

A CASE REPORT OF IMMUNOSUPPRESSION RELATED COMPLICATIONS IN A KIDNEY TRANSPLANTED PATIENT

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Abstract

Immunosuppressed transplant recipients have a higher rate of prolonged survival with a functioning graft, but also prolonged exposure to complications of chronic immunosuppression. Registry data found cancer to be the third most common cause of death after cardiovascular accidents and infections in these patients.

In the following case, we present a kidney transplanted patient, successfully treated for *Diffuse large B-cell lymphoma*, generalized *Herpes Zoster*, and *CMV infection*. The patient was a 60 years-old man with a kidney transplant from a cadaver 5 years ago. After the transplantation, no complications occurred. He regularly referred for medical monitoring, and was adherent to medical treatment and investigations.

His long term immunosuppressive therapy consisted of a low dose of corticosteroids, tacrolimus, and mycophenolic acid. The patient presented with acute pain and tenderness all over the abdomen that lasted for a few hours. After CT imagining confirmed intussusception at left colic flexure, urgent surgery was performed. Tissue sampling diagnosed Large B-cell lymphoma.

The patient underwent 4 cycles of dose-rationalized R-CHOP therapy with a normal PET scan afterward. Herpes Zoster generalized infection and CMV occurred in two months.

Treatment with acyclovir was successful. The regular immunosuppressive regime was re-introduced, consisting only of corticosteroids and sirolimus. The creatinine level remained stable for the next two years, and all subsequent PET scans and CT images were in normal range. The patient remained free of infections as well.

Key words: kidney, transplant, immunosuppression, B-cell lymphoma, malignity.

Introduction

This success of organ transplantation has led to a growing population of immunosuppressed transplant recipients with prolonged survival with a functioning graft, but also with prolonged exposure to side effects and complications of chronic immunosuppression (i.e. opportunistic infections, malignancies, diabetes mellitus, hypertension, etc [1]).

In patients with transplanted kidney compared to the general population, the observed incidence of malignancy surpassed the threshold three to five times. It has also been reported that after 25 years of immunosuppression, about half of the recipients are at risk of developing some kind of tumor [2]. Registry data found cancer to be the third most common cause of death after cardiovascular accidents and infections in these patients [3].

The incidence of lymphoma is increased 2- to 4-fold in kidney transplant patients. Immunosuppression is considered the most important risk factor, as it decreases the immunologic control of oncogenic viral infection and cancer immune surveillance[4].

Gastrointestinal (GI) lymphomas comprise a group of distinct clinicopathological entities of B- or T- cell type. The GI tract is the predominant site of extranodal non-Hodgkin lymphoma, accounting for 30–40% of all extra-nodal lymphomas.

Several chronic inflammatory and immune-mediated disorders that predispose to accelerated cell turnover may lead to the malignant transformation of gut lymphocytes and ultimately manifest as GI lymphoma. These tumors may have varied presentations, ranging from nonspecific symptoms, such as

dyspepsia or bloating, to abdominal pain, nausea, vomiting, GI bleeding, diarrhea, weight loss, or bowel obstruction[5].

More than 90% of early-onset B-cell Post-transplant lymphoproliferative disorder (PTLD) are Epstein-Barr virus (EBV)-positive, whereas over 50% of late-onset B-cell PTLD cases are EBV-negative [6].

Other viral infections have been proposed as potential risk factors in the development of PTLD, including hepatitis C virus (HCV) and cytomegalovirus (CMV) [7-9]. Patients who are EBV-naive pre-transplant are more likely to develop PTLD post-transplant as a result of primary EBV infection in an immunosuppressed state, often acquired from the donor organ, with 24 times higher rates to those seen in EBV-seropositive patients[10,11].

Our transplantation center performs pre-transplantation screening for cytomegalovirus and Epstein-Barr virus for both donor and recipient. IgM negative and IgG negative or positive results are acceptable.

Similarly, younger age at the time of transplantation has also been correlated with higher rates of PTLD, with pediatric patients having a four to eightfold increased risk of PTLD compared with their adult counterparts[12,13].

On average, the time of diagnosing cancer from transplantation is estimated to be 3-5 years, but the median overall delay between kidney transplantation and lymphoma is 18 months. Some recipients have late lymphoma occurrence ranging from 4-10 years after transplantation. [4,14].

In this case, we present a kidney transplanted patient, successfully treated for consecutive Diffuse large B-cell lymphoma, Herpes Zoster, and CMV infection.

Case presentation

The patient was a 60 years-old man with chronic renal disease of unknown origin that was transplanted with a kidney from a cadaver 5 years ago. Prior transplantation, he was treated by hemodialysis for 6 years, and remained in stable medical condition after the transplantation. Namely, no complications occurred, he regularly referred for medical monitoring, and was adherent to medical treatment and investigations. The patient was EBV and CMV negative.

In respect of comorbidities, only hypertension that well regulated by therapy was noted. No change in the bowel habit or stool was present. His body weight was stable, as well. The long term immunosuppressive therapy of the patient consisted of a low dose of corticosteroids (5mg per day), tacrolimus (1-2miligrams per day, according to regularly monitored blood trough level 5-8ng/mL) and mycophenolic acid (360mg twice per day).

Three and a half years after transplantation the patient presented at the outpatient clinic with acute pain and tenderness all over the abdomen that lasted for a few hours. After the CT imagining conformed intussusception at left colic flexure, urgent surgery was performed. The result was terminal colectomy. Tissue sampling from the big 2.5x4cm invasive lump diagnosed Large B-cell lymphoma (Figure 1-4). PET scan after surgery showed activity only at the sight of surgery.

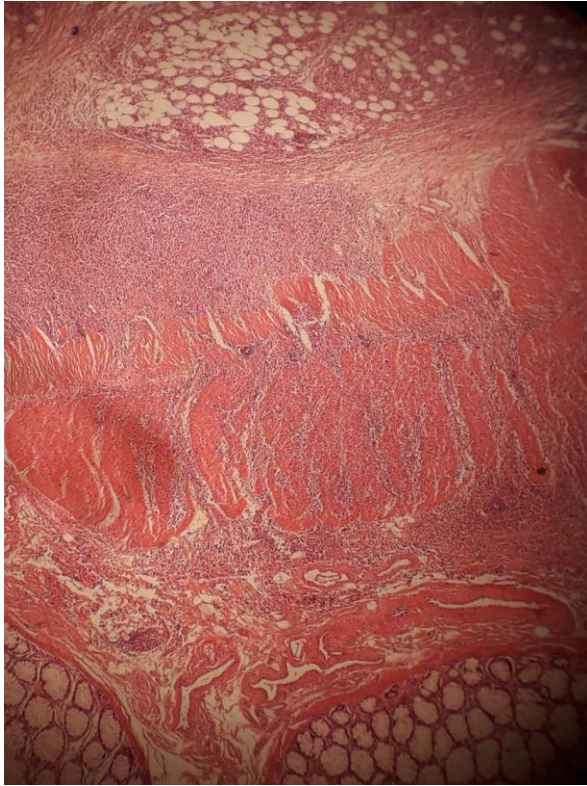


Figure 1.

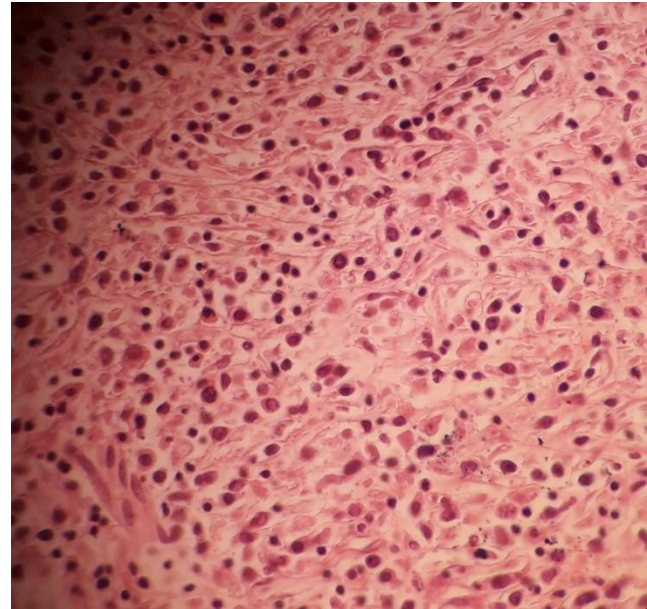


Figure 2.

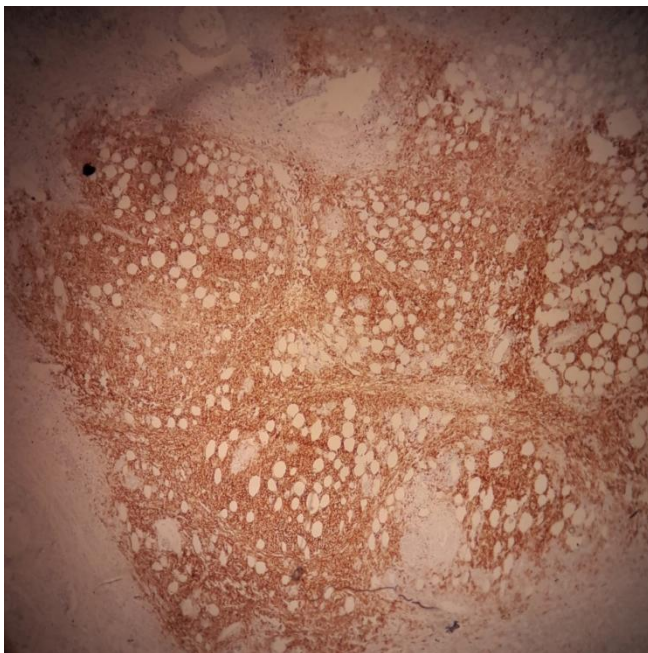


Figure 3.

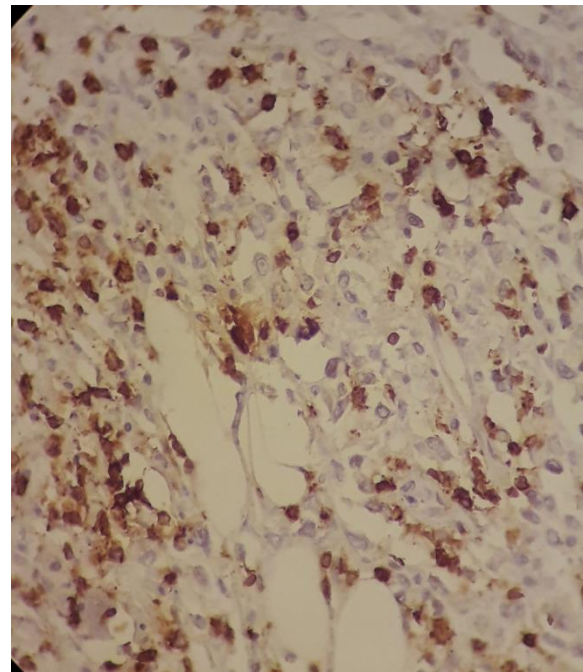


Figure 4.

Figure 1. Diffuse infiltration of intestine wall with atypical lymphoid cell population. Neoplastic cells are focally seen in adipose tissue (H&E staining). Figure 2. Lymphoid cell population is made of discohesive

large cells which look like immunoblasts and centroblasts (H&E staining). Figure 3. Immunohistochemical staining CD20 positivity. Figure 4. Immunohistochemical staining CD3 positivity for lymphoid tumor population.

The patient underwent 4 cycles of dose-rationalized R-CHOP therapy with a normal PET scan afterward. One month after the completion of regular immunosuppression cycles with corticosteroids, tacrolimus was re-introduced. In this period, the creatinine level remained at 160 mmol/l, but after four months, another complication occurred. The patient was admitted to hospital because of generalized *Herpes Zoster* infection and recovered during the course of one week under acyclovir therapy.

CMV positivity was also successfully treated. The regular immunosuppressive regime was re-introduced and changed, consisting only of corticosteroids and sirolimus. Sirolimus trough level was monthly obtained and within the target range. The creatinine level remained stable for two years and all subsequent PET scans and CT images were in normal range. The patient remained free of infective complications as well.

Discussion

In the peri-operative period and early post-transplantation, the recipient confronts strong immunosuppressive therapy, in order to lower the risk of graft rejection. After stabilization of the graft function, the immunosuppressive doses are being reduced, striving to achieve the delicate balance between effective prevention of rejection and avoidance of toxicity.

The doses of immunosuppressive drugs are usually adjusted according to target trough levels. The long term exposure to immunosuppression endures the patient with susceptibility to infections, malignancy, and other complications.

In the presented case, our patient tolerated well the immunosuppression without complications for five years. His therapy implemented relatively low doses of tacrolimus achieving stable trough levels, low corticosteroid dose, and mycophenolic acid. Prior to transplantation, he was EBV and CMV free and received post-transplant regular CMV prophylaxis.

Previous studies have shown that similarly to the EBV status, CMV-negative patients who receive a CMV-positive organ are 4–6 times more likely to develop PTLD than CMV-positive recipients[9].

The use of anti-thymocyte globulin (ATG) has also been associated with increased rates of PTLD[13]. It has been used in our high-immunologic risk protocol for induction therapy in cadaveric transplantation.

Also, when compared to cyclosporine, tacrolimus has been associated with a two to fivefold increase in the PTLD rate, in both adult and pediatric populations[13]. Both of these drugs have been administered to our patient, and might be related to complications. In spite of a well-dosed regime and relatively low dose of tacrolimus and only 5 mg of corticosteroids per day, Herpes Zoster and CMV infection occurred. Assuming the need for further adjustment of immunosuppressive treatment, mycophenolic acid and tacrolimus were excluded. Instead, sirolimus was introduced.

The maintenance immunosuppression including calcineurin inhibitors, antimetabolite and corticosteroids are associated with the risk of post-transplant malignancy. As both CD4 and CD8 T cells are crucial in adaptive antiviral immunity, depletion of both populations of T cells with T cell-depleting antibodies would increase the susceptibility of individuals to a higher risk of virus-associated diseases [4].

Clinical data have shown beneficial effects of the use of mTOR inhibition (sirolimus) in preventing cancer development in transplant recipients. It is likely that these effects present the rest of sirolimus' antitumor and antiangiogenic properties [15,16]. Our patient tolerated the new immunosuppressive regime well for the next two years.

Conclusion

Long term close monitoring is needed in order to prevent and treat complications related to immunosuppressive treatment. Sirolimus is shown to be safe and effective in this vulnerable group of patients.

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