Clinical Case Report

Medicine®

OPEN

Ischemia reperfusion injury in kidney transplantation

A case report

Carole Philipponnet, MD[a,*], Julien Aniort, MD[b], Cyril Garrouste, MD[c], Jean-Louis Kemeny, MD, PhD[d], Anne-Elisabeth Heng, MD, PhD[e]

Abstract

Rationale: Kidney transplantation is considered the best treatment for patients with end stage renal disease. Ischemia- reperfusion injury (IRI) is an evitable event after deceased donor transplantation and influences short term and long term graft outcome. Few data on IRI's histology in the setting of kidney transplantation are available in the literature despite its frequency and its severity.

Patient concerns: A 64-year-old patient was admitted for his 1st kidney transplantation. There were no pre-existing immunization. The surgery proceeded without complications; with cold ischemia estimated at 37 h 50 min and warm ischemia at 44 min. The immunosuppression protocol was as follows: induction by thymoglobulins, mycophelonate mofetil, corticosteroids. Few hours after transplantation, the patient remained anuric and the biological assessment highlighted in addition to renal failure, hyperlactatemia at 5 mmol/L and a high increase in lactate deshydrogenase (LDH) at 5239 U/L. An abdominopelvic angio-scanner was performed urgently to eliminate the hypothesis of thrombosis of the artery or vein of the graft. A kidney biopsy was performed the day after the transplant and revealed massive lesions of acute tubular necrosis including apoptosis, autophagy-associated cell death, and necrosis. Microvascular dysfunction with increased vascular permeability and endothelial cell inflammation were also present. Activation of coagulation is represented by thrombi in the lumens of the glomerular capillaries.

Diagnosis: The diagnosis was ischemia reperfusion injury responsible for delayed graft function (DGF).

Interventions: Immunosuppressive regimen was delayed use of calcineurin inhibitors, mycophenolate mofetil, and corticosteroids.

Outcomes: At 1 year post transplant, the patient has a renal autonomy with a graft function stable and physiological proteinuria.

Lessons: The main clinical consequences of IRI in kidney transplant are DGF, acute and chronic graft rejection, and chronic graft dysfunction. Reducing IRI is one of the most relevant challenge in kidney transplantation.

Abbreviations: ATP = adenosine triphosphate, CMV = cytomegalovirus, DGF = delayed graft function, IRI = ischemia reperfusion injury, LDH = lactate deshydrogenase.

Keywords: delayed graft function, ischemia reperfusion, kidney transplant outcome, microvascular dysfunction, tubular necrosis

1. Introduction

Ischemia reperfusion is a pathological condition due to an initial restriction of blood supply to an organ followed by the subsequent restoration of perfusion and concomitant reoxygenation.[1] Ischemia reperfusion injury (IRI) contributes to morbidity and mortality in a wide range of pathologies like acute coronary syndrome, acute kidney injury, intestinal ischemia and reperfusion, stroke, sickle cell disease, sleep apnea, and solid organ transplantation.[1]

Kidney transplantation is considered as the best treatment for patients with end stage renal disease. The IRI is an evitable event after deceased donor transplantation and influences short term and long term graft outcome.[2]

Understanding IRI physiopathology is essential to improve it management and graft survival. We describe renal histopathology of severe IRI lesions in a patient after 1st kidney transplantation with delayed graft function (DGF); the patient has provided informed consent for publication of the case.

2. Case report

A 64-year-old patient was admitted to the nephrology department for his 1st kidney transplantation. His main medical antecedents were autosomal dominant polycystic kidney disease requiring chronic hemodialysis for 2 years and a right nephrectomy. There were no pre-existing immunization to

Editor: N/A.

The authors have no conflicts of interest to disclose.

[a] Department of Nephrology, Dialysis and Transplantation, [b] Department of Nephrology, Dialysis and Transplantation, UFR Medecine, [c] Department of Nephrology, Dialysis and Transplantation, [d] Department of Anatomy and Pathology, [e] Department of Nephrology, Dialysis and Transplantation, Clermont Ferrand, University Hospital, Clermont Ferrand, France; UFR Medecine, Clermont Ferrand, France.

[*] Correspondence: Carole Philipponnet, Nephrology, Dialysis and Transplantation Unit, Clermont Ferrand University, Hospital, Clermont Ferrand 63000 France (e-mail: cphilipponnet@chu-clermontferrand.fr).

Medicine (2018) 97:52(e13650)

Received: 9 August 2018 / Accepted: 20 November 2018

http://dx.doi.org/10.1097/MD.0000000000013650

kidney transplantation. The donor was a 52-year-old obese, diabetic type 2 man who died of brain death after a cardiac arrest resuscitated after 40 min of reanimation. Cytomegalovirus (CMV) status was donor positive/recipient negative. The surgery proceeded without complications; with cold ischemia estimated at 37 h 50 min and warm ischemia at 44 min. The immunosuppression protocol was as follows: induction by thymoglobulins, mycophelonate mofetil, corticosteroids. Few hours after transplantation, the patient remained anuric and the biological assessment highlighted in addition to renal failure, hyperlactatemia at 5 mmol/L and a high increase in lactate deshydrogenase (LDH) at 5239 U/L.

An abdominopelvic angio-scanner was performed urgently to eliminate the hypothesis of thrombosis of the artery or vein of the graft; it showed a heterogeneous enhancement of the graft.

A kidney biopsy was performed the day after the transplant (Fig. 1).

In light microscopy, we observed acute tubular injury with loss of epithelial lining with desquamation of tubular cells, necrosis and dilatation of the tubules, cytoplasmic debris and hyaline casts in the tubular lumens, and tubular vacuolization. Interstitial tissue was normal without inflammatory infiltrate. Eight Glomeruli were present, there architecture were respected but some thrombi were present in the lumens of the glomerular capillaries. Microvascular lesions were also present, especially in the medulla part, with massive congestion of peritubular capillaries filled with red blood cells and interstitial hemorrhagic suffusion plaques.

The immunofluorescence study was negative.

The diagnosis was ischemia reperfusion injury responsible for delayed graft function and release of several toxins (lactates, LDH...). The causes of IRI were: donor factor: brain and cardiac arrest; recipient factor: male gender; storage preservation: duration of storage and long cold ischemia.

Immunosuppressive regimen was delayed use of calcineurin inhibitors, mycophenolate mofetil, and corticosteroids. Apart from an absence of graft function recovery, there was no other immediate complications. The patient was weaned off hemodialysis 1 month after kidney transplant.

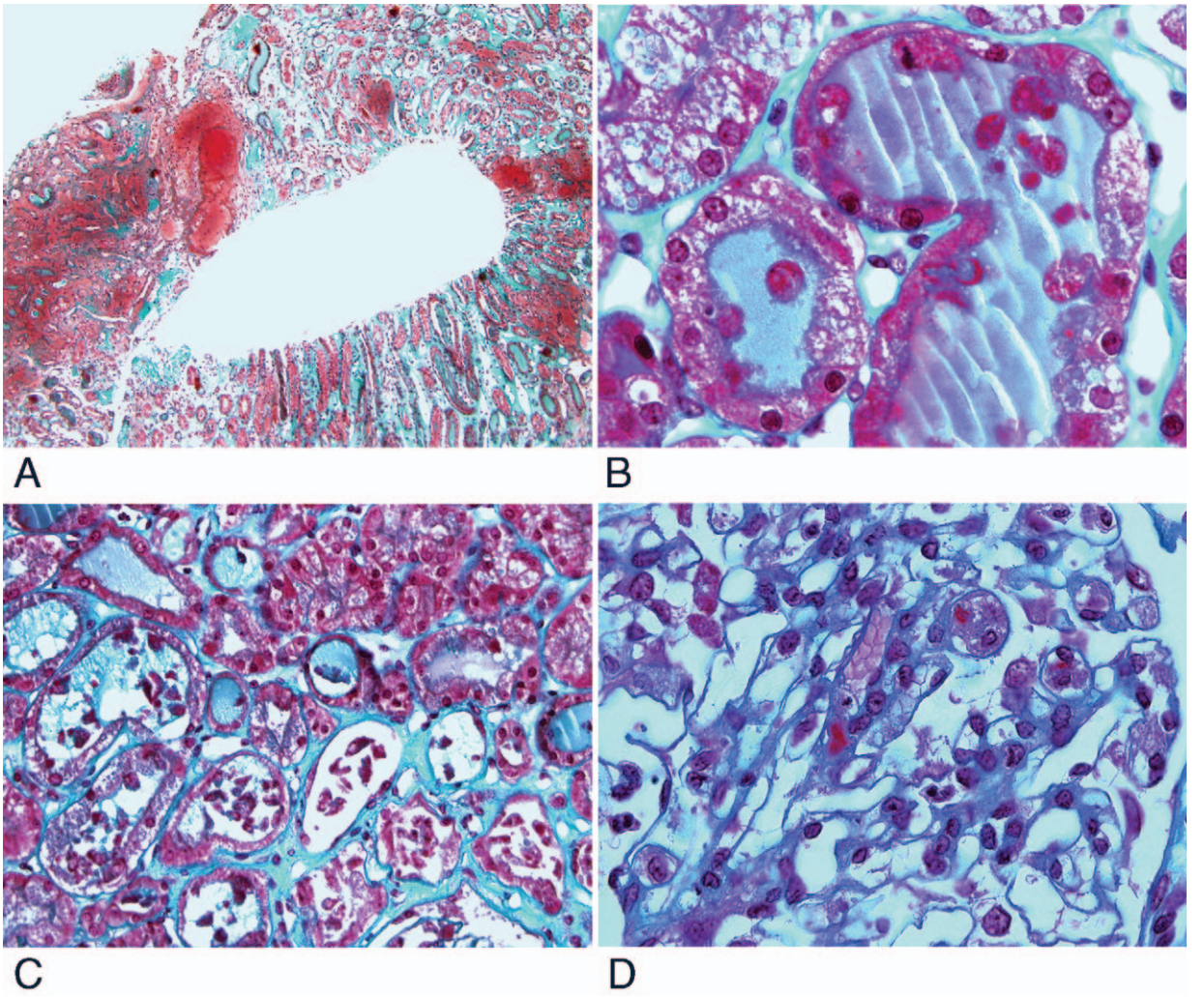

Figure 1. Renal histology: ischemia reperfusion injury. (A) Massive congestion of peritubular capillaries filled with red blood cells and interstitial hemorrhagic suffusion plaques. (Masson trichrome stain; original magnification, X10). (B) Acute tubular necrosis. Dilatation of the tubules and hyaline casts in the tubular lumens. Some tubular cells are swollen and contain vacuolization. (Masson trichrome stain; original magnification, X40). (C) Acute tubular necrosis. Loss of epithelial lining with desquamation of tubular cells, necrosis, cytoplasmic debris, and hyaline casts in the tubular lumens. (Masson trichrome stain; original magnification, X40). (D) Thrombi in the lumens of the glomerular capillaries. (Masson trichrome stain; original magnification, X100).

At 1 year post transplant, the patient always has a renal autonomy with a graft function stable (creatinine 240 μmol/L) and physiological proteinuria. Several complications occurred during this 1st year including repeated graft pyelonephritis secondary to a vesicoureteral reflux that has been treated with teflon, CMV infection complicated with gastritis and episodes of neutropenia.

3. Discussion

Ischemia reperfusion occurs when the blood flow supply is either interrupted or severely disturbed. This event is always associated to kidney transplantation. Depending on the degree of ischemia, the organ will either completely recover or will sustain cellular injuries. The risk factors associated with severe IRI in the setting of kidney transplant are: donor factors: donor age, brain, and cardiac arrest; recipient factors: male gender, African American race, body mass index greater than 30 and high panel reactive antibodies;[3] storage preservation: duration of storage and long cold ischemia.[2] In our case, 3 factors were identified.

The 1st change induced by ischemia is the decreased oxygen delivery inducing a switch from aerobic to anaerobic glucose metabolism. Intracellular ATP levels becomes insufficient and lactate dependent ATP production causes intracellular acidosis by accumulation of lactic acid in the cells and interstitium. These processes lead to, the destabilization of lysozyme membrane which leaks various hydrolases leading to disruption of the cell structure; the inhibition of the ionic pumps in particular the Na/K ATPases inducing a massive intracellular increase of Na ions and water with consequent edema. Intracellular Ca levels increase by the stop of the Na/Ca pumps and the inhibition of Ca reuptake due to ATP depletion. This calcium overload leads to, the activation of calcium dependent proteases such as calpain which are inhibit by the low intracellular pH; the generation of few reactive oxygen species (ROS) at mitochondrial level. After reperfusion, the increase in oxygen delivery and the pH normalization induce the activation of calpain and a large burst of ROS leading to cell death through different mechanisms as apoptosis, necrosis, and autophagy. The IRI is associated with a vascular dysfunction with increased vascular permeability and endothelial cell activation. In addition the recruitment of inflammatory cells like neutrophils, activation of coagulation and complement cascade induce other lesions.[1,2,4]

Ischemia reperfusion is also associated with a pathological activation of the innate and adaptive immune system.[5] Numerous cells and mechanisms are involved, 3 actors play a crucial role: toll like receptors, dendritic cells, and complement system. Toll like receptor activation results in the transcription of nuclear factor kinase B leading to transcriptional activation of inflammatory gene programs. Dendritics cells are essential to present the antigen to T cells. Interaction between T and B cells can generate different alloimmune responses. Complement system is activated in ischemia reperfusion via brain death in donor and dendritics cells activation leading to activation of Th1 and adaptive immunity.[1,2,4]

The IRI may cause cell damage through several pathways as cell death, microvascular dysfunction, transcriptional reprogramming, activation of innate and adaptive immune system, autoimmunity, and endothelial mesenchymal transition.[2,4–6]

Few data on IRI's histology in the setting of kidney transplantation are available in the literature despite the frequency and the severity of this event.

In our case, the kidney biopsy revealed massive lesions of acute tubular necrosis including apoptosis (nuclear fragmentation), autophagy-associated cell death (cytoplasmic vacuolization), and necrosis. Microvascular dysfunction with increased vascular permeability and endothelial cell inflammation were also present with the congestion of peritubular capillaries filled with red blood cells with interstitial hemorrhagic suffusion plaques. Activation of coagulation is represented by thrombi in the lumens of the glomerular capillaries. Tubular and microvascular lesions are predominant because endothelial cells and tubular epithelial cells are the 1st to suffer for oxygen supply, especially in the medulla.

The main clinical consequences of IRI in kidney transplant are delayed graft function via tubular damage, acute and chronic graft rejection via immune system activation, and chronic graft dysfunction via endothelial mesenchymal transition.[2,4]

Effectively, IRI has a pejorative outcome on kidney graft.[7] Reducing IRI is one of the most relevant challenge in kidney transplantation. Strategies including an optimal management of donor and recipient, anti-inflammatory and anti-oxidant therapies are ongoing.[8–10]

Author contributions

Data curation: Jean-Louis Kemeny.
Supervision: Cyril Garrouste, Anne-Elisabeth Heng.
Validation: Julien Aniort.
Writing – original draft: Carole Philipponnet.
Writing – review & editing: Carole Philipponnet.
Carole Philipponnet orcid: 0000-0002-6116-1452.

References

[1] Eltzschig HK, Eckle T. Ischemia and reperfusion–from mechanism to translation. Nat Med 2011;17:1391–401.
[2] Salvadori M, Rosso G, Bertoni E. Update on ischemia-reperfusion injury in kidney transplantation: Pathogenesis and treatment. World J Transplant 2015;5:52–67.
[3] Doshi MD, Garg N, Reese PP, et al. Recipient risk factors associated with delayed graft function: a paired kidney analysis. Transplantation 2011;91:666–71.
[4] Ponticelli C. Ischaemia-reperfusion injury: a major protagonist in kidney transplantation. Nephrol Dial Transplant 2014;29:1134–40.
[5] Fuquay R, Renner B, Kulik L, et al. Renal ischemia-reperfusion injury amplifies the humoral immune response. J Am Soc Nephrol 2013;24:1063–72.
[6] Curci C, Castellano G, Stasi A, et al. Endothelial-to-mesenchymal transition and renal fibrosis in ischaemia/reperfusion injury are mediated by complement anaphylatoxins and Akt pathway. Nephrol Dial Transplant 2014;29:799–808.
[7] Yarlagadda SG, Coca SG, Formica RN, et al. Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis. Nephrol Dial Transplant 2009;24:1039–47.
[8] Cavaillé-Coll M, Bala S, Velidedeoglu E, et al. Summary of FDA workshop on ischemia reperfusion injury in kidney transplantation. Am J Transplant 2013;13:1134–48.
[9] O'Callaghan JM, Morgan RD, Knight SR, et al. Systematic review and meta-analysis of hypothermic machine perfusion versus static cold storage of kidney allografts on transplant outcomes. Br J Surg 2013;100:991–1001.
[10] Dong VM, Tilney NL. Reduction of ischemia/reperfusion injury in organ transplants by cytoprotective strategies. Curr Opin Organ Transplant 2001;6:69–74.