

Acute myeloid leukemia after kidney transplantation: a case report and literature review

A leucemia mielóide aguda após transplante renal: um relato de caso e revisão da literatura

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ABSTRACT

The incidence of malignancy is greater in kidney transplant recipients compared to the general population, though the higher risk is not equally distributed to all types of cancers. In face of the increased longevity of renal transplant recipients, certain cancers, such as acute leukemias, are becoming more prevalent. Acute myeloid leukemia (AML) typically presents with cytopenias and infections, both common findings after kidney transplantation. Therefore, the diagnosis of AML may be initially overlooked in these patients. We report the case of a 33-year-old man who presented with fever, pancytopenia and acute worsening of his renal allograft function 9 years after a living unrelated kidney transplant. After initial negative infectious work-up, a kidney biopsy revealed C4d-positive antibody-mediated rejection in combination with scattered atypical inflammatory cells. A subsequent bone marrow biopsy confirmed AML. He underwent successful induction chemotherapy with daunorubicin and cytarabine and ultimately achieved a complete remission. However, he developed a Page kidney with worsening renal function and abdominal pain three weeks after biopsy in the setting of chemotherapy-induced thrombocytopenia. Herein, we discuss the prevalence, risk factors, presentation and management of leukemia after kidney transplantation.

Keywords: kidney transplantation; leukemia, myeloid, acute; neoplasms, second primary.

INTRODUCTION

After solid organ transplantation, an increased incidence of malignancy has been reported compared to the general

RESUMO

A incidência de cancer é maior em receptores de transplante renal em comparação com a população em geral, entretanto, o maior risco não é igualmente distribuído em todos os tipos de cancers. Em face do aumento da longevidade de pacientes transplantados renais, certos cancers, tais como leucemias agudas, são cada vez mais prevalentes. Leucemia mielóide aguda (LMA) normalmente se apresenta com citopenias e infecções, quadro comum após o transplante renal. Portanto, o diagnóstico da LMA pode ser inicialmente negligenciado nestes pacientes. Relatamos o caso de um homem de 33 anos de idade que se apresentou com febre, pancitopenia e agravamento agudo da função do enxerto renal de 9 anos após transplante de rim de doador vivo. Após inicial testes negativos para infecção, uma biópsia renal revelou rejeição por anticorpos com C4d positivo e dispersas células inflamatórias atípicas. A subsequente biópsia de medula óssea confirmou LMA. A quimioterapia de indução foi bem-sucedida com daunorubicin e citarabina e, finalmente, obtida uma complete remissão. No entanto, ele desenvolveu uma "Page kidney" com piora da função renal e dor abdominal, três semanas após a biópsia no contexto da trombocitopenia induzida pela quimioterapia. Aqui, discutimos a prevalência, fatores de risco, apresentação e manejo da leucemia pós-transplante renal.

Palavras-chave: leucemia mielóide aguda; transplante de rim; segunda neoplasia primária.

population. In fact, malignancy is the third leading cause of death in solid organ transplant recipients.¹⁻⁴ The incidence and prevalence of cancer in transplant

patients have increased over the past 10 years, partly related to the older age of recipients as well as the use of more potent immunosuppression.³ Therefore, understanding the different facets of cancer after kidney transplantation and its early presenting signs and symptoms have become essential for the long-term care of transplant recipients.

The increased incidence of cancer in the transplant population seems to be a multi-factorial process, involving genetic, immune, environmental and in some cases, viral components. Transplant recipients have an increased risk for only certain types of malignancies. For example, the rate of both breast and prostate cancer are not significantly increased after transplantation, while lymphoma and skin cancers are up to 30-fold more common after transplantation.⁴⁻⁶ Although leukemia accounts for a small percentage of non-cutaneous cancers post-transplantation, there is still a five-fold higher incidence than in the general population.⁵

Among leukemias, acute myeloid leukemia (AML) accounts for 43% of post transplant leukemia.⁷ Based on the significant mortality of malignancy post-transplant, early diagnosis and treatment is critical for the improvement of transplant recipients' survival. Herein, we present a case and a literature review of AML after transplantation.

CASE REPORT

CLINICAL HISTORY AND INITIAL LABORATORY DATA

A 33-year-old man with a history of end-stage renal disease from focal segmental glomerulosclerosis was managed solely with steroid therapy until he underwent a living-unrelated donor kidney transplant in 2004 after progressive deterioration in renal function. Patient had a panel reactive antibody (PRA) of zero.

At the time of the transplant, immunosuppressive agents included thymoglobulin for induction therapy, followed by tacrolimus, mycophenolate mofetil and prednisone as maintenance. Despite the absence of hypotension, rejection or surgical complications, the patient's allograft function never improved beyond a creatinine of 2 mg/dL. At 6 months post-transplant, a biopsy was performed, which demonstrated calcineurin inhibitor toxicity.

The patient was then switched from tacrolimus to sirolimus. Prednisone was discontinued several months post-transplant due to the development of severe acne. His creatinine stabilized at 2.5 mg/dl over

the following eight years, during which time he was followed at another Transplant Center.

In 2013, nine years after his renal transplant, the patient presented to the hospital with fever, chills and left-sided buccal pain. Upon arrival, the patient's temperature was 39.2 degrees Celsius, blood pressure was 162/102 mm Hg and heart rate was 133. His physical examination was remarkable for a small area of induration on his buccal mucosa consistent with an aphthous ulcer and facial erythema suggestive of cellulitis. No lymphadenopathy or splenomegaly were present.

At the time, the patient's medications included sirolimus, mycophenolate mofetil and metoprolol. The blood work demonstrated a white blood cell count of 1,400/ μ L (35% neutrophils, 44% lymphocytes, 8% monocytes, 13% atypical lymphocytes), a hemoglobin of 9.6 g/dL, and a platelet count of 111,000/ μ L. Examination of the peripheral smear was only significant for the presence of a few atypical lymphocytes. His renal allograft function had worsened with a serum creatinine of 4 mg/dL. Sirolimus level was 3.5 mg/mL.

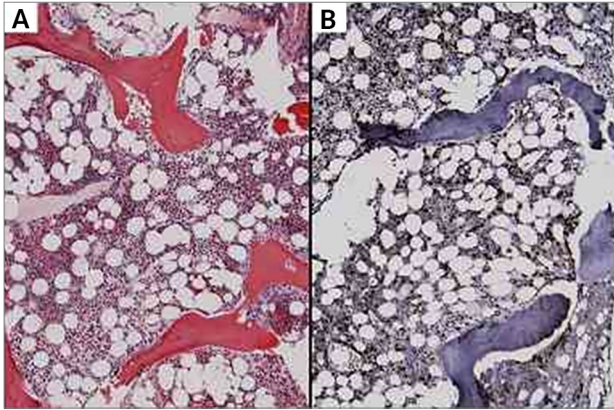
The patient's urine sediment was significant for 2+ protein and trace blood with few non-dysmorphic red blood cells. An ultrasound demonstrated a kidney allograft of 13 cm with normal resistive indices; multiple parapelvic cysts and one cortical cyst.

The patient's infectious work up was negative despite multiple blood and urine cultures and extensive studies for viral etiologies, including cytomegalovirus, adenovirus, HTLV-1, and Epstein Barr virus. The patient's serum creatinine remained elevated even after hydration with intravenous fluids. Circulating anti-human leukocyte antigen (HLA) class I and class II donor specific antibodies (DSA) were detected by single antigen solid phase assay. A bone marrow biopsy and a kidney biopsy were performed to further investigate his hematologic abnormalities and worsening kidney function, respectively.

BONE MARROW BIOPSY/ASPIRATE

Bone marrow biopsy demonstrated a hemorrhagic, normocellular marrow with 50% fat. Twenty five percent of the cells were blast forms as was evident by the CD34 immunostain (Figure 1). Myeloid elements were moderately proportionally increased and exhibited maturation but included frequent immature forms. The bone marrow aspirate confirmed the presence of 28% blasts.

Figure 1. Bone marrow biopsy, representative images; (A) Approximately 25% of the cellularity is comprised of small to intermediate sized cells with irregular nuclei and small amounts of cytoplasm, consistent with blast forms occurring singly and in small clusters. The lesion was focal and the figure represents a more involved area. (H&E, 200x). (B) Immunostain for CD34 highlights approximately 25% of the cellularity.



Flow cytometry revealed a population of immature cells positive for CD45, CD34, HLA-DR, CD13, CD117, CD15, and negative for CD33 and other monocytic, B and T lymphoid markers. The overall findings were consistent with involvement by AML. Cytogenetics revealed no aberrations, including a normal FISH test. Molecular diagnostics on peripheral blood revealed a mutation on KRAS (p.G12D), which has been identified in approximately 3-10% of cases of AML.

KIDNEY BIOPSY

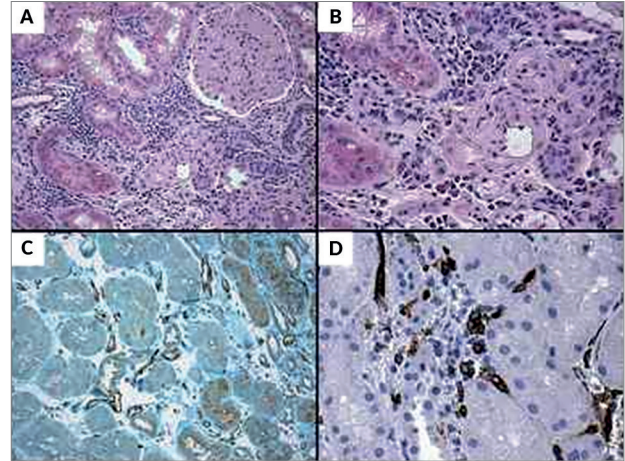
The kidney allograft biopsy specimen contained 28 glomeruli and showed marked interstitial inflammatory infiltrate and edema, and focal mild to moderate tubulitis. Immunofluorescence was negative for IgG, IgM, IgA, and C1q. The staining for C4d was diffusely positive in the peritubular capillaries by immunofluorescence microscopy.

There were also moderately advanced chronic changes of the parenchyma, with severe transplant glomerulopathy, moderate global glomerulosclerosis, tubular atrophy, and interstitial fibrosis, and severe arterial and arteriolar sclerosis. The stains for CD3, CD20, CD34 and C-kit were performed to help evaluate the nature of the infiltrate.

The infiltrate was T-cell rich, with several MPO-positive cells and scattered CD34-positive cells (blasts), suggesting involvement by myeloid leukemia. Other cells appeared to be of reactive nature and probably a component of rejection was present. Overall, the findings suggested chronic antibody-mediated allograft rejection (ABMR), with a moderate

cellular component that was represented by mixed inflammatory and leukemic infiltrates (Figure 2).

Figure 2. Light microscopy of the kidney biopsy, representative images; (A) Glomerulus with mesangial expansion and capillary wall remodeling and thickening, consistent with transplant glomerulopathy (H&E, 200X). In addition, focal inflammatory infiltrate is noted, better appreciated on (B), with mixed infiltrate with frequent eosinophils, lymphocytes and atypical inflammatory cells (H&E, 400X). (C) The C4d stain is positive circumferentially along the peritubular capillaries (C4d, immunoperoxidase stain, 400X) (D) The CD34-positive blast forms are seen frequently within the interstitial infiltrate (CD34, immunoperoxidase stain, 400X).



DIAGNOSIS

The morphologic and immunophenotypic features in the bone marrow were consistent with involvement by AML with maturation. Based on the C4d positivity of the renal biopsy and the presence of circulating DSAs, the patient also had antibody-mediated rejection of the allograft.

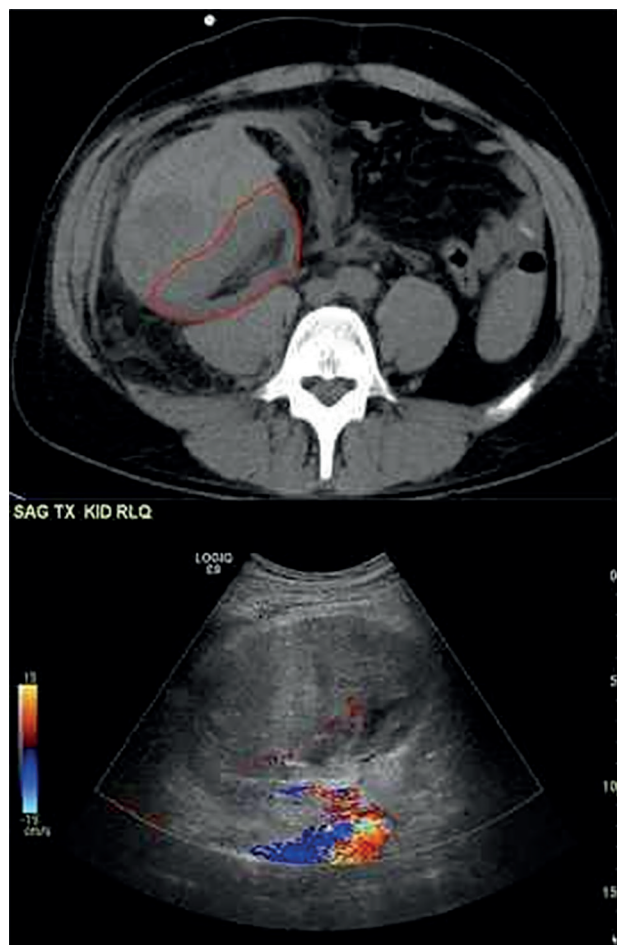
CLINICAL FOLLOW-UP

After the implementation of antibiotic treatment for suspected facial cellulitis, the patient was started on chemotherapy with 3 days of daunorubicin 60 mg/m² and 7 days of cytarabine at a dose of 100 mg/m².

Ten days after the renal allograft biopsy, the patient developed acute pain over the allograft site, which coincided with a thrombocytopenia of 10,000/ μ L. A renal ultrasound was repeated, followed by an abdominal CT, which revealed a new large subcapsular hematoma within the allograft (Figure 3).

This compressive collection of blood significantly reduced renal perfusion leading to further deterioration of his kidney function. Due to persistent thrombocytopenia and concern for further bleeding, an expectant management was chosen with platelet and red blood cell transfusions.

Figure 3. Subcapsular hematoma after kidney biopsy. Abdominal CT scan with kidney demarcated in red (A) and renal ultrasound with Doppler (B) demonstrating subcapsular hematoma and minimal blood flow on compressed kidney cortex.



The patient otherwise responded well to chemotherapy. His day 30 post-treatment bone marrow biopsy demonstrated less than 5% blasts, consistent with a complete remission. Due to poor renal function, consolidation with daunorubicin 45 mg/m² for two days and cytarabine 100 mg/m² for 5 days were administered over standard high-dose cytarabine.

A second cycle of consolidation was administered upon count recovery but utilizing a higher dose of daunorubicin at 60 mg/m². After one year on remission, he experienced an AML relapse and underwent ten-day decitabine and entered a second remission, being maintained on long-term decitabine. He was considered for a combined kidney and bone marrow transplantation, but his poor functional status was a significant limitation.

DISCUSSION

The post-transplant population has an increased incidence of malignancy over time. Furthermore, Hall *et al.*³ demonstrated a higher cumulative incidence of malignancies in the more recent transplant era (2000-2008), compared to the previous era (1987-1999). This finding may be attributed to the increased life expectancy of the transplant population as well as the increased implementation of more potent immunosuppression in recent years. Currently, malignancy is the third, second and fourth cause of death in kidney, liver, and lung transplant recipients, respectively, at 5 years after transplantation.³

Some of the most common diagnosed malignancies include lymphoma, non-melanoma skin cancer, Kaposi sarcoma, renal cancer, genitourinary cancer, oral cancer, lung cancer (especially in lung transplant recipients), and liver cancer (in liver transplant patients). In a recent meta-analysis of five population-based studies, Vajdic and van Leeuwen demonstrated that 23 out of 28 types of malignancies examined had an increased incidence in transplant recipients compared to the general population.⁸

Although leukemia is not among the most common malignancies following solid organ transplantation, its incidence seems to be on the rise.⁹ AML is caused by the clonal proliferation of myeloid precursors resulting in the accumulation of immature blast forms within the bone marrow and consequently a decline in the production of other mature cell lines.

The most common manifestations of AML are due to complications of pancytopenia, which include fatigue, secondary infections, and bleeding. The discovery of cytopenias is not uncommon among the organ transplant population and can be due to medications or viral infections. As a consequence, the diagnosis of AML can be initially overlooked or missed.

A peripheral blood smear should be ordered when a post transplant patient presents with cytopenias. Flow cytometry panels specific for leukemia (if blasts present peripherally) or lymphoma should also be considered. A diagnosis should be confirmed with a bone marrow biopsy. The WHO criteria require the presence of more than 20% myeloblasts in the bone marrow for the diagnosis of AML.

Common treatment regimens include the combination of an anthracycline (daunorubicin or idarubicin) with IV cytarabine. The benefits of consolidative hematopoietic allogeneic transplantation for AML have been well described in patients with poor molecular markers or high-risk cytogenetics.¹⁰ Unfortunately, this patient's transition to hemodialysis due to graft failure precluded him from receiving an allogeneic bone marrow transplant. The patient was considered for a combined kidney and stem cell transplant but this was ultimately not pursued.

Rashidi and Fisher systematically reviewed 51 previously reported cases of post transplant AML.^{11,12} Of these patients, 23 were kidney, 20 liver, 6 heart and 2 lung transplant recipients. The median time between the transplant and the development of AML was 3.8 years, with more than 70% of the cases occurring during the first 5 years after transplant.

Our case is one of the rare cases, which happened more than 5 years after transplantation. Another difference between our patient and the majority of the patients in the Rashidi's study is that despite kidney transplant failure, our patient is still alive more than 2 years after the AML diagnosis, while in the Rashidi study the median overall survival was only 3 months.¹¹

The use of immunosuppressive agents is thought to be the leading culprit for the development of cancer in solid organ transplant recipients. Immunodeficiency leads to a reduction in the immune response against malignant cells. A similar pathophysiology has also been described in HIV-infected patients, who are at higher risk of developing malignancies compared to the general population.¹³

If immunodeficiency leads to increased risk of malignancy, it should be evident that the greater the immunosuppression, the higher the chances of developing a malignancy. A study from Gale and Opelz¹⁴ supports this concept by specifically addressing the risk of developing AML.

In their study, data from more than 200,000 kidney and more than 30,000 heart transplant patients were analyzed for the risk of AML compared to matched controls from Cancer Databases. Both kidney and heart transplant patients had an increased incidence of AML, with the risk being the highest among heart transplant patients (standardized incidence ratio of 5.1) compared to kidney transplant patients (standardized incidence ratio of 1.9).

Since heart transplant recipients tend to receive stronger immunosuppression than kidney recipients, this supports the association of increased incidence of AML following more intense immunosuppression.¹⁴

A limited retrospective analysis of transplant recipients from the Brigham and Women's Hospital and Massachusetts General Hospital conducted between 2000-2014, identified 21 cases of leukemia among 2,403 kidney recipients corresponding to an incidence of 1.2% in 10 years.

While liver transplant recipients had similar incidence (1.5%), heart and lung transplant recipients had higher incidences (1.9% and 4.2%, respectively), also suggesting a potential association of AML development with the higher intensity of immunosuppression (personal, unpublished data). Furthermore, medications independent of their immunosuppressive properties can contribute to the risk of malignancy after transplantation. It is known that medications that induce DNA damage can increase the rate of therapy-related malignancies.¹⁵

Offman *et al.*⁹ reported that transplant-related AML had microsatellite instability, which is diagnostic of defective DNA mismatch repair. It was also suggested that azathioprine might contribute to the development of AML by selective proliferation of DNA mismatch repair within defective azathioprine-resistant myeloid cells.

Of course, not all patients exposed to this class of medications will develop a neoplasm. This likely indicates an underlying genetic susceptibility and/or an acquired event,¹⁵ which can predispose to polymorphisms in the metabolism of these medications. The patient in our report was not exposed to alkylating agents, such as cyclophosphamide, nor to the antimetabolite azathioprine.

The use of mTOR inhibitors in AML is under investigation. Although there are preliminary studies suggesting mTOR inhibitors may be beneficial if added to conventional induction treatment,^{16,17} it seems that sirolimus did not help in preventing the development of AML in our patient.

A confounding factor in our patient's history was his previous exposure to Thymoglobulin. Although there have been attempts at determining the different susceptibilities to cancer with different immunosuppressive agents, there have not been statistically significant differences clearly demonstrated in regards to type of immunosuppression and AML.¹⁸⁻²¹

Viral infections are possible contributors to the development of malignancies after transplantation. In a meta-analysis, most of the observed cancers in transplant patients had a known or possible infectious cause.⁸ Associations between the Epstein-Barr virus and lymphoma, the human herpesvirus 8

and Kaposi sarcoma, and the human papillomavirus and anogenital/oropharyngeal cancers have been well described. To date no virus has been associated with the development of AML.

Interestingly, it seems that for some viral-mediated malignancies, an underlying immunosuppressive state is necessary. This effect was suggested by van Leeuwen *et al.*²² who analyzed data from kidney transplant recipients from the Australian and New Zealand Dialysis and Transplant Registry. These patients were followed once immunosuppression was reduced following a return to dialysis.

They noted that immunosuppression effect on malignancy risk was reversible for most cancers associated with an infectious etiology.²² In van Leeuwen's study,²² the incidence of leukemia remained elevated despite the return to dialysis and the tapering of immunosuppressive agents, while Offman's findings support that AML has an association with higher immunosuppression.⁹

In patients with end-stage renal disease, it is reasonable to think about a possible combined kidney and bone marrow transplantation. Although this option is not widely available, its benefit for other hematologic diseases, i.e. multiple myeloma, is emerging.

Spitzer *et al.*²³ reported more than 12 years of follow up on 7 patients affected by multiple myeloma and end-stage renal disease treated with HLA-matched bone marrow and kidney transplantation. In their report, all the patients underwent a conditioning regimen, which consisted of cyclophosphamide, antithymocyte globulin and thymic irradiation.

After the transplant, the patients were continued on cyclosporine, which was stopped as early as 73 days after the transplant. Four patients had no evidence of myeloma after 4-12 years of follow-up while five patients had normal or near normal kidney function. Of these, 3 patients were off immunosuppression, and 2 patients were restarted on immunosuppressive medications after they developed graft-*versus* host disease.

This small pilot study suggests that HLA-matched combined bone marrow and kidney transplantation can result in prolonged anti-myeloma effect and kidney allograft tolerance.²³ More research and clinical experience is needed to understand if combined bone marrow and kidney transplantation is beneficial for other hematologic malignancies such as AML.

Finally, our patient's kidney transplant biopsy showed chronic active ABMR, which was

characterized by chronic endothelial damage (e.g. transplant glomerulopathy) in the presence of circulating DSA and evidence of interaction of the antibodies with the endothelium, e.g. peritubular capillaries C4d staining.²⁴

It is difficult to understand why both AML, which is usually associated with over-immunosuppression, and chronic ABMR, which is usually associated with poor compliance with immunosuppressive medications, happened in the same patient. We cannot exclude that AML may have led to activation of the innate immunity with enhanced HLA-antigen expression and lowering the threshold of immune activation.

In conclusion, we presented a case of AML after kidney transplant in a patient who presented with fever, pancytopenia, and acute allograft dysfunction. For transplant patients with new pancytopenia, the differential diagnosis should include hematologic malignancies. Timely diagnosis and management is key in the successful outcome of leukemia following solid organ transplantation.

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