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Cerebral Glioblastoma in Renal Transplant Recipient: A Case Report

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Abstract

Cancers is a leading cause of mortality among transplant recipients. The most common cancers are skin tumors. Glioblastoma is the most frequent brain tumor in adults aged 45 - 70 years. It accounts for 12% - 15% of all intracranial tumors. It is characterized by its rapid development and poor prognosis. We report the case of a cerebral glioblastoma in a kidney transplant recipient. Clinical case: Mr G.R, 44 years old caucasian patient who underwent kidney transplantation. Immunosuppressive treatment included cyclosporine, mycophenolate mofetil and methylprednisolone. Creatinine levels after transplantation remained stable at 11 mg/L (96.8 µmol/l) with an estimated glomerular filtration rate (eGFR) of 77 ml/min/1.73m^2 after a 15 years of follow-up. A grade IV right fronto-callossal cerebral glioblastoma was diagnosed in our patient. EBV PCR was negative. Therefore, he underwent 25 sessions of radiotherapy combined with oral chemotherapy using temozolomide. One month later, the patient died due to cerebral edema with subfalcine herniation. Conclusion: This is a case of cerebral glioblastoma in a kidney transplant recipient, a population considered at risk for tumor development due to immunosuppressive treatment. This emphasizes the need for a lifelong surveillance and, more importantly a better balance between graft function preservation and the risks associated with immunosuppressants.

Keywords

Glioblastoma, Kidney Transplantation, Cancer, Immunossupression

1. Introduction

Renal transplantation is the treatment of choice for chronic end-stage renal fail-

ure. Unlike renal replacement therapy methods, kidney transplantation allows patients to maintain a better quality of life. Nonetheless, it comes with its own set of complications.

The immediate post-transplant period is characterized by the risk of acute graft rejection, surgical and infectious complications. Later, infections, neoplasia and cardiovascular complications are linked to the dose and duration of immunosuppression.

The most common neoplasms after transplantation primarily affect the skin and lymphoid tissues, often triggered by viral infections. However, the incidence of non-cutaneous cancers is also increased [1].

The treatment approach often requires reducing or discontinuing immunosuppression. However, the outcomes seem unsatisfactory as neoplasia remains the third most common cause of death among transplant patients [2].

Glioblastoma is the most common brain tumor in adults, accounting for 12% - 15% of intracranial tumors. Its incidence is 3 to 5 cases per 100,000 people in the USA and Europe [3]. It occurs mainly in adults between the ages of 45 and 70. Its prevalence rises with age and impacts more men than women [4].

Despite the standardized multimodal therapy of glioblastoma, the prognosis remains poor with a mean overall survival of 14 to 20 months [5].

We report the case of a cerebral glioblastoma occurring in a renal transplant recipient.

We obtained informed consent from the patient's family to publish this clinical observation.

2. Observation

Our patient is a 44 years old caucasian male, diagnosed with chronic end-stage renal failure due to undetermined nephropathy. He underwent a kidney transplant with his brother's kidney.

Immunosuppressive therapy consisted of cyclosporine, mycophenolate mofetil (MMF), and oral corticosteroids. Post-transplant, renal function was stable (baseline serum creatinine 11 mg/l or 96.8 µmol/l and a GFR of 77 ml/min/1.73m^2).

At a 15-years follow-up, the patient reported vertigo and vomiting. Neurological, ear, nose and throat (ENT) examinations showed no abnormalities. Brain MRI revealed a tumor-like right fronto-callosal process (**Figure 1**). Surgical resection was impossible due to its location and invasion of adjacent structures. A stereotactic biopsy was performed on the tumor. Anatomopathological and immunohistochemical studies concluded with the diagnosis of a grade IV glioblastoma. The images showed an infiltrative growth pattern with nuclear atypia, elevated mitotic activity, microvascular proliferation, and extensive necrosis. Tumor cells were positive for GFAP, OliG2, ATRx and negative for IDH1. Molecular biology studies were unavailable

The thoraco-abdomino-pelvic CT scan revealed no metastatic localization. Epstein Barr Virus (EBV) PCR was negative.

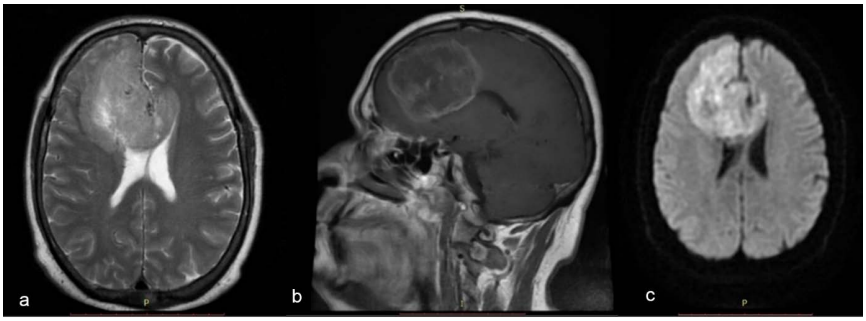

Figure 1. Cerebral MRI in axial T2 (a), sagittal T1 (b) and diffusion (c) sections, showing a frontal tissue lesion process associated with cerebral glioblastoma.

The patient received 25 sessions of radiotherapy over five weeks, combined with two cycles of Temozolomide chemotherapy (dose of 150 - 200 mg/m^2/day for 5 days every month). Frontal cutaneous erythema attributed to radiotherapy appeared following the treatment.

One month later, the patient developed mono-paresis of the left upper limb. A brain scan revealed extensive glove-finger edema with the onset of subfalcoral involvement. A treatment consisting of mannitol and intravenous corticosteroids was initiated. The course was marked by the onset of generalized tonic-clonic seizures. After spending 48 hours in the intensive care unit, the patient was declared brain dead.

3. Discussion

The incidence of cancer is significantly higher in kidney transplant patients. A recent American study reported a cumulative cancer incidence of 4.4%, 7.5%, and 11.4% respectively after 5, 10, and 20 years in a population of solid organ and hematopoietic stem cell transplant recipients [6]. In our case, the diagnosis of glioblastoma was established 15 years after renal transplantation.

The overall risk of cancer is 3 to 5 times higher in transplant recipients, and varies according to the type of cancer. The risk is 20 times higher for Kaposi's disease and lymphoproliferative syndromes, and 15 times higher for kidney cancers [1].

There are many risk factors predisposing to cancer such as age, genetic predisposition, smoking, and environment. In transplant recipients, specific risk factors related to the state of immunosuppression are also considered.

Foremost among the specific factors are infections caused by oncogenic viruses such as EBV, hepatitis B, and C viruses, HHV-8 (Human herpesvirus type 8), and HTLV (Human T-Lymphotropic Virus). Their implication in the development of cancers is now well-established [2].

For most cancers, the onset is favored by immunosuppressive treatment. Our patient developed a glioblastoma after 15 years under immunosuppressive treatment. No evidence of infection with oncogenic viruses was found.

Glucocorticoids are part of induction therapy and remain the first-line treatment for acute rejection. Despite their frequent use for symptom management in

solid tumors, their long-term use is associated with suppression of anti-tumor immunity, resistance of cancer cells to chemotherapy, and increased metastatic risk [7]. These in vitro effects are observed at higher doses. Our patient was on low-dose glucocorticoids (5 mg of oral methylprednisolone per day).

Antilymphocytic serum and OKT3 predispose more specifically to post-transplant lymphoproliferative syndromes [2].

Cyclosporine is a powerful immunosuppressant inhibiting the signal 1. Its potentially carcinogenic effects became known in the late 1990s. It promotes the metastatic dissemination of cancer cells [8] and increases the risk of developing cancer (26% of de novo cancers on cyclosporine vs. 12% without) compared with maintenance therapy using azathioprine and glucocorticoids. The anti-apoptotic effect of cyclosporine may also contribute to the higher incidence of tumors [9]. Our patient was on cyclosporine for 15 years, with serum levels between 50 - 100 µg/l during follow-up, not indicative of overdosage.

Mycophenolate mofetil (MMF) inhibits the proliferative responses of T and B lymphocytes to mitogenic and allospecific stimulation in transplant patients. It showed no effect on tumor cell proliferation in vitro in different cancer cell lines [10]. This inhibition was not observed in vivo using standard immunosuppressive doses of MMF. Another study found a significant association between renal cancer and the use of MMF in kidney transplant patients, especially over long periods ($p = 0.046$) [11].

Immunosuppression can be maintained by inhibitors of the mTOR pathway, which are capable of inhibiting tumor cell growth, tumor invasion, metastatic dissemination, and can induce apoptosis. In addition, mTOR inhibitors exert potent anti-angiogenic activity by controlling vascular endothelial growth factor-induced signal transduction [12]. The use of mTOR inhibitors could be interesting in curative or preventive strategies for the treatment of de novo cancers.

Glioblastoma is the most common brain tumor in adults (12% - 15%). It occurs mainly between the ages of 45 and 70. Its incidence increases with age and affects more men than women [4]. This corresponds to our patient, who was a 44-year-old Caucasian male. The prevalence of glioblastoma in transplant patients is poorly understood, as few cases have been reported in the literature.

The clinical manifestation of glioblastoma is non-specific, depending more on its location than on its pathological properties. Patients usually remain asymptomatic until the onset of neurological complications. Our patient presented with vertigo, headache and vomiting, followed by seizures and monoparesis.

The treatment approach aims to completely remove the tumor. It involves a complete surgical resection to reduce the mass effect of the tumor, followed by concomitant radiochemotherapy. The Temozolomide-radiotherapy combination significantly improved survival compared with radiotherapy alone: 2-year survival 27.2% vs. 10.9%, HR 0.6 [95% CI, 0.5 - 0.7] $p < 0.001$ [13]. Our patient underwent complete radiotherapy combined with a single cycle of chemotherapy.

Surgical eradication was not possible due to the tumor location and its invasion of adjacent structures.

The US Food and Drug Administration (FDA) has approved the use of the anti-vascular endothelial growth factor (VEGF) antibody Bevacizumab in the treatment of recurrent glioblastoma based on two phase II studies. However, two other phase III clinical trials evaluating its role in the treatment of newly diagnosed glioblastoma failed to demonstrate any benefit in terms of overall survival [14] [15] [16].

Tumor-treating-fields (TTF) therapy has also been approved by the FDA for the treatment of newly discovered and recurrent glioblastoma. However, this therapy is not commonly used [17].

Glioblastoma is a particularly aggressive tumor. Its molecular mechanisms of resistance to treatment have been the subject of numerous studies. The identification of overexpression of the DNA repair enzyme O6-methylguanine DNA methyltransferase (MGMT) has helped to explain the replication of tumor DNA despite Temozolomide treatment. [18] Extensive work has also characterized alterations in the DNA repair system (MSH6 deficiency, down-regulation of MLH1 and PMS2) which explains Temozolomide resistance [19] [20].

Molecules designed to inhibit these enzymes could serve as sensitizing agents for chemotherapy, presenting promising therapeutic possibilities. New perspectives for the treatment of glioblastoma are currently being explored: oncolytic virotherapy, vaccination with peptides or dendritic cells, and inhibition of immune checkpoints [21] [22] [23].

Although early detection of neoplasia may improve survival in kidney transplant patients, no surveillance protocol has been established. Screening protocols for skin, breast and prostate cancer have been standardized [24]. No consensus has been reached on screening for glioblastoma, which is not accessible by clinical examination and requires imaging.

4. Conclusions

The higher risk of cancer after transplantation calls for lifelong monitoring of transplant recipients: pre-transplant, by identifying risk factors and screening for cancer, and post-transplant, with regular screening and risk-adapted treatment. The challenge is to find the best balance between preserving graft function and the risks associated with immunosuppressive drugs, particularly anticalcineurins. However, immunosuppression can be preserved with mTOR inhibitors, which have interesting anti-tumor activity.

Cerebral glioblastoma remains an exceptional tumor in renal transplant patients. Further studies are required to identify the risk factors in this population.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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