could result in cerebral hemorrhage as well as hemorrhage from other mucosa.

Hematological adverse events like leucopenia, and thrombocytopenia were significantly higher in ATG group than Basiliximab group [16,18-20]. Acutely fall in hemoglobin which was out of proportion to intra-operative blood loss in this patient was due to intravascular hemolysis as a result of hypersensitivity reaction to ATG; it was supported by acute rise in serum bilirubin and LDH level. It also caused severe thrombocytopenia. There was a case report on kidney transplant recipient who developed ATG induced severe hemolytic anemia and thrombocytopenia with a subsequent perirenal hematoma immediately after kidney transplantation [30]; nevertheless, the patient did not have hypotension or multi-organ involvement like our case. Moreover, it produced multi-organ failure: acute liver injury [marked elevation of serum transaminases and mild elevation of serum bilirubin level], delay graft function and acute lung injury. Severe anaphylaxis to ATG was seen in rare case report; liver transplant [31]; islet cell transplant [32]. The awareness of hypersensitivity reaction and prompt treatment among physicians was important [33]. Lower platelet count after induction with ATG was commonly seen and it had positive impact in transplant cases; less acute cellular rejection in heart transplant cases; reflecting platelet involvement in antirejection mechanisms of rATG [34]. However, the timing of fall of platelets was 'Day 7' after transplant and the level was rarely below normal. According to Kamel et al [2006], platelet count started to fall 24 hours after infusion of ATG in pediatric renal transplant recipients and the lowest level was found on 'Day 3' post-transplant period. Nevertheless, the level was not below normal i.e., 150x109/L [35]; and it reduced the incidence of graft thrombosis in children. In this patient, the timing was too early (20 hours after ATG infusion) and the level was dangerously low (30x109/L); it was never seen in former reports. This is one reason for doing case report.

Mild to moderate liver function abnormality was seen in patients aplastic anemia who received ATG for treatment; and it was probably due either a non-specific binding effect of ATG to hepatocytes or infection with an unidentified agent [36]. Sudden and severe hepatocyte toxicity was seen in this patient; onset was 20 hours after infusion of ATG. The hepatic profile results improved though the remaining organ failure progressed. The similar case report after receiving the first dose of equine ATG was seen in patient with allogeneic hematopoietic stem cell transplant; she was successfully treated with the rabbit form of antithymocyte globulin and equine ATG was withdrawn [37]. Severe acute hepato-toxicity was also seen in patients with allogenic stem cell transplant following therapy with ATG, according to one retrospective study [38]; it was reported in renal transplant recipients too [39]. Therefore, it highlighted the awareness of physician to avoid any potential hepatotoxic drugs. This is another reason for reporting. Acute lung injury or non-cardiogenic pulmonary oedema during or following infusion of ATG was reported in renal allograft recipients [40,41]; patients with aplastic anemia [42]; patients with liver transplant [43]; patients undergoing bone marrow transplant [44].

Although sudden dropped in blood pressure and cardiac arrest occurred 5 minutes after infusion of second dose of Basiliximab, it might also be related with ATG. It may be severe anaphylaxis of second dose of Basiliximab or biphasic reaction of its first dose. Moreover, it might also be related with initial hypersensitivity to ATG or combination of all reactions having additive effects. Furthermore, the patient might have autonomic neuropathy due to long standing diabetes mellitus; it aggravated sudden death. Fatal anaphylaxis to Basiliximab was mentioned by Barros as well as Sasaki [23,24]. Severe Cytokine Release Syndrome After Basiliximab Induction Therapy in lung transplant recipient was reported from US in 2018. As a rule of thumb, the balance of harms and benefits are always judged prior to the usage of immunosuppressive drugs particularly in transplant medicine [7]. We usually aim for the best clinical benefits; however, we cannot anticipate the likelihood of fatal hypersensitivity reactions in our patients. Future research should be focused to identify high risk patients for severe anaphylaxis. Basiliximab induced acute pulmonary oedema was reported from Korea in 2018 [45].'

Conclusion

Awareness of severe anaphylaxis to ATG/ Basiliximab is very important though the incidence was very low. No reaction during the test dose infusion of ATG does not mean no anaphylaxis with succeeding therapeutic dose. Hypotension due to anaphylaxis usually manifests suddenly; nonetheless, it may develop gradually when the patient is under fluid infusion. One dose of ATG produced fatal multi-organ damage due to hypersensitivity reaction though anaphylactic shock recovered. Patients with diabetic kidney disease with end stage renal disease may have autonomic neuropathy; patient with autonomic neuropathy are vulnerable to sudden death.

Acknowledgements

The authors would like to thank the family for giving consent to this article. Also, to all doctors and nursing team for making great efforts in caring him. The authors acknowledged the following team: Professor Khin Maung Maung Than, our teacher, Professor Saw Yan Naing and team for uro-surgery, Dr Yan Naung for vascular surgery, Professor Yu Aye Latt and Anaesthesia/ICU team, Dr Tin Tin San for laboratory support, Dr Thet Tin Win for radiological support, Dr Hlawn Moe, Professor Kyaw Zay Ya and Professor Ko Ko Lwin for administrative support.

Declaration of conflict of interest

The authors declared no potential conflicts of interests with respect to authorship and publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting cases.

Funding

The authors received no financial support for publication of this article.

Informed consent

The informed consent for publication in this artic

le was obtained from wife of patient.

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DOI: 10.32474/JCCM.2023.05.000214