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Immunopathology of Kidney Transplantation

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Abstract

Renal transplantation is currently the best alternative for patients with end-stage renal disease. Immune responses activated against the allograft are a decisive factor in transplantation outcomes and patient survival. Although short-term graft and patient survival have improved significantly as a result of better donor matching systems, novel immunosuppressive agents and enhanced care, long-term outcomes remain unfavorable and reflect sub-clinical injury caused by chronic rejection. The immune system lies at the intersection of immunogenic tolerance and graft failure; thus, it is a major determinant of pathology in the context of renal transplantation. During the early stages of transplantation increased expression of cytokines has been observed in addition to increased expression of adhesion proteins and immune cells. This early inflammatory response does not necessarily end in graft rejection, although this will depend on the severity of the inflammation. Activation of Toll-like Receptors (TLRs), damaging molecular patterns (DAMPs), and other components of innate immunity is key to the formation of atherosclerotic plaques and the development of autoimmune diseases. Initially the donor antigens are presented to the T lymphocytes of the recipient. This activation induces their proliferation, differentiation and cytokine production. Successful kidney transplant recipients need to develop immunologic tolerance against donor antigens. In this chapter, we address some of the innate and adaptive immune mechanisms associated with kidney transplantation; emphasizing their role in allograft rejection.

Keywords: kidney, transplantation, immunopathology, graft rejection, immunology

1. Introduction

According to statistics from the United States Renal Data System (UNOS) and the U.S. Department of Health & Human Services Organ Procurement and Transplantation Network

(OPTN), there are currently close to 100,000 people in the U.S. waiting for a lifesaving kidney transplant. Only between January and May 2017, 14,075 kidney transplants took place in the United States; of which 11,702 organs came from deceased donors and 2373 came from living donors. Renal transplantation has become the treatment of choice for patients with end-stage renal disease (ESRD); though its success and widespread use are still limited by the availability of suitable organs and allograft rejection [1]. In recent decades, short-term graft survival has improved significantly as consequence of better donor matching systems, novel immunosuppressive agents and enhanced care. Unfortunately, long-term outcomes remain unfavorable and reflect subclinical injury caused by antibody-mediated allograft rejection (ABMR) [2]. The immune system lies at the intersection between immunogenic tolerance and graft failure and as such, it is a major determinant of pathology in the context of renal transplantation [3]. The immune system is a complex network of lymphoid organs, cells, and molecules responsible for body homeostasis and host defense. Although the main function of the immune system is to protect against external pathogens and molecules, the presence of foreign antigens on the donor organ also triggers innate and adaptive immune responses in the recipient that will largely determine graft performance and patient survival.

2. Activation of innate immunity in kidney transplantation

Innate immune responses are required for the activation of cellular and molecular mechanisms behind the physiopathology of kidney transplantation [4]. During the early stages of transplantation, innate immunity is essential for the activation of the adaptive immune system, whereas at later stages, innate components promote an inflammatory microenvironment that enhances allograft damage.

2.1. Cells of the innate immune system

The cellular components of innate immunity are phagocytic leukocytes (neutrophils, monocytes, eosinophils, and basophils), natural killer (NK) cells, and dendritic cells (DCs). Ischemic injury that occurs during organ transplantation promotes alloimmune responses including innate cell recruitment [5]. Infiltrating neutrophils release proteases, free radicals, and proinflammatory molecules such as interleukin 6 (IL-6), interleukin 8 (IL-8), and tumor necrosis factor alpha (TNF- α) within the graft. It has been demonstrated that a high neutrophil-lymphocyte ratio amplifies the inflammatory process during acute renal failure [6]. Furthermore, neutrophil-depleted mice and intracellular adhesion molecule 1 (ICAM-1) knockouts are more resistant to renal ischemic injury; suggesting that neutralizing neutrophil activity could increase transplant success rates by reducing early graft damage [7]. Macrophages are also an important source of interleukin 1 (IL-1), IL-6, transforming growth factor beta (TGF- β), interferon γ -induced protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), and macrophage inflammatory protein 2 (MIP-2) during ischemia [8]. In the context of renal damage, monocytes are recruited within the

first few days thanks to C–C chemokine receptor type 2 (CCR2) and CX3C chemokine receptor 1 (CX3CR1) ligand release. Subsequently, these monocytes are transformed into macrophages able to phagocyte damaged cells and present peptides to alloreactive T cells in peripheral lymph nodes [8, 9]. There is NK cell recruitment after ischemia and during the early stages of renal transplantation [10, 11]. NK cells keep other cells in check for major histocompatibility complex (MHC) surface expression through killer Ig-like receptors (KIR) [12]. In allotransplantation, lack of MHC Class I recognition triggers NK effector mechanisms, including perforin-dependent cell lysis and cytokine production [13]. NK cells seem to play an important role in the induction of acute renal damage and long-term graft survival as demonstrated in mice that exhibit abnormalities in recruitment of these cells and are more resistant to kidney damage [10, 11].

2.2. Role of pattern recognition receptors and damaging molecular patterns in renal transplantation

In the early 1990s, Janeway proposed that all innate immune cells had pattern recognition receptors (PRRs) that can discriminate between self-components and pathogens. Soon after, Polly Matzinger suggested that our immune system is designed to recognize signs of harm rather than to discriminate between self and nonself, which could explain how innate immune activation can occur under sterile conditions such as in allotransplantation [14]. Consequently, pathogen-associated molecular patterns (PAMPs) and DAMPs are designed to signal damage threats [15]. DAMPs and PAMPs arise in the allograft during pre- and post-transplant periods; and activation of vascular PRRs such as TLRs, C-type lectin receptors, Nod-like receptors, and retinoic acid-inducible gene-I-like receptors can trigger production of proinflammatory cytokines [4].

The surgical process as well as ischemic injury, precondition for a systemic inflammatory reaction by releasing high mobility group box 1 (HMGB1) and heat shock proteins; as well as by increasing Toll-like receptor 4 (TLR4) expression in endothelial and peripheral blood cells [16]. The immunosuppressant cyclosporin A also induces HMGB1 release and promotes immune cell infiltration into the renal graft [17]. Furthermore, blocking HMGB1 reduced cellular infiltrate, IL-6 and TNF- α production in kidneys subjected to ischemia, and decreased of MCP-1 which is reflected in reduced nephrotoxicity [18]. On the other hand, HMGB1 appears to play a protective role; the administration of recombinant HMGB1 prevents dysfunction, tissue damage, and inflammation in animals subjected to ischemia [19].

2.3. The complement system

The complement system is a set of membrane-anchored and serum proteins that work in a coordinated way to eliminate microorganisms or damaged cells. The functions of complement include opsonization, inflammation through secondary products that result from the degradation of anaphylatoxins and formation of the membrane attack complex (MAC). There are three known complement pathways: the classical pathway that depends on the previous binding of antibodies, the alternate pathway that depends on the spontaneous hydrolysis and

binding of C3 and the pathway of lectins that depends on the binding of proteins to carbohydrates. Currently, there is evidence to suggest the participation of the three complement pathways during renal transplantation [20–22].

2.4. Innate-adaptive immunity interactions

Communication between innate and adaptive immunity largely depends on antigen presentation. T and B cells express antigen-specific receptors (TCR and BCR). The signals elicited by the TCR and BCR are insufficient to achieve the proper activation state, and costimulatory molecules and cytokines provided by innate immune cells are necessary [4]. Although DCs are the most efficient APCs, neutrophils, basophils, and eosinophils also influence the outcome of adaptive immunity. Neutrophils can recruit IL-17-producing Th17 lymphocytes by releasing CCL2 and CCL20. Interestingly, patients with a history of chronic renal dysfunction showed a significant increase in IL-17 producing cells [23]. Basophils are normally activated by IL-3 or immunoglobulin binding in different renal structures; and are an important source of cytokines, thymic stromal lymphopoietin, leukotrienes and histamines which may influence the outcome of adaptive immune responses [24, 25]. Basophils express MCH Class II and are considered important regulators of T and B cell activation. Moreover, an increase in eosinophils in renal transplant, recipients has been proposed as a predictor of allograft success [26].

3. Adaptive immune responses

3.1. Allorecognition, T-cell activation, T cell-mediated cytotoxicity, and B lymphocytes

The term allorecognition refers to recognition of diverse forms of genes between a member of the same species by T cells and involve Human major histocompatibility complex (MHC) glycoproteins. MHC is a family composed by the most studied antigens in transplantation field. These antigens are widely known as human leukocyte antigens (HLA). The genes encoding HLA antigens are highly polymorphic, this feature represents a big obstacle in the study of mechanisms of graft rejection. Class I HLA are present in membranes of the nucleated cell of humans and its function is to present small endogenous antigens to CD8 T lymphocytes. Class II are expressed on dendritic cells, macrophages, B cells, endothelial, and some types of epithelial cells. This T cell recognition event is the first step of graft rejection. There are two different ways in which T cells recognize allo-antigens, i.e., direct and indirect. Direct recognition is when CD8⁺ and CD4⁺ T cells from the recipient recognize MHC class I and class II presented by APCs and donor peptides. Indirect recognition is mediated by specialized APCs from the recipient presenting to T cells [27]. Donor endothelial cells express molecules that stimulate T cells, these activated cells provide help to B cells resulting in the production of alloantibodies [28]. Although the most studied role of B cells is associated with alloantibodies and donor specific antibodies, there are controversial opinions about the deleterious role of these antibodies and its association with poor graft outcomes [29].

4. Immunotolerance in transplantation

The term immunotolerance implies the absence of recognition and renal graft attack by the immune cells of the recipient. One of the most important developments in the field of organ transplantation has been the use of immunosuppressive therapies that interfere with immune recognition and consequently delay graft rejection. Nonetheless, although immunosuppression is used, some immune adaptation may develop in the graft. To choose a clinically successful immunosuppressive therapy, several factors must be considered: they must be easily applicable in clinical practice, there should be enough evidence of their effectiveness, they must be stable over time even in conditions where the immune system is altered, and their mechanism of action should not have cross-reactions with other therapies. As a final point, it should be possible to measure and control its levels in the transplanted patient [30]. Induction of tolerance can occur through various mechanisms that include thymic deletional, central and peripheral deletional, and nondeletional mechanisms.

4.1. Mechanisms of T-cell tolerance

T cell tolerance in transplantation is a regulated process that ensures the tolerance and permanence of antigens, similarly to tolerance required for the maintenance of self-antigens [31]. It consists of several stages: deletion, anergy, suppression, and ignorance. Tolerance is maintained by several mechanisms initiating in the thymus, where T cells are chosen by negative selection. The main mechanism of transplanted antigens tolerance is through intrathymic deletion of donor-reactive T cells [32]. Although there are additional mechanisms of peripheral tolerance, most T cells are eliminated by this mechanism. Peripheral deletion of T cells is an important mechanism of tolerance, in which CD4 T cells reactive to donor antigens show activation, as well as apoptotic cell death. Once the tolerance is given T cells cannot respond to antigens, a state known as anergy. A costimulatory block induces anergy and has been successfully applied for tolerance induction. The activation of the T cell requires at least two signals: an antigen-dependent T cell receptor-mediated signal 1 and an antigen-independent costimulatory signal 2 [33]. CD4 and CD25 T cell regulators are actively involved in the development of immunological tolerance toward the graft. Ignorance is another mechanism that occurs when donor antigens are not recognized by the lymphoid system of the recipient or when lymphocytes fail to invade the graft. However, this mechanism applies to nonvascularized grafts.

The aim of tolerance induction in renal transplantation is to block direct and indirect alloresponse pathways. In the first, it is necessary to establish the depletion of the recipient T cells and the activation of suppressor cells capable of regulating T cells. Some drugs can induce the death of alloreactive T cells. On the other hand, oral administration of allopeptides may also produce specific tolerance to corresponding alloantigens and generate specific production and activation of regulatory T cells.

4.2. Induction of immunologic tolerance

Tolerance induction requires alloreactive T-cell deletion in the thymus before these cells can be released to the periphery. Hematopoietic chimerism is a widespread method to

induce tolerance. Animal models have improved our understanding of this mechanism that ranges from tolerance induction through the injection of allogeneic cells into newborn mice to the use of adult irradiated animals injected with allogeneic donor bone marrow [34]. Tolerance induction at the peripheral systemic level needs to target mature T cells by blocking T cell molecules located on its surface, which have important roles in the activation of signaling pathways that impact cell function directly. To this end, antibodies directed against CD4 or CD8 or costimulatory molecules have been used. CD28 receptor blockade prevents proinflammatory cytokine production, as well as T cell survival and proliferation. It is also possible to interfere with the signaling pathways involved in T cell survival and proliferation, which is the case of the mTOR pathway inhibitor rapamycin. Clinical studies in humans have focused on graft tolerance induction by pretransplanting donor hematopoietic cells in human leukocyte antigen (HLA)-matched and mismatched kidney transplant recipients [35, 36].

4.3. Immunosuppressive therapy in renal transplantation

The discovery of effective immunosuppressive drugs has had great impact in the field of transplantation. Currently available immunosuppressive therapies focus on three main objectives: induction, maintenance, and treatment of rejection. For induction therapy three types of antibodies are used, the lymphocytes depleting agents, antithymocyte globulin and alemtuzumab, and basiliximab (nondepleting) [37]. Basiliximab, an IL-2 receptor antagonist and it is used in combination with other immunosuppressants, significantly reduces acute rejection in large clinical studies [38]. The use of antithymocyte antibodies in diseased donor recipients also reduces early acute rejection incidence. Nevertheless, its use has been associated with reversible leukopenia, thrombocytopenia, and cytomegalovirus infection [39].

The use of calcineurin inhibitors cyclosporine and tacrolimus has been key in reducing the risk of rejection and has greatly improved short-term graft survival outcomes. Unfortunately, in the long run they also help develop histological changes typical of nephropathy that diminish kidney graft function and increase risk of graft loss [40, 41]. A T cell costimulatory inhibitor called belatacept was introduced to avoid the deleterious effects of calcineurin inhibitors. In several studies, belatacept prevents acute rejection in renal transplantation comparable to cyclosporine [42]. Since the 1980s, several options have been developed to reduce kidney transplant rejection. Monoclonal muromonab-CD3/OKT3, monoclonal interleukin-2 receptor (IL-2R) antibodies (daclizumab and zenapax), and antiproliferative agents (mycophenolate mofetil) are part of a large list of options currently available in renal transplantation [43]. Nevertheless, some transplant experts propose a reduction in the use of immunosuppressive drugs in order to reduce the nephrotoxicity that can also end in fibrosis and graft rejection. Additionally, some transplant recipients develop diabetes, cardiovascular disease, dyslipidemia associated to immunosuppressant therapies. For this reason, it is estimated that kidney grafts can function on average 10 years after the transplantation [44, 45].

5. Graft rejection

Current immunosuppressant therapies have drastically reduced acute rejection events in kidney transplant recipients [46, 47]. Unfortunately, there is still a high percentage of short- and long-term kidney graft losses secondary to ABMR [2]. Here, we will discuss the contribution of adaptive and innate immune cells; as well as antibodies, molecules from the complement system and chemokines to disease states that lead to kidney graft rejection (**Figure 1**).

5.1. T cell-mediated rejection

T cell mediated rejection (TCMR) is characterized by infiltration of the donor graft interstitium by host CD4 and CD8 T effector and memory cells, macrophages, and dendritic cells; followed by epithelial dedifferentiation and tubulitis [48, 49] (see histopathological findings in **Figure 2**). TCMR is the predominant phenotype found in kidney transplant recipients with early rejection and it is still an important cause of graft dysfunction that when left untreated causes fibrosis, tubular atrophy, and irreversible nephron loss [50]. Genes expressed by effector T cells, APCs, and macrophages stimulated with IFN- γ are abundant in the transcriptomic signature of TCMR. These transcripts are mostly related to T cell receptor signaling, T helper differentiation and communication between adaptive and innate immune cells; highlighting the importance of these pathways in TCMR [51]. Cytotoxic molecules like perforin, granulysin,

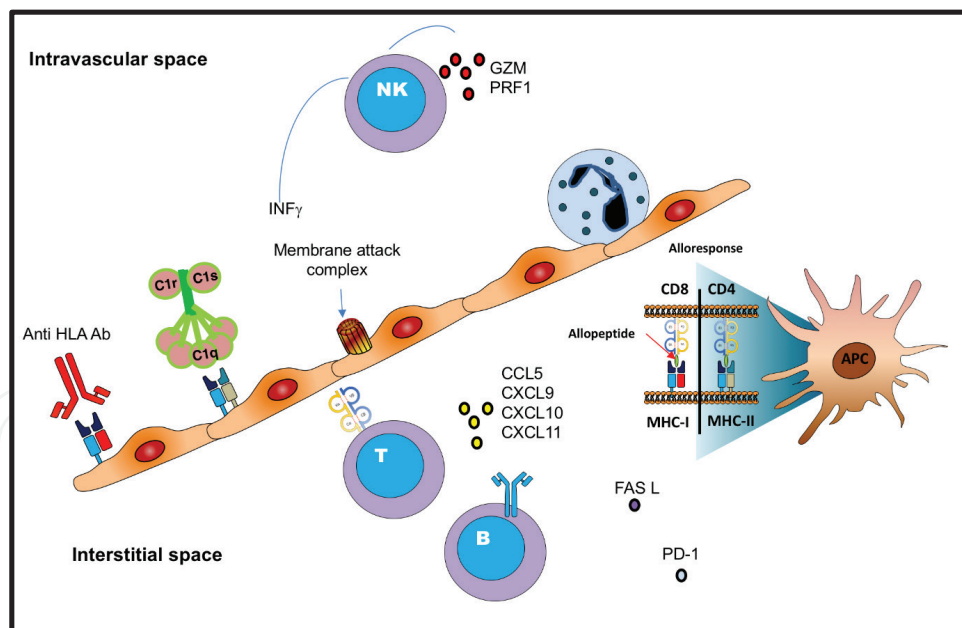


Figure 1. Mechanisms of ABMR and TCMR in kidney transplantation. Preformed and *de novo* DSAs, complement proteins, and antibody-dependent NK cell-mediated IFN- γ release and cytotoxicity have emerged as key immune players in the development of the microvascular damage characteristic of ABMR. Meanwhile, in TCMR the interaction of infiltrating T cells with intra-graft APCs and macrophages triggers an inflammatory response dependent on TCR synapse and subsequent activation, and characterized by chemokine (CCL5) and cytokine (CXCL9, CXCL10, and CXCL11) release.

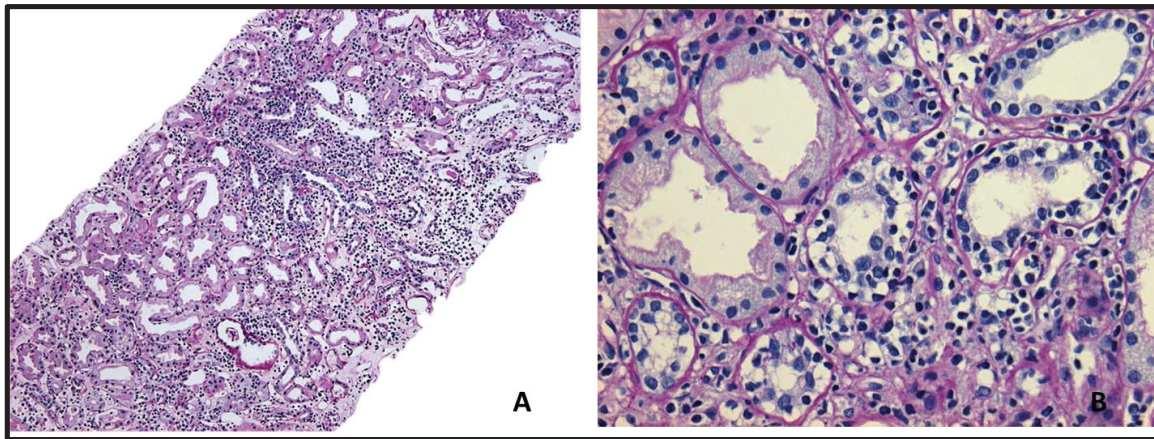


Figure 2. T cell-mediated rejection. The hallmark of TCMR is the infiltration of mononuclear cells to the interstitium and tubules. (A) Prominent interstitial inflammatory cell infiltrate. PAS 5 \times . (B) Higher magnification reveals infiltration of the tubular epithelium by mononuclear cells (tubulitis). PAS 40 \times . Courtesy of Dr. Claudia Mendoza-Cerpa, Laboratory of Pathology, IMSS-CMNO, Guadalajara; México.

Fas ligand, and granzyme A and B are also expressed in TCMR; though it has been demonstrated that they are not directly linked to the mechanism of injury [48, 52]. Instead, TCMR is considered an inflammatory reaction initiated by the engagement of TCR on cognate T cells with its antigen on APCs [53, 54]. It has been suggested that a very small proportion of infiltrating T cells are able to establish a TCR-mediated interaction with the allograft [55]. However, this interaction is important in the establishment of TCMR inflammatory phenotype since it activates the effector T cell and APC, induces $\text{INF-}\gamma$ secretion and further promotes myeloid and T cell recruitment by inducing chemokines and adhesion molecules [56]. Interestingly, increased expression of immune checkpoints responsible for modulating T cell activation such as cytotoxic T-lymphocyte antigen 4, programmed death-ligand 1 and 2 have also been associated with TCMR; suggesting these molecules might be regulating some of the interactions between T cells and APCs within the graft microenvironment [51]. Moreover, evidence that the programmed cell death protein 1 (PD1) pathway may be critical in maintaining tolerance and preventing TCMR comes from a report case in which administration of an anti-PD1 antibody to a kidney transplant recipient with metastatic cutaneous squamous-cell carcinoma resulted in allograft rejection [57].

B cells are robust APCs that can readily capture, process and present antigen for T cell recognition. Still, the role of B cells in TCMR development was initially overlooked since studies in B cell-deficient mice reported similar rejection rates in skin and heart transplants, as well as efficient CD4 T cell priming [58, 59]. The first evidence of a possible role of B cells in TCMR came from a systematic study of gene expression patterns using DNA microarrays in biopsy samples from renal allografts that found a surprising association between dense CD20+ B cell infiltrates and both, steroid resistance and graft loss [60]. Although the prognostic significance of CD20+ B cell infiltrates in acute cellular rejection is a matter of debate, the presence of these B cell clusters in cases of pure TCMR and their close proximity to CD4+ T cells suggests they might have antibody-independent functions in allograft rejection by acting as APCs [61–64]. Interestingly, reversible rejection episodes with monocytic infiltrates and scant T cells have been described in severely T cell-depleted patients, emphasizing the central role of macrophages in allograft rejection [65].

Macrophages in TCMR exert dual functions by promoting initiation and progression of kidney injury through secretion of proinflammatory mediators and interaction with other cells in the graft; whilst also in charge of tissue remodeling and repair during the recovery phase [66, 67]. Interestingly, reversible rejection episodes with monocytic infiltrates and scant T cells have been described in severely T cell-depleted patients, emphasizing the central role of macrophages in allograft rejection [65].

An increase in IFN- γ induces CCL5, CXCL9, CXCL10, CXCL11, and MHC class I and II expression; and is an important feature of TCMR [68, 69]. In the context of TCMR, IFN- γ has protective and proinflammatory functions as evidenced by IFN- γ -deficient recipient animals or donors lacking IFN- γ receptors or IFN- γ -regulated factor 1 [68, 70].

5.2. Antibody-mediated rejection

Evidence from multiple studies supports the humoral theory of transplantation strongly advocated by Dr. Paul Terasaki, in which antibodies are not only responsible for immediate hyperacute allograft rejection but can produce chronic vascular damage, fibrosis, and graft rejection months or even years posttransplantation [71]. Hyperacute allograft rejection occurs soon after the graft is perfused with blood of the recipient due to preformed

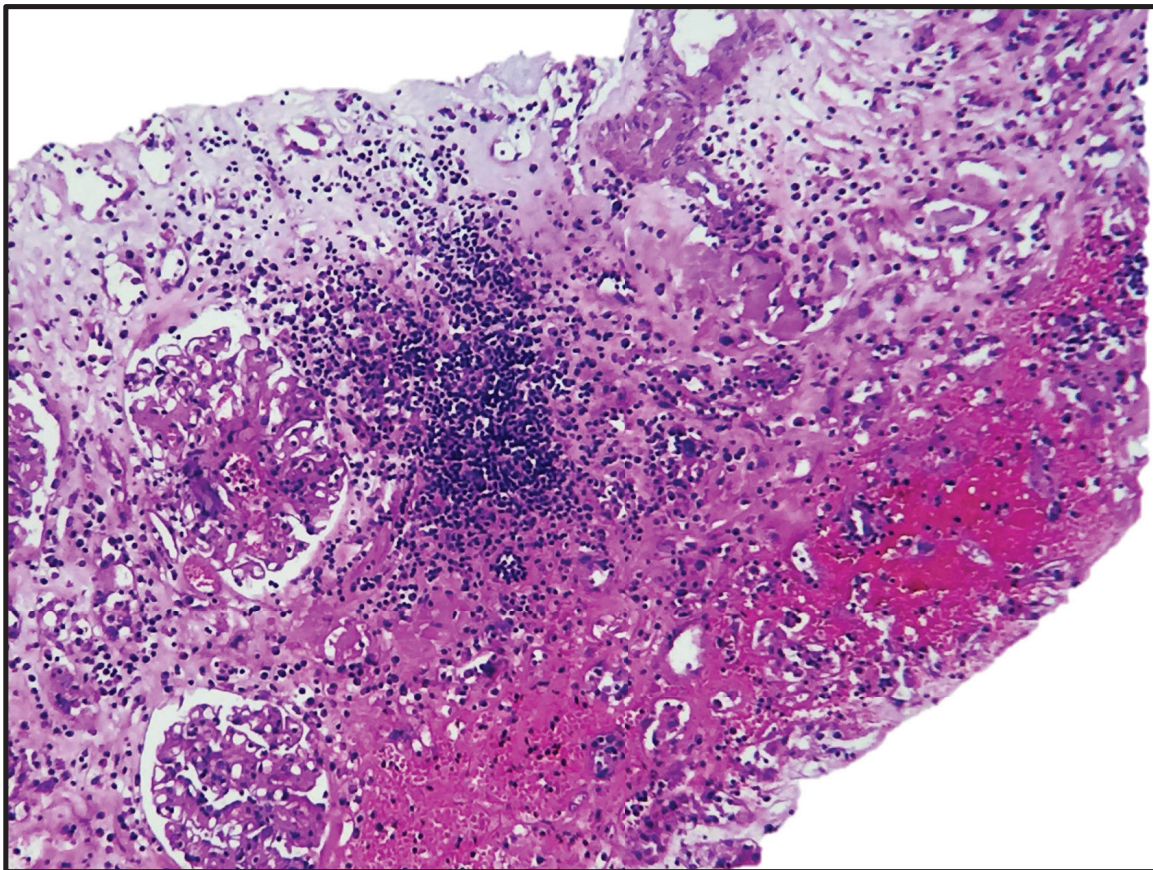


Figure 3. Interstitial hemorrhage in hyperacute allograft rejection. Microphotography shows severe capillary injury with subsequent peritubular capillary disruption. Hematoxylin & eosin 10 \times . Courtesy of Dr. Claudia Mendoza-Cerpa, Laboratory of Pathology, IMSS-CMNO, Guadalajara; México.

antibodies directed primarily at the vasculature of the donor organ [72]. These antibodies activate the complement cascade and induce neutrophil infiltration, endothelial damage, interstitial hemorrhage (**Figure 3**), edema, fibrin deposition, platelet aggregation, and thrombosis; causing the organ to fail within a few hours after transplantation. Hyperacute rejection used to be a frequent occurrence in transplantation before cross-match tests were designed to screen potential recipients for circulating anti-HLA antibodies to the prospective donor [73].

Antibody-mediated rejection (ABMR) pathogenesis involves mechanisms of graft injury caused by donor-specific anti-HLA antibodies (DSAs) and non-HLA antibodies; and has been associated with progressive decline in graft function and poor transplantation outcomes [74]. Molecular changes in the microvasculature characteristic of tissue remodeling and repair are common manifestations of ABMR, as well as neutrophilic infiltration and fibrosis (**Figure 4**) [50]. ABMR can be acute or chronic, and can also manifest in cases of mixed TCMR/AMBR rejection [2]. It is estimated that close to 20% of renal allograft recipients will develop *de novo* DSAs within 10 years posttransplant [75]. DSAs bind to allogenic HLA and non-HLA targets

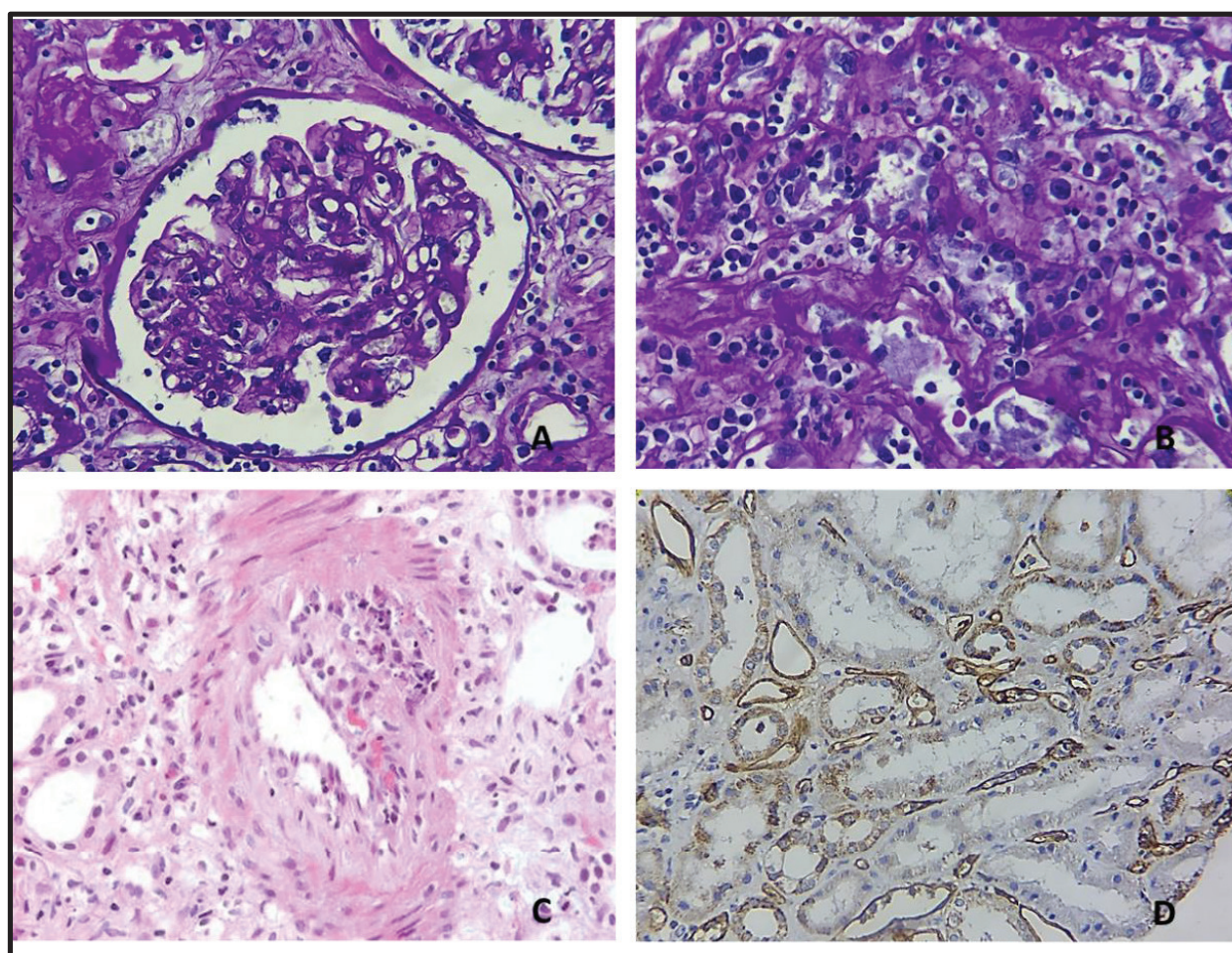


Figure 4. Antibody-mediated rejection. Two of the three criteria required for AMR. (A to C) Microvascular inflammation: glomerulitis, peritubular capillaritis, and intimal arteritis. PAS and H&E 40 \times . (D) Linear staining of C4d in peritubular capillaries IP 40 \times . Courtesy of Dr. Claudia Mendoza-Cerpa, Laboratory of Pathology, IMSS-CMNO, Guadalajara; México.

expressed by graft microvasculature and induce antibody-dependent cell cytotoxicity, complement activation and modulation of signaling pathways within vascular cells. These events promote the development of irreversible lesions that compromise graft function that eventually lead to rejection [76].

Complement activation is a well-established mechanism of ABMR [22, 77–79]. Although in some models, a causal relationship between antibody-mediated complement activation and graft damage has not been demonstrated [80]. DSAs bind to their targets on donor endothelial cells where they cause complement activation, and membrane attack complex formation. Interestingly, DSAs also activate an endothelial proinflammatory gene program to support allograft injury through noncanonical NF- κ B signaling [81]. The graft microvasculature limits antibody injury by inducing the expression of the complement inhibitors CD55 and CD59 [82]. IgG subclasses exhibit variability in their hinge region that controls Fc region affinity for Fc γ R and complement components [83]. Transcriptomic studies of ABMR biopsies have revealed an enrichment of endothelial, NK cells and IFN- γ -inducible transcripts. NK cells secrete IFN- γ upon Fc γ R crosslinking, a positive feedback mechanism that enhances HLA expression on endothelial cells and results in more DSA deposition and activation of local immunity [82].

6. Future directions

Improving kidney transplantation outcomes and patient survival is a challenging task. It is now clear that the cooperation between the innate and humoral arms of the immune system plays complex roles in graft tolerance and rejection. For this reason, understanding the immune mechanisms responsible for graft rejection in allotransplantation has become essential in our quest to develop better diagnostic tools and immunosuppressant therapies that can successfully be translated into the clinic.

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