The influence of Lewis, Duffy and Kidd blood groups on renal allograft rejection: Review

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ABSTRACT The blood groups antigens are not restricted to erythroid cells and are widely distributed in several tissues and fluids. The purpose of this study is to describe the influence Lewis, Duffy and Kidd blood groups on renal graft rejection.

KEYWORDS Kidney transplant, Rejection, Lewis, Duffy and Kidd blood group system

Introduction

Renal transplantation is the standard form of therapy for patients with end-stage renal disease[1]. However, acute and chronic rejections remain the main cause of allograft failure, even with the introduction of new and more powerful immunosuppressants[2].

The immunological mechanisms that can explain rejections may include a T cell immune response, along with the recognition of histocompatibility antigens, activation of T lymphocytes, and induction of a cellular and humoral cascade, resulting in intravascular and extravascular hemolysis and graft failure caused by the action of complement fixation antibodies [3,4,5].

The Lewis, Duff (FY) and Kidd (JK) blood groups are antigens of minor histocompatibility, polymorphic and immunogenic. Immunization directed against minor histocompatibility antigens in renal allograft rejection has been established for some time, but the specificity of these antigens and the influence on external renal failure remains uncertain [6,7].

This study aimed to investigate the influence of Lewis, FY and JK blood groups on renal graft rejection.

DOI:10.5455/IJMRCR.lewis-duffy-kidd-blood-groups
First Received: July 21, 2019
Accepted: August 21, 2019
Associate Editor: Ivan Inkov (BG)

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Methods

The electronic searches were carried out in PUBMED, LILACS and SCIELO. The search strategy used in PUBMED was "renal allograft" [MeSH Terms] OR "kidney transplant * [Text word] and "rejection" [sb]. The terms "renal allograft rejection" were used for LILACS, "blood group system" for SCIELO and "Lewis, Duffy and Kidd" for PUBMED.

Influence of Lewis blood group on renal graft rejection

The Lewis blood group system is an essential set of histocompatibility antigens. Lewis antigens are derived from plasma and adsorbed onto erythrocytes[8]. Its expression depends on the interaction of two fucosyltranferases, products of the FUT2 and FUT3 genes on chromosome 19p13.3. They are expressed in different human tissues, including, for example, the renal cortex, pancreas, stomach mucosa, intestine, skeletal and adrenal muscle [9,10].

Few studies report the influence of the combination of Lewis antigens on renal transplantation[11,12]. In the post-transplant period, anti-Lewis antibodies can injure the graft leading to C4d deposits in the peritubular capillary endothelium, as well as C3, IgG and IgM deposits in glomeruli and blood vessels[13,14]. In receptors with a positive Lewis phenotype, there is no influence on the graft outcome. However, for receptors with Le (a-b-) phenotype, graft survival seems to be inferior due to the formation and action of anti-Lewis antibodies before or after the transplantation. Anti-Leb antibodies seem to be responsible for the dysfunction of renal allografts, probably because of agglutination15. The correlation between HLA and Lewis is not only addictive, taking into consideration that renal graft failure may

develop in a variety of circumstances. Lewis's compatibility is essential for the prognosis of renal transplantation. Therefore, as it is shown in (table 1), three cases with anti-Lewis alloantibodies, out of a total of 339 submitted to kidney transplantation, suffered severe rejection of the kidney graft [13].

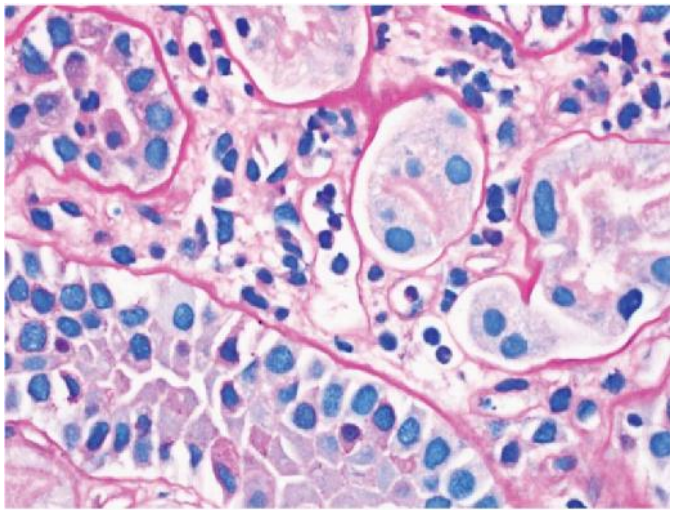

Figure 1: Renal biopsy (original magnification × 600) of the patient, a white 59-year male. In the center of the image, peritubular capillaritis is visible[37].

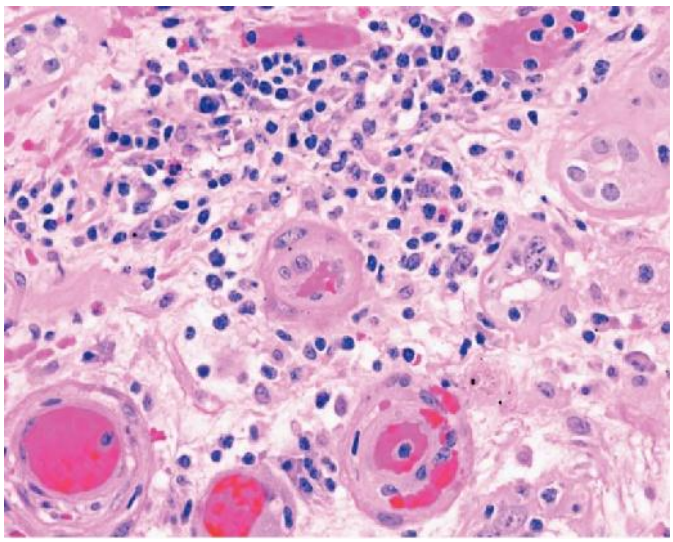

Figure 2: Renal biopsy (original magnification × 400) of the patient, a white 59-year male. The inflammatory lymphoplasmocytic infiltrate visible, with activation of the endothelial cells in the arterioles and renal tubular lesion with vacuolation[37].

Influence of Duffy blood group on renal graft rejection

The Duffy blood group system is of interest in different fields of medicine[16, 17]. Its antigens are immunologically distinct, referred to as Fya and Fyb[18]. The Fy (a-b-) phenotype is associated with African nephropathy and the lower rate of renal graft survival[19]. In the renal transplant model, the Duffy blood group is considered a minor histocompatibility system and can act as a CC chemokine receptor (MCP-1 [CCL- 2], RANTES [CCL-5]) and CXC class (i.e. IL-8 [CXCL-8], GRO-α [CXCL-1], NAP-2 [CXCL-7]), in endothelial cells in the postcapillary venules of the human kidney [20, 21, 22,23]. Chemokines can recruit inflammatory cells for renal allografts[24]. A characteristic of renal allograft rejection is the deposition of C4d in peritubular capillaries in combination with the accumulation of inflammatory cells, sometimes neutrophils[25]. In this case, the Duffy system may be the reason for the unfavourable outcome in renal transplantation for inflammatory reasons in the face of accumulation of chemokines in renal tissue [26-27].

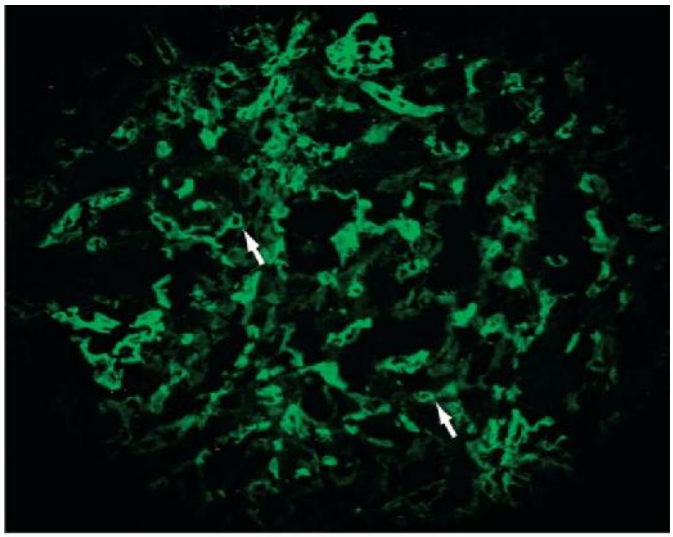

Figure 3: Immunofluorescence image that depicts humoral rejection and demonstrates complement deposits (C4d) in the peritubular capillaries (arrows)[37].

Influence of Kidd blood group on renal graft rejection

The Kidd blood group became interesting for renal transplantation because it acts as a transporter of (UTB) [28, 29]. The location of the JK antigens in renal cells raises questions about the impact of antigens of the Kidd system on renal disease[30]. The Kidd blood group has three antigens, Jka, Jkb and Jk3, found in red cells and endothelial cells of the inner lining of blood vessels in the renal medulla. Researchers have found that individuals with the Jk (a-b-) or Jk-null (UT-B null) phenotypes have a lower capacity for urine concentration and risk of severe renal impairment[31].

The Jk (ab-) phenotype is rare in most populations and is often detected after transfusion or pregnancy[32]. Studies indicate that the incompatibility of the Kidd blood group has an unfavourable effect on graft survival and, in some cases, it may be directly associated with the hyperacute graft rejection[33], [34].

In rejection of renal allografts, anti-Jk antibodies bind to Kidd antigens on endothelial cells, causing endothelial capillary destruction[35,36]. A renal biopsy revealed the humoral rejection of the allograft characterised by peritubular capillaritis, as shown in Figure 1, lymphoplasmacytic infiltration, activation of the tubular and arteriolar endothelium, as shown in Figure 2, complement deposition (by immunohistochemical staining) and C4d deposition in peritubular capillaries, as shown in Figure 3. The patient developed anti-Jka antibodies. The renal graft was removed due to chronic rejection[37].

These data confirm previous findings of the role of Kidd as a histocompatibility system in renal transplantation. Besides this,

Table 1 The results of histological and immuno-phonological examination of kidney allograft biopsy specimens in patients with anti-Lewis alloantibodies.

	Case 1; Biopsy1	Case1; Biopsy2	Case 2; Biopsy1	Case 2; Biopsy2	Case 3; Biopsy1
Neutrophils in PTC	+	+	+	+	+
Neutrophils in glomeruli	+	+	+	+	+
Arterial fibrinoidnecrosis	–	–	–	–	+
Glomerulitis	+	+	+	+	
Thrombi in glomerular capillaries	–	–	–	+	+
Thrombi in arterioles	–	–	–	–	+
Acute tubular injury	–	–	–	+	+
C4d in PTC	+/-	+	+	+	Necrosis
C3 in glomeruli and vessels	+	+	+	+	+ only in glomeruli
IgG in glomeruli and vessels	+	+	+	+	+
IgM in glomeruli and vessels	+	+	+	+	+

Abbreviation: PTC, peritubular capillaries[13].

they demonstrate that Kidd's influence is more significant in high-risk patients. Therefore, patients with renal transplant rejection episodes should be examined to verify the presence of antibodies against Kidd antigens using blood bank techniques[37]. On the other hand, studies also show that the Jk (a+b+) phenotype offers protection because they do not produce antibodies against these antigens[38].

Conclusion

With the improvements in renal transplantation, studies with less immunogenic blood groups have become more relevant as they may influence the success or failure of the renal graft. We argue here that the cumulative incompatibility of Lewis, Duffy and Kidd has an unfavourable effect on renal graft and if a transfusion is required, it is essential to guarantee compatible antigen blood components that do not correspond to any antibody specificity in the serum or plasma of the receptor.

Competing Interests

There were no financial supports or relationships between authors and any organization or professional bodes that could pose any conflict of interest.

Funding

None.

Acknowledgements

We thank Mariana Almeida for their valuable suggestions and linguistic support.

References

1. Peng B, Ming Y, Yang C. Regulatory B cells: the cutting edge of immune tolerance in kidney transplantation.Cell Death Dis 2018; Jan 25;9(2):109.
2. Shrestha BM. Immune System and Kidney Transplantation. JNMA J Nepal Med Assoc. Oct-Dec 2017; 56(208):482-486.
3. Brand A. Immunological complications of blood transfusions. Presse Med. 2016 Jul-Aug;45(7-8 Pt 2):e313-24.
4. Nauser CL, Farrar CA, Sacks SH. Complement Recognition Pathways in Renal Transplantation J. Am. Soc. Nephrol 2017 28: 2571-2578.
5. Carter V, Shenton BK, Jaques B, et al. Vimentin antibodies: a non-HLA antibody as a potential risk factor in renal transplantation. Transplant Proc. 2005 Mar;37(2):654-7.
6. Oriol R, Cartron J, Yvart J, et al.: The Lewis system: new histocompatibility in renal transplantation. Lancet 1978; 18:574.
7. Lerut E, Van Damme B, Noizat-Pirenne F, et al. Duffy and Kidd blood group antigens: minor histocompatibility antigens involved in renal allograft rejection? Transfusion 2007; Jan;47(1):28-40.
8. Raynald Roy, Béatrice Des Marchais, Richard Bazin, et al. Role of ABO and Lewis Blood Group Antigens in Donor-Recipient Compatibility of Corneal Transplantation Rejection. Ophthalmology 1997; Volume 104 , Issue 3 , 508 - 512.
9. Mourant AE. A new human blood group antigen of frequent occurrence. Nature 1946; Aug 17;158: 237.
10. Reid ME, Mohandas N. Red blood cell blood group antigens: structure and function. Semin Hematol 2004; 41(2):93-117.
11. Fischer E, Lenhard V, Römer W, et al.The Lewis antigen system and its relevance for clinical transplantation. Z Immunitatsforsch Immunobiol 1979; Jun;155 (5):420-3.

12. Lenhard V, Hansen B, Roelcke D, et al. Influence of Lewis and other blood group systems in kidney transplantation. Proc Eur Dial Transplant Assoc 1983; 19: 432-7.

13. Boratyn´ska, M. Banasik, A. Hałon´, D. Patrzałek aM. Klinger Blood Group Lewis Alloantibodies Cause Antibody-Mediated Rejection in Renal Transplant Recipients. Transplantation Proceedings 2007; 39:2711–2714.

14. Daniels, G. Human Blood Groups. Blackwell Science1995; a Cap.2, p. 8-120: ABO, Hh, and Lewis Blood Group Systems.; Cap. 3, p. 121-226.

15. Shanthi B, Raju DS, Dasarath D, et al. Anti-Leb (Lewis) antibody in renal transplantation, emphasizing the role of transfusion medicine in organ transplantation. Asian Journal of Transfusion Science 2012; 6(1), 53–54.

16. Meny GM. The Duffy blood group system: a review. Immunohematology 2010; 26(2): 51-6.

17. Martins ML, da Silva AR, Santos HC, et al. Duffy blood group system: New genotyping method and distribution in a Brazilian extra-Amazonian population. Mol Cell Probes. 2017; Oct;35:20-26.

18. Then WL, McLiesh H, Aguilar MI, et al. Duffy blood group (Fya & Fyb) analysis using surface plasmon resonance. Biomed Microdevices 2016; Dec;18(6):101.

19. Akalin E, Neylan JF. The influence of Duffy blood group on renal allograft outcome in African Americans. Transplantation 2003; 75:1496-500.

20. Segerer S, Regele H, Mac KM, et al. The Duffy antigen receptor for chemokines is up-regulated during acute renal transplant rejection and crescentic glomerulonephritis. Kidney Int 2000; Oct 58(4):1546-1556.

21. Segerer S, Bohmig GA, Exner M, et al. When renal allografts turn DARC. Transplantation 2003; Apr 15 75(7):1030-1034.

22. Höher G, Fiegenbaum M, Almeida S. Molecular basis of the Duffy blood group system.Blood Transfus. 2018 Jan;16(1):93-100. Epub 2017 Jan 30. Review.

23. Neote K, Mak JY, Kolakowski LF Jr, et al. Functional and biochemical analysis of the cloned Duffy antigen: identity with the red blood cell chemokine receptor. Blood 1994; 84:44-52.

24. Nelson PJ, Krensky AM. Chemokines, chemokine receptors, and allograft rejection. Immunity 2001; 14: 377.

25. Bohmig GA, Exner M, Watschinger B, et al. Acute humoral renal allograft rejection. Curr Opin Urol 2002; 12: 95.

26. Liu XH, Hadley TJ, Xu L, et al. Up-regulation of Duffy antigen receptor expression in children with renal disease. Kidney Int. 1999; Apr 55(4):1491-500.

27. Watorek E, Boratyńska M, Hałoń A, et al. Anti-Fya antibodies as the cause of an unfortunate post-transplant course in renal transplant recipient. Ann Transplant 2008;13(1):48-52.

28. Heaton DC, Mcloughlin K. Jk(a–b–) red blood cells resist urea lysis. Transfusion 1982; 22: 70–71.

29. Daniels G. Other blood groups. In: Roback JD Combs MR Grossman BJ Hillyer CD, eds. Technical Manual . 16th edn. Bethesda: AABB, 2008:411–436.

30. Barros MMO. Kidd system antigens and kidney disease. Revista Brasileira de Hematologia e Hemoterapia 2017;39 (4):293-294.

31. Capriolli TV, Visentainer JEL, Sell AM. Lack of association between Kidd blood group system and chronic kidney disease. Revista Brasileira de Hematologia e Hemoterapia 2017;39(4):301-305.

32. Deelert S, Thippayaboon P, Sriwai W, et al. Jk(a-b) phenotype screening by the urea lysis test in Thai blood donors. Blood Transfusion 2010;8(1):17-20.

33. Holt S, Donaldson H, Hazlehurst G, et al. Acute transplant rejection induced by blood transfusion reaction to the Kidd blood group system. Nephrol Dial Transplant 2004; Sep 19(9):2403-2406.

34. Rourk A, Squires JE. Implications of the Kidd blood group system in renal transplantation. Immunohematology 2012;28(3):90-4.

35. Sanford KW, Bourikian S, McClain A, et al. Development and Detection of Kidd Antibodies. Lab Med 2015 Summer;46(3):235-40.

36. Hamilton MS, Singh V, Warady BA. Additional case of acute cellular kidney rejection associated with the presence of antibodies to the red blood cell Kidd antigen. Pediatr Transplant 2008 Dec;12(8):918-9.

37. Kimberly Williams Sanford, Seda Bourikian, Aryn McClain, et al. Development and Detection of Kidd Antibodies, Lab Med. 2015 Summer;46(3):235-40.

38. Bencomo HAA, Aquino RS, González DI, et al. Caracterización de los antígenos y anticuerpos eritrocitarios en pacientes en espera de trasplante renal. Rev Cubana Hematol Inmunol Hemoter 2016; Jun; 32(2).