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Educational Case

Educational Case: Renal allograft rejection

Harrison Dai, BS [a], Shirui Chen, MD [b], Jolanta Kowalewska, MD, PhD [a,*]

[a] Department of Pathology and Anatomy, Eastern Virginia Medical School, Norfolk, VA, USA
[b] Department of Internal Medicine, Division of Nephrology, Eastern Virginia Medical School, Norfolk, VA, USA

The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://www.journals.elsevier.com/academic-pathology/news/pathology-competencies-for-medical-education-pcme.[1]

Keywords: Pathology competencies, Disease mechanisms, Immunological mechanisms, Immune dysfunction, Transplantation, Rejection, Human leukocyte antigen

Primary objective

Objective IM1.8: Transplantation. Discuss the consequences of tissue transplantation, including mechanisms and pathophysiology of graft vs. host organ rejection, and the possible therapeutic interventions that can mitigate these effects.

Competency 1: Disease mechanisms and processes; Topic: Immunological mechanisms (IM); Learning goal 1: Immune dysfunction

Secondary objective

Objective IM1.7: Human leukocyte antigen (HLA). Discuss the structure and function of human histocompatibility antigens and describe the role of this system in both transplantation and susceptibility to certain diseases.

Competency 1: Disease Mechanisms and Processes; Topic: Immunological Mechanisms (IM); Learning Goal 1: Immune Dysfunction

Patient presentation

A 25-year-old man with a history of end-stage renal disease secondary to idiopathic membranoproliferative glomerulonephritis presents for a follow-up visit 6 months after renal transplantation. Prior to transplantation, the patient had been on hemodialysis for two years and was anuric. He received a deceased donor kidney transplant from a 32-year-old woman who died due to injuries sustained in a motor vehicle crash. After transplantation, he no longer required dialysis and his serum creatinine returned to the normal reference range. The patient is on a combination of immunosuppressive therapies including mycophenolate mofetil, tacrolimus, and prednisone. He admits to missing a few doses of his immunosuppressive medications in the week prior to the follow-up visit due to being distracted by a breakup with his partner.

Vital signs show a blood pressure of 122/58 mm Hg, heart rate of 74 beats per min, respiratory rate of 18 breaths per min, oxygen saturation of 98%, body mass index of 31.07 kg/m^2, and a temperature of 97.6 °F. On physical examination, the patient appears well-nourished and is not in acute distress. On neurologic examination, he is alert, fully oriented, and answering questions and conversing fluently. Cardiovascular examination shows a regular heart rate and rhythm, and is also negative for jugular vein distension or murmur. Pulmonary examination shows non-labored breathing and is negative for crackles or wheezes. Abdominal examination shows no tenderness in any quadrant over the right iliac fossa transplant site. There is no distension or bruits. The transplant incision in the right lower quadrant appears well healed without dehiscence, erythema, or discharge. Examination of the patient's extremities reveals no pitting edema and the presence of strong, palpable pulses in all four extremities.

Diagnostic findings, Part 1

Routine laboratory tests after renal transplantation are performed and are presented in Table 1.

* Corresponding author. Department of Pathology and Anatomy, Eastern Virginia Medical School, 700 W. Olney Road, Norfolk, VA, 23507, USA.
E-mail address: Kowalej@evms.edu (J. Kowalewska).

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Table 1
Laboratory values at six months after renal transplantation.

Laboratory Test	Result	Reference Range
Hematologic:		
White blood cell count	6200	4.5–11.0x109/L
Hemoglobin	15.5 g/dL	13.5–17.5 g/dL
Hematocrit	46%	41%–53%
Platelet count	320,000/mm3	150,000–400,000/mm3
Basic metabolic panel:		
Sodium, serum	140 mEq/L	136–145 mEq/L
Potassium, serum	3.6 mEq/L	3.5–5.0 mEq/L
Chloride, serum	100 mEq/L	95–105 mEq/L
Bicarbonate, serum	23 mEq/L	22–28 mEq/L
Urea nitrogen, serum	29 mg/dL	7–18 mg/dL
Creatinine, serum	1.9 mg/dL	0.9–1.3 mg/dL
Prior creatinine values at previous follow-up visits after transplant	1.0–1.3 mg/dL	
Glucose, serum	88 mg/dL	70–110 mg/dL
Urinalysis:		
Color	Light yellow	Straw, light yellow, yellow, dark yellow
Clarity	Clear	Clear
pH	5.5	4.5–8
Protein	Negative	Negative
Occult blood	Negative	Negative
Specific gravity	1.010	1.005–1.025
Glucose	Negative	Negative
Ketones	Negative	Negative
Nitrites	Negative	Negative
Leukocyte esterase	Negative	Negative
Bilirubin	Negative	Negative
Urobilinogen	1.0 mg/dL	< 2.0 mg/dL
Squamous epithelial cells	0–2/hpf	0–2/hpf
Hyaline cast	10/lpf	< 20/lpf
Immunosuppressant level:		
Tacrolimus	4.7 ng/dL	7–9 ng/dL in a patient 3–6 months post renal transplantation

Questions and discussion points, Part 1

What are the pertinent positive and negative findings among the hematologic tests and urinalysis?

The presence of a normal white blood cell count rules out the presence of severe infection (which may cause elevated or low white blood cell count). Low white blood cell count can be a side effect of some immunosuppressive drugs, such as mycophenate mofetil. The presence of normal serum hemoglobin and hematocrit rules out the presence of bleeding (although this is more of a concern in the immediate post-operative period rather than 6 months after transplantation). It also rules out the presence of hemolytic anemia, which can be a side effect of tacrolimus. The absence of leukocyte esterase and nitrite in the urinalysis rules out the presence of a urinary tract infection.

Why were serum creatinine, Blood urea nitrogen (BUN), and tacrolimus levels assessed?

Creatinine is a waste product as a result from creatine breakdown that occurs within muscle metabolism. Serum creatinine level is used as a standard to measure glomerular filtration rate to assess how efficiently kidneys filter.[2] In typical or routine clinical settings, creatinine and BUN (blood urea nitrogen) are included in standard metabolic panels, while tacrolimus levels are assessed separately in patients requiring therapeutic drug monitoring such as in transplant patients. Tests assessing serum creatinine and BUN are often used to assess kidney function following renal allograft transplantations. Any abnormalities in serum creatinine or BUN suggest renal insufficiency or possible renal failure. A rise in serum creatinine above a prior baseline, in particular, raises concern for an acute etiology of renal dysfunction. Additionally, levels of tacrolimus, an immunosuppressant often given to transplant recipients, are often monitored to ensure the drug is within its therapeutic range in efforts to decrease the probability of an allograft rejection. Inadequate blood concentrations of immunosuppressants in transplant recipients increase the risk of the recipient's immune system recognizing the donor graft as foreign and rejecting the donor tissue.

What is the differential diagnosis based on the initial clinical scenario?

As previously alluded to, elevated serum creatinine levels suggest possible renal insufficiency or failure. Given the clinical context of this patient, suspicions should be raised for the possibility of failure or dysfunction of the renal allograft itself. It is important to note that if a patient has evidence of renal failure in the absence of transplantation, other differential diagnoses need to be considered, for instance, drug reactions.

The differential diagnoses for elevated serum creatinine in renal allograft dysfunction are dependent on several factors, including the etiology and mechanisms of the allograft dysfunction. However, other factors such as the timing of an allograft transplant can be useful to narrow the differential diagnosis (Table 2)[2–4] When renal allograft dysfunction is observed shortly after post-transplantation, notable differentials include postischemic acute tubular necrosis, hyperacute antibody-mediated transplant rejection, volume depletion, and surgical complications. In cases where allograft dysfunction is observed after a significant amount of time after transplantation, differential diagnoses that are associated involve acute organ rejection, viral infections due to BK polymavirus (BKV) or cytomegalovirus (CMV), calcineurin inhibitor nephrotoxicity, and thrombotic microangiopathy.[3]

What further diagnostic tests should be done?

In a patient presenting with signs of allograft dysfunction less than 1 week after transplantation, daily urine output before transplantation needs to be compared with urine output post-transplantation. Renal imaging, such as ultrasound with Doppler and radionuclide renal scans should be used to rule out obstruction, vascular thrombosis, and urinary leaks. A bladder volume greater than 300 mL after voiding is generally considered indicative of urinary retention. Testing for the presence of donor-specific antibodies (DSAs) would also be needed. If clinically indicated, an allograft biopsy should be obtained to assess for acute cellular or antibody-mediated rejection. In patients presenting with signs of allograft dysfunction more than a week later after transplantation, several different lab values should be obtained: tacrolimus level, reverse-transcriptase polymerase chain reaction (PCR) to assess for possible BKV and CMV infection, DSA titers, and additional information about the donor kidney (for example, estimated glomerular filtration rate, kidney donor profile index that indicates the quality of deceased donor kidneys relative to other recovered kidneys). Volume status can be assessed by asking the patient

Table 2
Possible differential diagnoses of renal allograft dysfunction at different times after transplantation.[2–4]

Post-transplantation period <1 week	Post-transplantation period after one week
• Postischemic acute tubular necrosis • Hyperacute antibody-mediated rejection • Volume depletion, surgical complications (i.e., vascular thrombosis, urinary leaks, lymphocele) • Multiple renal arteries • Atheroemboli • Calcium oxalate deposits	• Acute rejection • Calcineurin inhibitor nephrotoxicity, thrombotic microangiopathy • Recurrent primary disease • Transplant renal artery stenosis • Urinary obstruction • Viral infections (i.e., BK virus and cytomegalovirus) • *de novo* glomerular disease • Chronic allograft nephropathy

about a history of poor fluid intake, vomiting, diarrhea, and decreased urination, as well as by physical examination of peripheral edema, capillary refill and skin turgor, and by measuring orthostatic vital signs.

Diagnostic findings, Part 2

Orthostatic vital signs are measured and are negative for orthostasis. PCR testing shows no detectable CMV or BKV. A renal and bladder ultrasound is then performed and shows no signs of hydronephrosis and a post-void bladder volume of 13 mL. Doppler ultrasonography is also performed on the transplant renal artery and vein and reveals no hemodynamically significant stenosis or evidence of thrombosis. Ultrasonography additionally did not identify the presence of any fluid collections in the iliac fossa that might represent a collection of urine (urinoma), blood, or pus.

A renal allograft biopsy is then performed and an adequate sample containing 20 open glomeruli is obtained.

Questions and discussion points, Part 2

What are histological findings seen in the biopsy (Fig. 1)?

The biopsy shows interstitial inflammation involving approximately 30% of the sampled parenchyma and the presence of frequent tubulitis (illustrated by the arrow in Fig. 1A). (See Fig. 1A and B). The interstitial inflammation observed in the biopsy is composed predominately of lymphocytes. Peritubular capillaries seen in the biopsy contain numerous leukocytes (illustrated in Fig. 1A by the arrowhead). The glomeruli, not shown, appear hypercellular due to increased number of circulating leukocytes (glomerulitis). The biopsy also shows no significant interstitial fibrosis or tubular atrophy. A few arterial cross sections in the sample also show lifting and endothelial cell swelling with leukocytes infiltrating underneath the endothelium (also known as endarteritis, illustrated by Fig. 1B). Routine immunofluorescence staining, not shown, is negative for IgG, IgA, IgM, C3, C1q, and kappa and lambda light chains.

How can the biopsy findings help to narrow the differential diagnosis?

The biopsy shows renal interstitial inflammation, also known as interstitial nephritis, which occurs when both the interstitium and renal tubules become infiltrated by leukocytes. Interstitial nephritis can be categorized as acute, lasting for a few days, or chronic, lasting up to months. There are many processes that can contribute to or cause interstitial nephritis in renal allografts. The differential diagnosis includes acute T cell-mediated organ rejection, drug reactions, and bacterial or viral infections. In this particular case, the pathologic findings are indicative of acute T cell-mediated rejection.

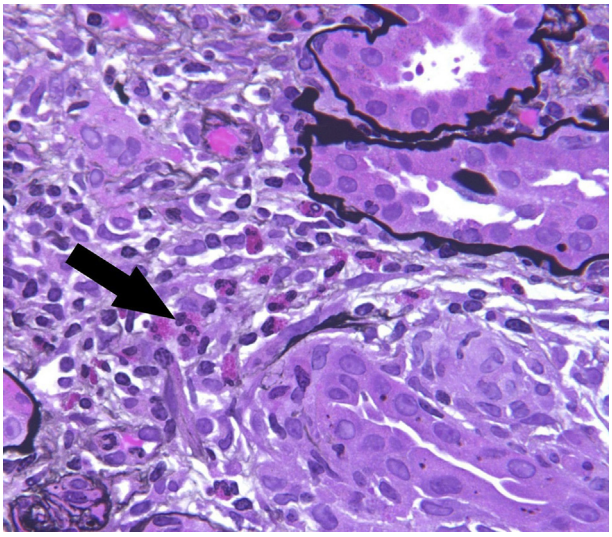

Fig. 2. Interstitial inflammation containing clusters of eosinophils (arrow) is suggestive of allergic drug reaction (Jones methenamine silver stain, original magnification 400x).

Acute organ rejection, mediated by T lymphocytes, is histologically characterized by interstitial nephritis containing a predominant population of $CD4^+$ lymphocytes admixed with $CD8^+$ lymphocytes and macrophages. By definition, interstitial inflammation involves both interstitium and tubules (tubulitis). Severe cases of T cell-mediated rejection involve arterial vessels with histologic changes ranging from mild infiltration of the intima (endarteritis) to transmural necrosis of the arterial wall. Classification of T cell-mediated rejection is based on the degree of interstitial inflammation, tubulitis, and arteritis.[5]

If a biopsy were to show a significant presence of eosinophil aggregates identified by hematoxylin and eosin (H&E) stained sections, then that would be strongly suggestive of a drug reaction (illustrated by Fig. 2). Biopsies with interstitial inflammation containing numerous polymorphonuclear leukocytes and leukocytic casts ("pus casts") would be indicative of an intrarenal bacterial infection (illustrated by Fig. 3). Viral infections, such as CMV and BK polyomavirus are characterized by inflammatory infiltrates containing lymphocytes and/or plasma cells and the presence of viral cytopathic effects in the tubular epithelial cell nuclei. The most common viral infection in the renal allograft caused by BK polyomavirus is characterized by the presence of basophilic "ground glass" intranuclear inclusions (illustrated by Fig. 4A).[6] Viral infection can be confirmed by the immunohistochemical stains for CMV and SV40, which is a marker for polyomaviruses (See Fig. 4B).

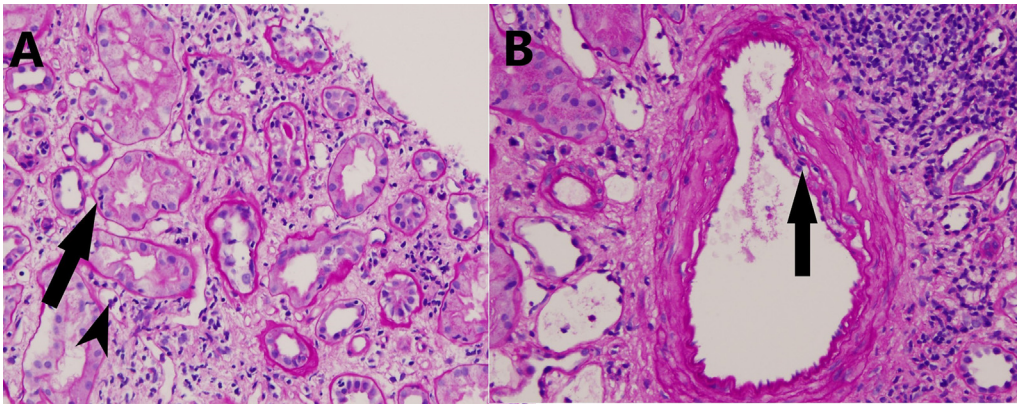

Fig. 1. Renal allograft biopsy. (A) Predominately lymphocytic inflammation with frequent tubulitis (arrow) (PAS, original magnification 200x). Peritubular capillaries contain numerous leukocytes (arrowhead). (B) Enadarteritis: lymphocytes infiltrating the intima (arrow), (PAS, original magnification 400x).

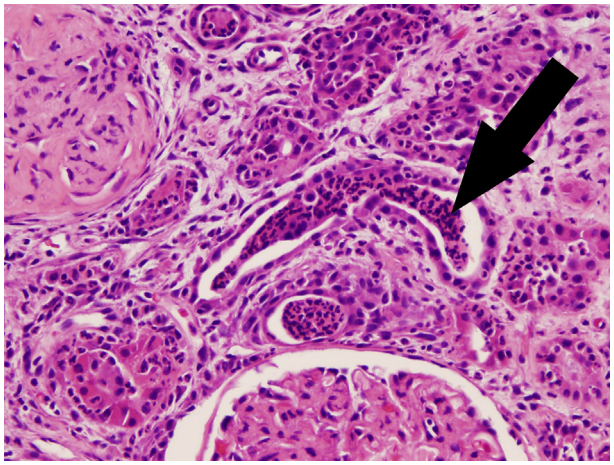

Fig. 3. Pyelonephritis is characterised by neutrophilic infiltrate along with tubular "pus casts" (arrow); (hematoxylin & eosin, original magnification 200x).

How can the various types of transplant rejections be differentiated from one another?

There are three types of transplant rejection each with unique onsets and pathogeneses: hyperacute, acute, and chronic (Table 3).[7,8] Hyperacute rejection is mediated by the presence of pre-existing antibodies in the recipient's immune system to the donor specific blood group or human leukocyte antigens. This type of rejection is characterized by a rapid onset from minutes to hours. Histologically, it is characterized by the presence of intravascular thrombosis that ultimately leads to ischemia or necrosis.[7] Donor grafts cannot be salvaged in hyperacute rejection and need to be immediately removed.

In acute transplant rejection, the symptoms of rejection are usually observed in the time span of days to months. In some situations, acute transplant rejection can present several months after initial transplantation. This type of rejection is caused by cellular responses involving $CD8^+$ and $CD4^+$ T cells that react to donor HLAs (T cell-mediated rejection). Histologically, acute cell-mediated rejection is characterized by various degrees of interstitial inflammation, tubulitis, and/or arteritis. Another mechanism of acute rejection involves *de novo* production of antibodies against donor HLAs (or DSAs that bind to the donor's endothelium and activate complement cascades leading to inflammation and allograft failure). This type of rejection is referred to as antibody-mediated or humoral rejection (ABMR). Histological hallmarks of ABMR include inflammation of renal capillaries (glomerulitis and peritubular capillaritis) or arterial vessels (vasculitis), and peritubular deposition of C4d.[5]

Table 3
Timing and pathogenesis of allograft rejection.[7,8]

Rejection Type	Time to Onset	Pathogenesis
Hyperacute rejection	Rapid; minutes to hours	Pre-existing antibodies to donor graft
Acute rejection	Slow; days to months	T cell-mediated reaction to donor graft or the development of antibodies against the donor graft after transplantation
Chronic rejection	Very slow; months to years	Humoral and cellular responses to donor graft

What is HLA and how does it relate to transplantation rejection?

Human leukocyte antigens or HLAs, are molecules that display peptide fragments of protein antigens for recognition by antigen specific T cells.[7] HLAs play crucial roles in maintaining immunological homeostasis and preventing the body's immune system from attacking itself. There are two major classes of HLAs: type I which are found on virtually every nucleated cell in the human body and type II which are found primarily on antigen presenting cells and can be recognized by $CD4^+$ T cells. Both class I and class II HLAs are implicated in organ or tissue graft rejection.[10]

A patient who undergoes an organ transplant will likely receive an organ or graft that will contain HLAs which differ from theirs. Differing HLAs on a donor organ will be perceived by the recipient's as a foreign entity and will subsequently trigger an immune response that will target and eventually destroy the transplanted organ. This process is commonly known as transplant rejection. Immune responses can involve the recipient's immune system containing pre-existing or *de novo* antibodies against the donor organ or recruiting T lymphocytes to directly attack the donor tissue. It is also possible that immune responses against foreign HLAs can involve a combination of antibodies and $CD8^+$ T lymphocytes.[11]

Describe the pathogenesis of cell-mediated rejection

The rejection of transplanted organs is a consequence of the recognition of foreign HLAs expressed in the transplanted organ. Following transplantation, the recipient's T cells recognize the donor's HLAs via two pathways. The direct pathway recognition involves the reaction to the recipient's T cells from the donor antigens presented by antigen presenting cells (APCs). In the indirect recognition pathway, the donor's antigens are first processed and then presented to the host T cells by the host APCs. Cell-mediated rejection of transplanted organs is an example of a type IV hypersensitivity reaction. Both direct and indirect pathways of antigen recognition lead to activation of $CD8^+$ and $CD4^+$ T cells. Direct cellular cytotoxicity is mediated by $CD8^+$ T cells, which develop into cytotoxic T lymphocytes (CTL). In contrast, $CD4^+$ T cells release pro-

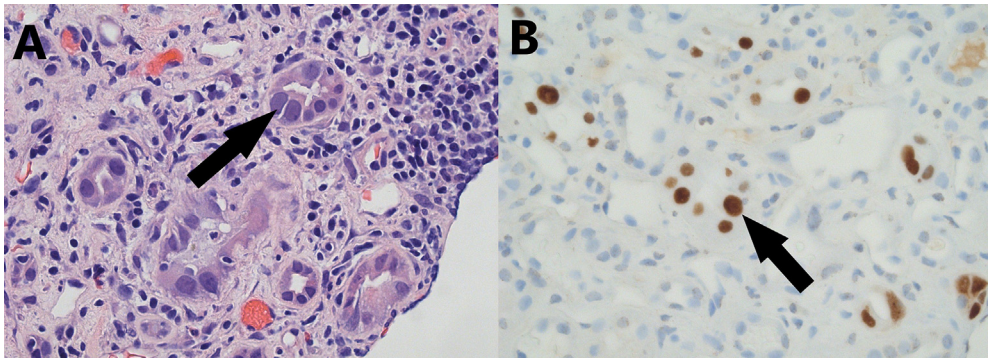

Fig. 4. (A) BK polyomavirus nephropathy with lymphoplasmacytic inflammatory infiltrate and characteristic basophilic viral inclusions in the tubular epithelial cell nuclei (arrow) (Hematoxylin & Eosin, original magnification 400x). (B) SV40 staining is positive in cells infected by polyomavirus (arrow; immunohistochemistry, original magnification 400x).

inflammatory cytokines such as IL-2 that subsequently recruit neutrophils and macrophages.[7]

Diagnostic findings, Part 3

Additional routine staining for C4d is performed on the biopsy.

Immunohistochemical staining for C4d shows diffuse positivity in the peritubular capillaries (Fig. 5).

Questions and discussion points, Part 3

What is C4d and how does the additional C4d staining add to the differential diagnosis?

C4d is the degradation product of the complement factor C4, a component of the classical complement cascade, which is typically initiated by binding of antibodies to specific target molecules. C4d covalently binds to endothelial cell surfaces and vascular basement membranes near the sites of C4 activation and can be easily detected by immunohistochemistry (as illustrated in Fig. 5). Detection of C4d in an allograft biopsy is regarded as an indirect sign, or a "footprint" of an antibody response, and together with glomerulitis and peritubular capillaritis, is considered a criterium for a pathological diagnosis of ABMR.[12–14]

What additional laboratory studies should be performed?

Antibody-mediated renal allograft rejection is mediated by DSAs that react with graft endothelium leading to the deposition of complements, notably C4d. This form of rejection, termed "acute humoral rejection," has a typical but variable morphology and is accompanied by a distinctly worse prognosis when compared to T cell-mediated rejection.[15] Presence of DSAs would help to confirm the diagnosis of antibody-mediated organ rejection. In this particular case, the patient tested positive for multiple *de novo* anti-HLA DSAs and thus would establish the presence of antibody-mediated organ rejection.

What is the pathogenesis of antibody-mediated (humoral) rejection?

Antibody-mediated rejection is a process in which the recipient's immune system generates antibodies specifically directed toward the donor antigens. In contrast with cell-mediated rejection, antibody-mediated rejection is a type II hypersensitivity reaction in which does not involve direct cellular combat with graft tissue. Antibody production occurs once the appropriate B-cells are stimulated. Exogenous antigen presentation occurs via dendritic cells through HLA class II and is recognized by $CD4^+$ receptors on naïve T lymphocytes. CD40 receptors on B-cells then bind to CD40 ligand (CD40L) on $CD4^+$ T-helper cells. Activated helper T cells then begin secreting cytokines that determine immunoglobin class switching of B-cells. Once B cells are activated, the cells then undergo affinity maturation, proliferation, and then subsequently proceed to produce antibodies against donor tissue.[16] Binding of antibodies to foreign allograft tissue can lead to a variety of consequences such as cellular destruction, inflammation, and cellular dysfunction.[7]

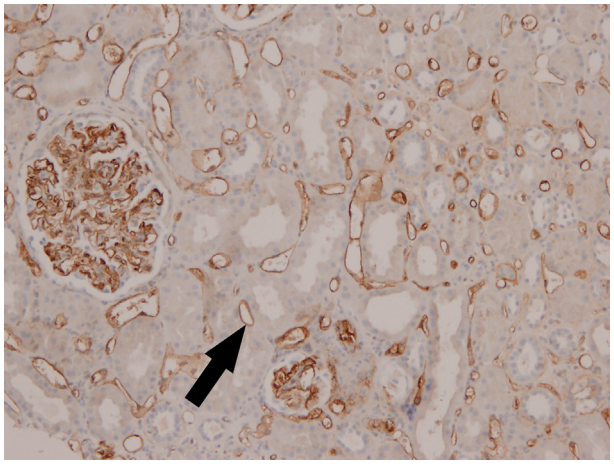

Fig. 5. Diffuse staining of peritublar capillaries for C4d (arrow; immunohistochemistry, original magnification 100x).

What is the final diagnosis in this case?

Acute tubulointerstitial and vascular T cell-mediated rejection and concurrent acute antibody-mediated rejection.

How is organ transplantation rejection typically treated?

All patients (except in recipients of HLA-identical allografts from a monozygotic twin) following solid organ transplantation require immunosuppressive treatment to prevent rejection. The major immunosuppressive agents that are available include glucocorticoids, azathioprine, mycophenolate mofetil, enteric-coated mycophenolate sodium (EC-MPS), cyclosporine, tacrolimus, everolimus, rapamycin (sirolimus), and belatacept.[17,18] Conventional maintenance regimens consist of a combination of, most commonly three, immunosuppressive agents that differ by mechanisms of action. Treatment of acute rejection is guided predominantly by the histopathologic severity of rejection, and includes increasing the dose of currently used medications or switching to a different drug. Although there is no specific therapy to treat chronic rejection, a modification of maintenance regimens should be initiated to prevent the loss of allograft function.[19] The primary goal of treating ABMR is to remove existing DSAs and to eradicate the clonal population of B cells or plasma cells that is responsible for antibody production. The most common approach includes a combination of glucocorticoids, plasmapheresis, intravenous immunoglobulin (IVIg), and, in some patients, rituximab (anti-CD20 antibody).[20]

Diagnostic findings, Part 4

The patient in this case was hospitalized and treated with high dose intravenous methylprednisolone, pulsed at a dose of 1 g daily for three days, followed by a return to his maintenance glucocorticoid dose of 5 mg prednisone daily. His serum creatinine peaked on hospital day 1 at 2.1 mg/dL, followed by a gradual decrease over the following 8 weeks to stabilize at 1.5 mg/dL. His serum creatinine did not return to his prior baseline of 1.0–1.3 mg/dL, and his nephrologists felt that he most likely sustained a degree of irreversible damage to his allograft due to the episode of rejection.

Questions and discussion points, Part 4

What follow-up measures should be taken for this patient?

First and foremost, any treatment and follow-up measures should be made in efforts to preserve the integrity of an organ transplant or allograft.[21] Routine laboratory tests, such as monitoring immunosuppressant medication levels, are imperative in terms of evaluating allograft transplant functionality. Transplant recipient patients should also be followed by their primary care providers and any other pertinent healthcare providers on a regular basis to ensure that recommended regimens are either being adhered to or readjusted based on a patient's clinical course.[18–20] For this patient in particular, initial efforts should be made to preserve the initial allograft, especially making sure that the patient is compliant with his immunosuppressant regimen. If the allograft is not salvageable, then it should promptly be removed. Additionally, this patient would also likely benefit from receiving education on the importance of

immunosuppressant adherence and the associated risks and complications of transplant rejection.

Teaching points

- HLA typing and compatibility are significant factors to consider whether an organ transplant recipient will develop an immune response to a graft.
- Transplantation recipients require immunosuppressive medications to reduce the probability of transplant rejection.
- It is important to educate transplant patients on immunosuppressive medication adherence and compliance.
- Organ rejection can either be mediated by humoral, cellular responses, or a combination of both.
- Hyperacute organ rejection is attributed to the pre-existing antibodies to the donor antigens.
- Acute cell-mediated allograft rejection is mediated predominately by $CD8^+$ T lymphocytes.
- Cell-mediated rejection is primary due to type IV hypersensitivity reactions which involves cell-mediated cytotoxicity.
- Antibody-mediated rejection is due to *de novo* production of donor specific antibodies and is considered a type II hypersensitivity reaction.
- C4d staining of peritubular capillaries serves as a diagnostic tool of antibody-mediated rejection.
- Serum creatinine values are used as a standard to assess for renal function.
- Increased serum creatinine levels typically indicate either renal insufficiency or injury.
- There are many differential diagnoses for renal allograft dysfunction in which require a considerable number of laboratory tests to narrow a possible diagnosis.

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Declaration of competing interest

No conflicts of interest need to be declared.

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