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Case Report

A-68-Years-Old Man with Thrombocytopenia, Acute Liver Injury, DIC and Non-Cardiogenic Pulmonary Oedema on Early Post-Transplant Period Following ABO Matched Living Donor Kidney Transplant: Lessons Learnt

Khin Phyu Pyar[1]*, Moe Zaw Myint[2], Win Kyaw Shwe[3], Soe Moe[4], Yan Naung[5], Yan Naung Win[6], Myo Swe Htay[5], Nyan Lynn[7], Thet Zaw Myat Cho[8], Phyo Min Zaw[9], Sai Aik Hla[2], Zin Zin Aung[10], Myo Maung Maung[10] and Aung Kyaw Khine[11]

[1]Professor and Head/ Senior Consultant Physician and Nephrologist, Department of Medicine/Nephrology, Defence Services Medical Academy/ No. (1) Defence Services General Hospital (1000-Bedded), Myanmar

[2]Senior Consultant Physician, No. (2) Defence Services General Hospital (1000-Bedded), Nay Pyi Taw, Myanmar

[3]Consultant Nephrologist, Department of Nephrology, No. (2) Defence Services General Hospital (1000-Bedded), Myanmar

[4]Consultant Anesthetist, Department of Anaesthesia, No. (2) Defence Services General Hospital (1000-Bedded), Myanmar

[5]Consultant Cardiovascular Surgeon, Department of Cardiac Surgery, No. (2) Defence Services General Hospital (1000-Bedded), Myanmar

[6]Consultant Uro-surgeon, Department of Urology, No. (2) Defence Services General Hospital (1000-Bedded), Myanmar

[7]Consultant Pathologist, Department of Pathology, No. (2) Defence Services General Hospital (1000-Bedded), Myanmar

[8]Consultant Radiologist, Department of Radiology, No. (2) Defence Services General Hospital (1000-Bedded), Myanmar

[9]Consultant Microbiologist, Department of Microbiology, No. (2) Defence Services General Hospital (1000-Bedded), Myanmar

[10]Nephrologist, Department of Nephrology, No. (2) Defence Services General Hospital (1000-Bedded), Myanmar

[11]Nephrology Fellow, Department of Nephrology, Defence Services Medical Academy, Myanmar

***Corresponding author:** Khin Phyu Pyar, Professor and Head/ Senior Consultant Physician and Nephrologist, Department of Medicine/Nephrology, Defence Services Medical Academy/ No. (1) Defence Services General Hospital (1000-Bedded), Yangon, Myanmar.

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Case Summary

A-68-years-old monk had long standing diabetes mellitus; it was complicated with both microvascular and macrovascular sequelae. He had multiple comorbid conditions: diabetic nephropathy and end stage renal disease; maintenance hemodialysis for 2years; proliferative retinopathy; coronary artery disease; 2 stents in LAD; right hemiparesis due to cerebral infarct; hypertension; obstructive sleep apnoea; COAD; obesity; and diabetic foot ulcer on right big toe. He received living ABO matched kidney transplant from his nephew who was 30years-old. He had Basiliximab as induction therapy together with triple immunosuppressive therapy: steroid, mycophenolate mofetil and tacrolimus. He developed multiple complications; staphylococcal septicaemia; thrombocytopenia; DIC, delayed graft function, hepatic encephalopathy, acute liver injury on post-operative Day 3; non-cardiogenic pulmonary oedema on Day '9'; cardiac arrest on Day '9'.

Keywords: Thrombocytopenia, Acute liver injury, Non-cardiogenic pulmonary oedema, Renal transplant

Introduction

Renal transplant is the best renal replacement therapy for patients with End Stage Renal Disease (ESRD). In countries where the deceased donor transplant program is not established, living related ABO matched donors are the prime savers for them.

According to KDIGO guideline, the absolute contra-indications to transplant (recipient perspectives) are active infection, malignancy, dementia and poor compliance etc. The relative contraindications are old age, respiratory failure, pulmonary hypertension, decompensated cirrhosis and bleeding diathesis. There are several controversial issues on contraindications. Generally, patients with ESRD due to long standing diabetes mellitus has other multi-organ involvement and organ failure. Having multiple comorbidities is a high risk for morbidity and mortality not only intra-operative period but also post-operative period. There is no clear-cut decision on number of comorbidities for absolute contraindication to renal transplant. This case report gave some information in considering for living kidney transplant.

Case Presentation

A-68-years-old monk had long standing diabetes mellitus; it was complicated with both microvascular and macrovascular sequelae. He had diabetic nephropathy and end stage renal disease; maintenance hemodialysis for 2years; proliferative retinopathy; coronary artery disease; 2 stents in LAD; right hemiparesis due to cerebral infarct; hypertension; obstructive sleep apnoea; COAD; obesity; and diabetic foot ulcer right big toe. He had been on Rosuvastatin 10mg OD, Aspirin 80mg OD, Glyceryl trinitrate SR 26 mg BD, Nicorandil 5mg BD, Ivabradine 5mg BD, Allopurinol 50mg OD, trimetazidine MR 35mg BD, Bisoprolol 2.5mg OD and insulin. Echocardiogram revealed LVEF (48-52%); mild to moderate mitral regurgitation and trivial aortic regurgitation; mild LV dilatation (LVIDd 5.6cm); moderate tricuspid regurgitation; mild left ventricular hypertrophy; Grade 2 diastolic dysfunction; and hypokinesia in LAD territory. Coronary angiogram showed dense calcification in proximal part of left anterior descending coronary artery and long diffuse stenosis in right coronary artery compatible with two vessel coronary artery disease. Therefore, PTCA to LAD was done 10months prior to transplant. He received living ABO matched non-related kidney transplant from 30years-old man. Two right renal veins were anastomosed with external iliac vein; and renal artery was connected with external iliac artery. Total ischemic time was 135minutes; 55seconds for 1st warm ischemic time; 87minutes for cold ischemic time; and 48minutes for 2nd warm ischemic time. During the re-anastomosis of artery, the artery of the recipient was very hard and fragile. The vascular surgeon found some difficulties in vascular anastomosis; however, he could make it finally. His hemodynamic status was stable during surgery and post-operative period.

Induction therapy with Basiliximab 20mg 2 doses for 2 days was given at Day '0' and Day '4'; he received maintenance immunosuppression with prednisolone, tacrolimus and mycophenolate mofetil. Immediate post operative period (15.7.23) was fairly stable; blood pressure was 136/61mmHg with infusion dobutamine and noradrenalin; heart rate was 84/min; SpO_2 was 100% with O_2. Fluid infusion was maintained according to hourly urine output. If last hour urine output was more than 1,000 cc, only 1,000 cc was given. If last hour urine output was 500 cc to 1,000 cc, only 500 cc was given. If last hour urine output was less than 500cc, same amount as last hour urine output was given as total volume of intravenous fluid for succeeding hour.

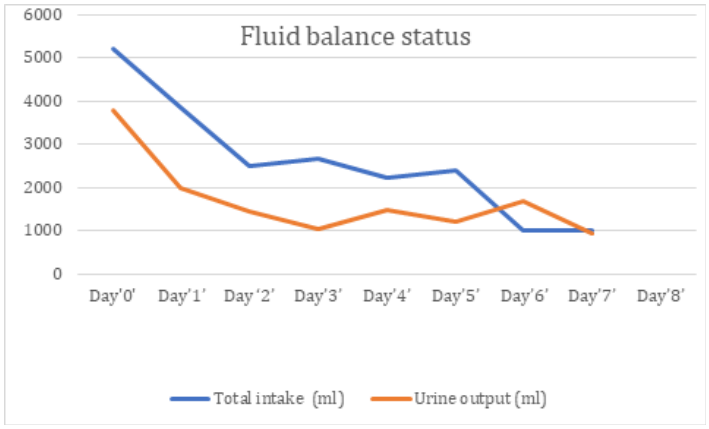

Figure 1: Changes in fluid balance (total intake & urine output).

On 1st Post op (16.7.23), temperature rose to 101°F; blood pressure was 110/80mmHg with infusion dobutamine and noradrenalin; heart rate was 123/min (tachycardia); SpO_2 was 98% with O_2; and, few bilateral basal crepitations were heard in both lungs. Total positive balance including OT was 3.3liters (1440cc on Day '0' plus 1865cc on Day '1'); body weight gain was 5.4Kg (61Kg on pretransplant day to 66.4Kg on Day '1'). Urine output was nearly 2,000cc on first Day; it dropped to 1,500cc on next day; 1,000cc on Day '3';

less than 950cc on Day '7'. His body weight was gradually increased from 61Kg to 66.4Kg on Day '1'; 68.4Kg on Day '2'; 69.4Kg on Day '5'; 69.5Kg to 70.4 Kg on Day '7'. The fluid balance status was revealed in Figure 1 (Figure 1).

As shown in Figure 2, platelet count dropped to $162x10^9$/L on immediate post-operative period and it continued to fall gradually to $56x10^9$/L on Day '7'. Hemoglobin decreased to 8.6gm% on Day '1' as demonstrated in Figure 3. Figure 4 reveals changes in total WBC count. The total WBC count rose to 13x109 /L on Day '2'; $16x10^9$ /L on Day '5'; then, decreased to 11x109 /L on Day '8'. Although the ulcer on big toe was clean and wound swab culture was sterile, Staphylococci hominis was grown in blood culture. Therefore, linezolid and imipenem and cilastatin were given according to sensitivity result. Blood sugar was controlled well with soluble insulin. Total WBC count was responding; however, the patient developed jaundice and serum bilirubin level increased. Figure 5 shows changes in serum bilirubin level. He was fully conscious and orientated; though he was irritable. Liver parenchymal enzymes started to rise on Day '2'; ALT was 8 times normal (396.5U/L) and AST was 18 times normal (845.4IU/L) on Day '7'. They were illustrated in Figure 6,7. Serum bilirubin rose to 3mg% on Day '7'. Tacrolimus level done on 'Day 5" was raised (17.4ng/ml); therefore, the dose was reduced. The serial reduction in serum creatinine and blood urea were demonstrated in Figure 8,9. The vital signs (blood pressure 130/80mmHg, pulse rate 80/minutes, SaO_2 96% on air) were stable for 3 days i.e., till Day '8' evening. At 20:00Hr (23.04.23) Day '8', he had sudden onset of dyspnoea; SaO_2 dropped to 90% on air; blood pressure 100/70 mmHg; pulse rate 98/minute; both lungs were full of crackles (Figures 2-10).

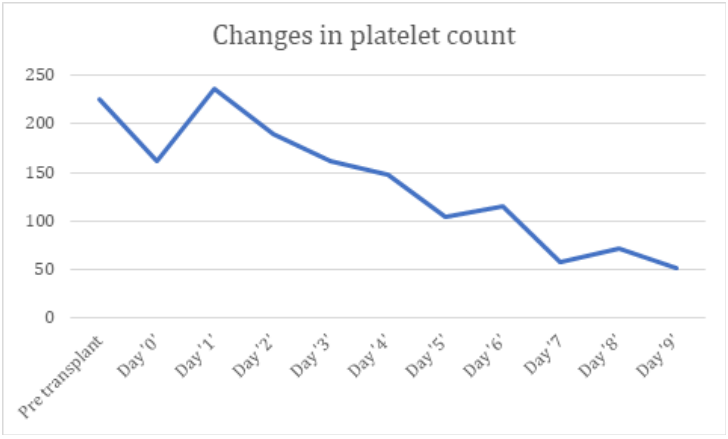

Figure 2: Serial changes in platelet count ($x10^9$ /L).

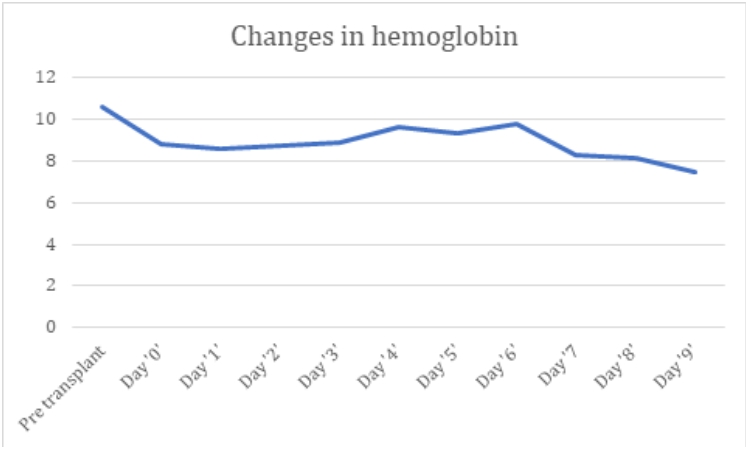

Figure 3: Serial changes in hemoglobin (gm%).

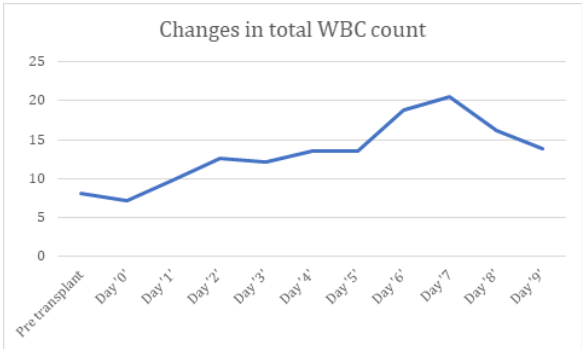

Figure 4: Serial changes in total WBC count (x10^9 /L).

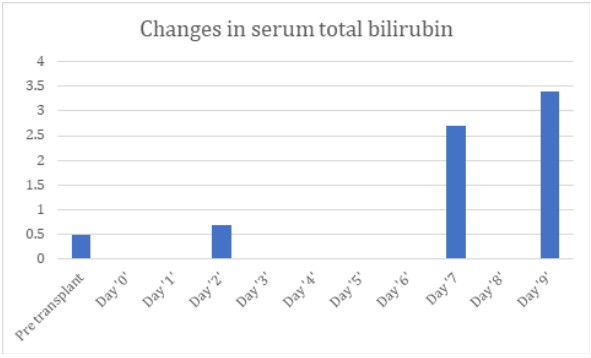

Figure 5: Serial changes in total bilirubin (mg%).

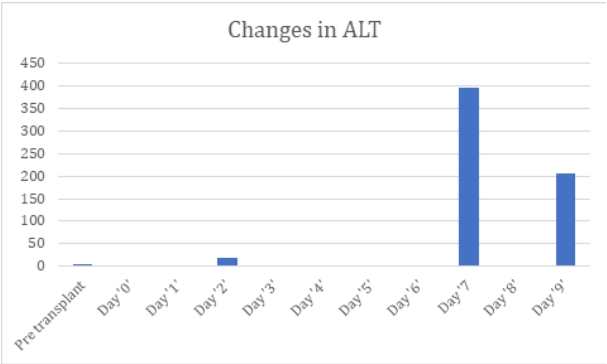

Figure 6: Serial changes in blood ALT (U/L).

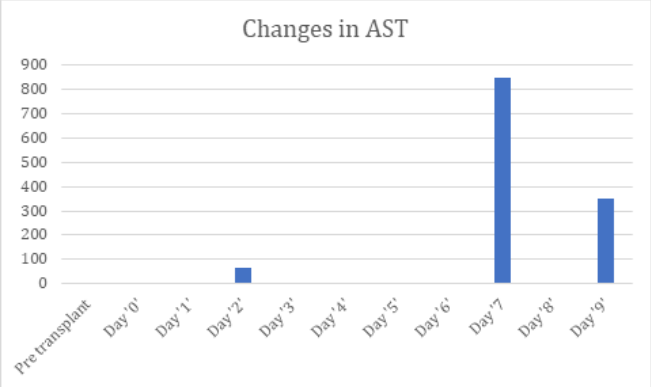

Figure 7: Serial changes in blood AST (U/L).

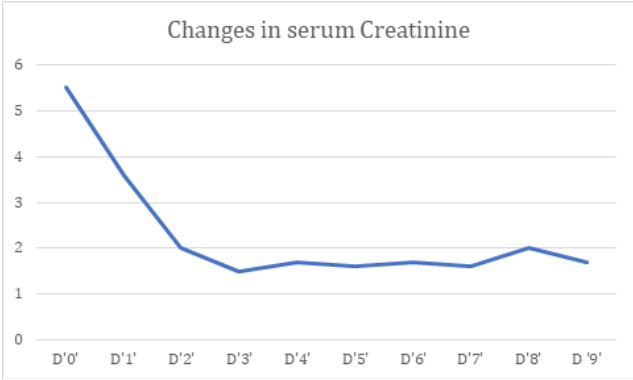

Figure 8: Serial changes in serum creatinine (mg%).

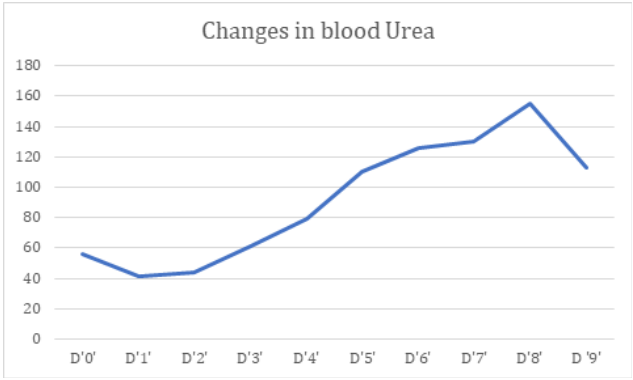

Figure 9: Serial changes in blood urea (mg%).

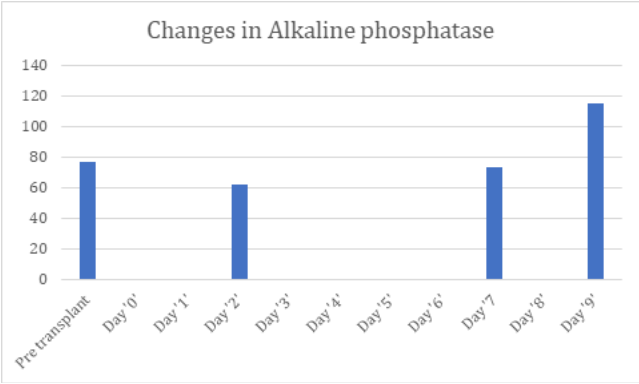

Figure 10: Serial changes in blood Alkaline phosphatase (U/L).

ECG showed sinus tachycardia (100/minute) without evidence of acute coronary syndrome or pulmonary embolism. Echocardiogram revealed no new wall motion abnormality or acute right ventricular strain. Therefore, the patient had acute non-cardiogenic pulmonary oedema. It was not due to kidney as the intake and output status was balanced though there was slow fall in serum creatinine. However, we decided to do hemodialysis in addition to high concentration oxygen therapy. The cause of acute non-cardiogenic pulmonary oedema was likely to be due to delayed reaction of Basiliximab.

While doing hemodialysis, intravenous acetyl cystine was given as a supportive care to drug induced acute liver injury. For further decreased in SaO_2, the intensivist did tracheal intubation and ventilatory support. Nonetheless, there was sudden cardiac arrest and cardiopulmonary resuscitation did not revive him.

Discussion

As shown in Figure 2, platelet count dropped to $162x10^9$/L on immediate post-operative period. It was unlikely to be due to DIC on immediate post-operative period. Moreover, the likelihood of

hemolytic uremic syndrome was impossible because the patient had good urine output with satisfactory fall in serum creatine and the blood film did not reveal evidence of hemolysis. Therefore, the cause of thrombocytopenia was likely to be due to hypersensitivity reaction to Basiliximab; it's hypersensitivity reaction also attributed to non-cardiogenic pulmonary oedema on Day '8'. There were some case reports on similar events following Basiliximab; drug-induced thrombocytopenia was usually abrupt onset and it could be associated with bleeding [1]. Luckily, the patient did not have overt bleeding. The likely cause of thrombocytopenia in kidney transplantation is generally due to either myelosuppression from immunosuppressants or idiosyncratic immune reaction to ATG/ Basiliximab.

Gradual fall in platelet count ($56x10^9$/L on Day '7') and neutrophil leucocytosis with Staphylococci septicaemia in this elderly diabetic immunocompromised patient pointed out that the patient had DIC. The reduction in total WBC count from $16x10^9$ /L on Day '5' to $11x10^9$ /L on Day '8' indicated that the patient had fairly good response to antibiotics-linezolid, imipenem and cilastatin which were given according to sensitivity results.

Drug induced liver injury in kidney transplant recipients was not uncommon and it was recorded in 25% of them [2]. They also found that the incriminated drugs were immunosuppressants, diureties, antimicrobials and painkillers. They were managed principally by dose reduction, momentary drug cessation or switch to another drug. In addition, Contreras et al suggested to use azathioprine, lipid lowering drugs (Statin) and other hepatotoxic drugs with caution in renal transplant recipients; close monitoring of liver function was crucial particularly in patients with chronic viral hepatitis [3]. This patient had acute liver injury; ALT was 8 times normal and AST was 18 times normal. The patient had multifactorial reasons for transaminitis; septicaemia; drug induced liver injury due to linezolid, imipenem and cilastatin, mycophenolate mofetil, tacrolimus, rosuvastatin. Drug induced liver injury due to tacrolimus produced cholestatic pattern; they also mentioned that it was common in young age, low body weight and abnormal baseline serum alkaline phosphatase level [4]. Therefore, acute liver injury in this patient was unlikely to be related with tacrolimus; he had high BMI; he was not young age; serum alkaline phosphatase was normal. Although Thirot and colleagues found that linezolid had many adverse effects notably hematological disorders (anemia, thrombocytopenia), neuropathy, or lactic acidosis; drug induced liver injury due to linezolid was likely in this patient. Early identification of the offending drug and swift to non-hepatotoxic drugs was important; however, the choice of antibiotics in this patient was according to sensitivity results [5]. Tacrolimus drug level was monitored and it was within therapeutic range; and the serum level of mycophenolate mofetil could not be done.

Managing acute liver injury in this patient was challenging. Persistent transaminitis may lead to acute liver failure of varying severity. On the contrary, reducing or stopping immunosuppressive medications in these events may provoke acute rejection. It was the delicate dilemma of balancing transaminitis and rejection from adjustments of immunosuppressive regimen. Furthermore, dose reduction of antibiotics for acute liver injury may augment septicaemia and multi-organ failure. It is one reason for case writing.

This patient had living kidney transplant. Sola-Porta found that early post-kidney transplant hypertransaminasemia was frequent and usually transient event. It was related to the kidney donor type; the frequency of developing acute liver injury in deceased donor kidney transplant recipients was higher than that of living donor transplant recipient. They also recognized that it was more common in uncontrolled circulatory death donor recipients than brain-death donors and controlled circulatory death donors [6]. This patient received kidney from ABO matched living donor; therefore, this finding was not applicable in this patient.

If the patient did not have Staphylococci septicaemia, linezolid, imipenem and cilastatin were not be prescribed; subsequently he would have not developed acute liver injury. Having irritability in this patient with normal sodium and calcium level might be early features of hepatic encephalopathy though flapping tremor and constructional aprexia were not detected.

In this patient, ECG and echocardiogram at the time of pulmonary oedema excluded acute myocardial infarction and pulmonary oedema. It was not due to delayed graft function as the intake and output status in this patient was fairly balanced though there was slow fall in serum creatinine. Therefore, the patient had acute non-cardiogenic pulmonary oedema/acute lung injury. However, we decided to do hemodialysis in addition to high concentration oxygen therapy. The cause of acute non-cardiogenic pulmonary oedema was likely to be due to delayed reaction of Basiliximab although one report on kidney transplant recipient with acute dyspnoea was blamed to acute lung injury caused by mycophenolate sodium [7]. Having thrombocytopenia in immediate post-operative period pointed out hypersensitivity reaction to Basiliximab. Basiliximab It was also reported as safe and tolerable [8]; it was 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, incidences of Cytomegalovirus infection, leucopenia, and thrombocytopenia were significantly lower in Basiliximab group than ATG group [11-14]. Life-threatening reactions due to Basiliximab were reported following re-exposure to basiliximab in recipients [15]. Severe non-cardiogenic pulmonary oedema within 2 days of renal transplantation following basiliximab induction therapy was mentioned in adolescents as well as young pediatric patients [16,17]. This is one reason for doing case report.

Acetyl cystine was reported as favorable agent in kidney transplant; however, the indication in this patient was for drug induced liver injury [18]. While doing hemodialysis, intravenous acetyl cystine was given as a supportive care to drug induced acute liver injury. For further decreased in SaO2, the intensivist did tracheal intubation and ventilatory support; it was shortly followed by car-

diac arrest. The event was unlikely to be due to acetyl cystine because most of the reports mentioned that cutaneous reaction was the common side effects of acetyl cystine. Cutaneous reactions and angioedema were common anaphylactoid reactions to intravenous acetyl cystine was reported in one patient; it was prescribed for acetaminophen overdose [19-22]. Nonetheless, one report described 'a-40-year-old brittle asthmatic patient who died after treatment with intravenous N-acetylcysteine'. Asthma is a risk factor for adverse reactions to N-acetylcysteine and special caution should be exercised in its use in brittle asthmatic patients [23]. Therefore, physicians should aware of hypersensitivity reaction to intravenous acetyl cystine particularly in patients with acute dyspnoea: pulmonary oedema (both cardiogenic and non-cardiogenic), COAD, bronchial asthma and obstructive sleep apnoea. This is the important message we would like to convey.

In patients with long standing diabetes mellitus, microvascular complications are usually simultaneous; diabetic kidney disease and retinopathy. This patient had florid microvascular sequelae. Moreover, he had multiple macrovascular effects: coronary artery disease, cerebrovascular accident, peripheral vascular disease and peripheral neuropathy. Furthermore, he had infected foot ulcer; would swab revealed the growth of Staphylococcus aureus; and Xray foot revealed no evidence of chronic osteomyelitis. According to culture and sensitivity results, linezolid and Baquer (Imipenem and Cilaststini combination) had sensitivity. In addition to multi-organ sequelae, he had obesity (BMI 30kg/m) and obstructive sleep apnoea. Besides, his blood pressure required 3 drugs to control at 160/90mmHg. The question was 'Was it worth to do living kidney transplant in this patient with multi-organ involvement/failure?'

In fact, the patient would have carried on maintenance hemodialysis. If the patient had not undergone renal transplant, he would have survived. He might have another vascular event as he had multiple risks. The academic board would have rejected him for living kidney transplant. We should review the criteria for absolute contraindication to living donor kidney transplant recipient particularly diabetes mellitus with multiple comorbidities [24-34].

Conclusion

Thrombocytopenia may result from hypersensitivity reaction to Basiliximab. Early recognition and awareness of drug induced liver injury is crucial. Balancing transaminitis and drugs (immunosuppressants and antibiotics) in early post-operative period in kidney transplant is not easy. Basiliximab induced acute lung injury/non-cardiogenic pulmonary oedema should be considered after exclusion of common vascular events like acute coronary syndrome, acute pulmonary oedema and pulmonary embolism. Acetyl cystine should be used very cautiously in patient with acute dyspnoea. We should review the criteria for absolute contraindication to Potential living donor kidney transplant recipient with diabetes mellitus and multiple comorbidities/end organ damage should not be prioritized in the waiting list for living donor kidney transplant. Individualized approach should be considered in living donor kidney transplantation.

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Informed Consent

The informed consent for publication in this article was obtained from both recipient and donor.

Ethical Approval

Our institution does not require ethical approval for reporting cases.

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Conflict of Interest

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

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