Acute graft dysfunction secondary to rhabdomyolysis following intra-operative lower limb ischemia in a renal transplant recipient

Umapati Hegde[1*], Amitkumar Jojera[2], Shailesh Soni[3], Mohan Rajapurkar[4]

[1]Vice Chairman, [2]Consultant, [3]Consultant Pathologist and Head, [4]Director of Postgraduate Service and Research, [1,4]Dept. of Nephrology, [2,3]Dept. of Pathology, Muljubhai Patel Society for Research in Nephro Urology, Dr V V Desai Road, Nadiad, Gujarat, India

***Corresponding Author: Umapati Hegde**
Email: umapatih@gmail.com

Abstract
We present a case of second renal transplant recipient, who developed myoglobinuric Acute Kidney Injury (AKI). He was given Basiliximab induction with Cyclosporine, Mycophenolate and steroid as immunosuppression. The blood supply to both the lower limb was from left external iliac artery due to due to ligation of right external iliac artery fungal aneurysm following nephrectomy of the previous graft in in right iliac fossa. During present transplant vascular anastomosis left external iliac artery was clamped. He developed both lower limb pain in post-operative period. Graft biopsy showed acute tubular necrosis and no evidence of rejection or clacineurin toxicity. His urine and serum myoglobulins were raised. Immuno-histochemical (IHC) staining of the biopsy with anti- myoglobin antibody showed presence of myoglobin in the tubular cells.

Keywords: Acute kidney Injury, Rhabdomyolysis, Renal transplant, Muscle ischemia.

Introduction
Renal allograft survival rates after renal transplant has improved with potent immunosuppressant and better understanding of immunology and immunosuppressive drugs. Acute graft dysfunction is commonly due to acute rejection or calcineurin toxicity but myoglobinuric Acute Kidney Injury (AKI) is uncommon. Most of the myoglobinuric AKI in post-transplant period are drug induced. We present a rare case of renal transplant patient who developed rhabdomyolysis and myoglobinuric AKI due to intra-operative lower limb muscle ischemia.

Case History
17 year boy with chronic kidney disease secondary to Posterior Urethral Valve(PUV) was evaluated for preemptive renal transplantation. Mother was evaluated as the kidney donor and found to be suitable for donation. He underwent transplantation. He had immediate graft function and discharged on 10th post-operative day (POD) with Serum creatinine 1.1mg/dl. On 29th POD he presented with fever & acute graft dysfunction (Creatinine of 3.86 mg/dl). His graft biopsy showed acute tubular necrosis (ATN). On 34th POD, he had graft site pain and swelling. There was decreased perfusion by Doppler studies. He underwent graft nephrectomy. There was a pseudo-aneurism of the external iliac artery. The external iliac artery had to be ligated during graft nephrectomy. The histology showed mucormycosis. He was treated with injectable amphotericin followed by oral Iitraconazole in adequate doses. Right lower limb was revascularised by left femoral artery to right femoral artery using polytetrafluoroethylene (PTFE) graft (Fig. 1). He was found to have HCV infection due to Genotype 3 and treated with PEGylated Interferon for 6 months. His had rapid virological response (HCV undetectable in 1 month). He underwent second renal transplantation with donor being his paternal Aunt. He was given Basiliximab induction with 3 drug immunosuppression consisting of Cyclosporine, Mycophenolate and Prednisolone. The graft was placed in left iliac fossa. Graft artery was anastomosed with left external iliac artery. During the vascular anastomosis external iliac artery was clamped. Total ischemic time was 60 minutes with Warm ischemic time of 8 minutes. Post-transplant he had decrease in urine output and creatinine remained at 6 mg/dl. There was no need for dialysis and he had urine output of 2-2.5liters. He complained of pain in his lower limbs. He underwent re-exploration and good blood supply to the graft was confirmed. Doppler evaluation also confirmed the good vascularity to the graft kidney with Resistive index of 0.8. Graft biopsy was performed, which showed ATN with tubular casts. There was no evidence of rejection (C4d negative). Immuno-histochemical (IHC) staining for myoglobin showed presence of myoglobin in renal tubular cells as well as in the tubular casts (Fig. 2). His serum electrophoresis was normal. His serum and urine samples revealed markedly elevated myoglobin (Serum Myoglobin -35mg/L and Urine myoglobin- 7.4mg/dl) levels. Serum Creatinine phosphokinase (CPK) levels were elevated after 24 hours (560 U/L). His creatinine slowly improved and on 50th day it was 1.7mg/dl.

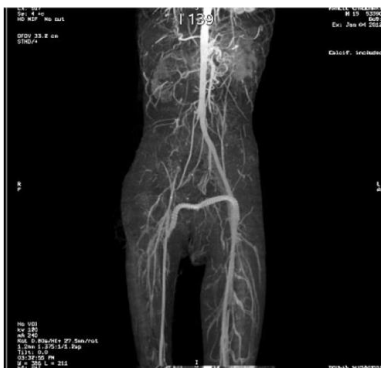

Fig. 1: CT Aortogram showing absence of right common iliac, external iliac and internal iliac artery.

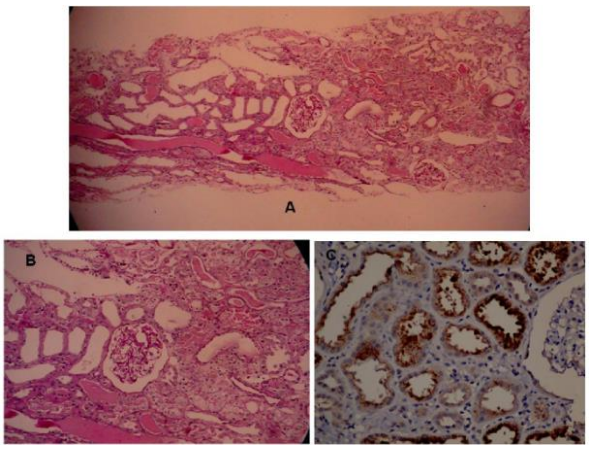

Fig. 2: A pas showing with tubular cast and no evidence of rejection. B Higher magnification (20X) showing no evidence of rejection and tubular cast. C. Immunohistochemistry showing positive with anti-myoglobulin antibodies.

Discussion

There are many causes of acute renal failure (ARF) in the renal transplant. Common etiologies include acute rejection, calcineurin inhibitor toxicity and ATN. Rhabdomyolysis is an uncommon complication after transplant. The reported incidence rate of Rhabdomyolysis in renal transplant recipients varies from 19[1] -137[2] cases per 100 000 person-years, which is high compared to the general population. Rhabdomyolysis may be because of eight basic categories: (a) direct muscle injury, (b) drugs and toxins, (c) genetic disorders (decreased energy production), (d) infections, (e) excessive muscular activity, (f) ischemia, (g) electrolyte and endocrine/metabolic disturbances, and (h) immunologic diseases. Acute kidney injury due to rhabdomyolysis in renal transplant recipients is predominantly drug induced. Calcineurin inhibitors (Cyclosporine, tacrolimus) with other myotoxic drugs such as statins, colchicine, Iitraconazole, mibefradil and clarithromycin have been shown to increase the risk of Rhabdomyolysis. Cyclosporine causes more Rhabdomysis than Tacrolimus due to following reasons. (i) Cyclosporine has also been shown to inhibit respiration in isolated mitochondria, resulting in mitochondrial dysfunction.[3] (ii) Hypomagnesaemia caused by cyclosporine can lead to mild rhabdomyolysis.[4,5] (iii) Several pharmacokinetic studies have demonstrated that cyclosporine increases statin drug levels more as compared to Tacrolimus. (iv) Hyperlipidaemia[2] is a frequent complication of cyclosporine therapy. This adverse effect could obligate statin use and possibly necessitate higher statin dosing, both of which would presumably increase the risk of Rhabdomyolysis. Many intraoperative conditions can lead to skeletal muscle ischemia, including prolonged immobilization, tight dressings, malignant hypertension and vasospasm.[6]

Muscle ischemia causes interferences in the oxygen delivery to the cells there by limiting the production of ATP. ATP depletion leads to high intracellular Ca^{2+} concentration, which activates neutral proteases, phospholipases, and other degradative enzymes that cause myofibril and membrane damage. As the myocyte degenerates, intracellular compounds are extruded into the extracellular fluid and plasma. These compounds include myoglobin, aldolase, potassium, uric acid, lactate dehydrogenase, aspartate transaminase, creatine kinase (CK), and phosphate. Myoglobin is the iron- and oxygen-binding protein of striated muscle. Myoglobin dissociates into ferrihaemate and globin in acidic pre-urine. Ferrihaemate has a direct cytotoxic effect on tubular epithelial cells mediated by free radicals, whereas myoglobin binds Tamm–Horsfall proteins; the latter may lead to cast formation and distal tubular obstruction. In the presence of acidosis and hypovolemia, myoglobin reacts with Tamm-Horsfall protein and precipitates into casts, which may then obstruct tubular flow. Hypovolemia and overall decreased renal perfusion also can compound renal injury. Lysis of as little as 100 g of skeletal muscle results in myoglobinuria.[15] Destruction of 200 g of muscle causes a noticeable reddish-brown discoloration of the urine. Specific immunostaining is helpful in differentiating these casts from myoglobin casts. Differentiation of myoglobinuric *versus* hemoglobinuric injury may also be done by examination of the patient's blood and urine. Circulating myoglobin, in contrast to hemoglobin, is not highly protein bound and is readily filtered into the urine. Thus, rhabdomyolysis rarely results in serum myoglobin concentrations >25 mg/L, whereas serum discoloration occurs when concentrations are >100 mg/L. Therefore, light pink discoloration of serum is very unusual in rhabdomyolysis and should suggest additional hemolysis. Serum myoglobin levels rise early in the course and disappear after 24 hours. Serum CK, the most sensitive biochemical indicator of rhabdomyolysis, increases 2 to 12 h after the onset of muscle injury and peaks at 3 to 5 days.[8] Serum creatinine kinase (CK) levels correlate with the degree of muscle injury and can be used to assess the severity of rhabdomyolysis.

Rhabdomyolysis may be asymptomatic or may lead to acute renal failure which may lead to graft loss in transplant recipients. Usually present with malaise, fever, abdominal pain, nausea vomiting and dark colored urine. Early in the course of illness, hyperkalemia, hyperuricemia, hyperphosphatemia, and hypocalcaemia are frequently seen. Measurement of urine electrolytes and creatinine allows for computation of fractional excretion of sodium, which may help differentiate AIRF caused by rhabdomyolysis (> 1%) from prerenal azotemia (< 1%).

In our case, patient had ligation of the right external iliac artery. Both the lower extremities are supplied from left common iliac artery. Right leg blood supply is maintained via the graft from left external iliac artery to right femoral artery. There was no collateral circulation from right side supplying the blood to left lower limb. Cross clamping the left external iliac artery during anastomosis of the graft kidney to left external iliac artery, lead to ischemia of the both the lower limbs. The diagnosis of Myoglobinuric AKI was made by raised serum and urinary myoglobin levels. Graft biopsy was subjected to immuno-

histochemistry staining for myoglobin.[7] Intratubular casts were positive for myoglobin on immunoperoxidase staining with an antibody against human myoglobin, confirming the diagnosis of acute myoglobinuric renal failure. We could have prevented the rhabdomyolysis using clamps which do not completely occlude left external iliac artery lumen.

The therapy of Rhabdomyolysis consists of stopping the offending agent, adequate hydration and watchful expectancy. The levels of Calcineurin inhibitors should be lowered to reduce concomitant Calcineurin nephrotoxicity. Assessment of serum potassium levels is essential for averting malignant cardiac dysrhythmias in rhabdomyolysis-induced AKI. Volume resuscitation with isotonic crystalloid is the primary therapy for preventing rhabdomyolysis-induced renal injury. Infusions of 10 to 15 mL/kg/hour of normal saline should be used initially, followed by hypotonic saline after the initial resuscitation is completed. Increasing intravascular volume increases glomerular filtration rate (GFR), dilutes myoglobin and other nephrotoxins extruded during muscle injury, and improves overall oxygen delivery to ischemic tissue. Dehydration and metabolic acidosis favor precipitation of myoglobin in renal tubules, enhancing and exacerbating its nephrotoxic effects. Urinary alkalization is thought to enhance renal myoglobin clearance by increasing its solubility. Mannitol should be given only after adequate volume resuscitation has occurred and should be avoided in cases of oliguria. Mannitol also may draw fluid from the interstitial space, thus decreasing muscle edema in a concomitant compartment syndrome. It increases the urine flow and prevents the intratubular obstruction by preventing cast formation. Dialysis and plasmapheresis may be needed till the recovery of graft function.

A rapid identification of the cause of rhabdomyolysis is important as any suspected cause to induce rhabdomyolysis should be discontinued. Adequate fluid therapy and diuresis are also essential. When necessary, hemodialysis should be applied to maintain electrolytes and plasmapheresis may be indicated in severe case of rhabdomyolysis to remove myoglobin.

Conclusion

Rhabdomyolysis is a rare complication in renal transplant which can occur due to ischemia to the skeletal muscles and calcineurin inhibitors. High degree of suspicion and early therapy improves the graft outcome. Adequate hydration, reducing the calcineurin dose and preventing complications hastens the recovery of Acute Kidney injury.

Source of funding

None.

Conflict of interest

None.

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