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Case Report

Primary central nervous system lymphoma post kidney transplantation: a case report

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Abstract

Introduction: Primary central nervous system (PCNS) posttransplant lymphoproliferative disease (PTLD) is a rare complication of solid organ transplantation and treatment is not yet standardized.

Case presentation: Here we report the case of a 54-year-old man who underwent renal transplantation 22 years ago for end-stage renal disease. He had been on long-term immunosuppressive treatment consisting of orally administered prednisolone 10 mg and then 5 mg daily and orally administered Mycophenolate Mofetil 500 mg twice daily. He presented in January 2019 to emergency with aphasia and then partial seizure. On brain MRI there was an expansive cortical mass in the left temporal lobe with perilesional edema. Biopsy revealed a diffuse large B-cell lymphoma. He was treated with one cycle of Cytarabine with his usual immunosuppressive treatment. In view of his renal allograft, he was not suitable for Methotrexate due to the risk of toxicity. He died on day 15 caused by a sepsis choc secondary to febrile neutropenia.

Conclusion: PCNS-PTLD is regarded as one of the most serious posttransplant complications due to its high mortality. Further clinical and experimental investigations are required to develop optimal diagnostic and treatment modalities.

More Information

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Introduction

Post-transplant lymphoproliferative disorders (PTLD) are a serious complication after solid organ or allogeneic hematopoietic stem cell transplantation and include a range of diseases from benign proliferations to malignant lymphomas. Risk factors for developing PTLD include Epstein-Barr virus (EBV) infection, recipient age, transplanted organ, type of immunosuppression, and genetics [1]. Uncontrolled proliferation of EBV-infected B cells is implicated in EBV-positive PTLD, whereas the pathogenesis of EBV-negative PTLD may be similar to non-Hodgkin's lymphoma in the general population Patient's survival after transplantation has been dramatically improved. Immunosuppression following transplantation is known to increase the risk of malignancies especially post-transplantation lymphoproliferative disorders which are among the more common malignancies diagnosed [2-4]. They occur greater than 10 times more frequently in kidney transplant recipients than in the general population [5,6]. Clinically, extranodal involvement is common including the central nervous system (CNS), which is reported to occur in approximately 7% - 15% of cases (involvement consists mostly of primary CNS posttransplant lymphoproliferative disease (PCNS-PTLD)) [7–10].

Furthermore, CNS involvement has consistently been shown to be a poor prognostic factor predicting inferior survival in pediatric and adult PTLD series [7,11-13].

Case report

A 54-year-old patient was diagnosed 22 years ago with end-stage renal disease of unknown etiology. So he underwent kidney transplantation. He tolerated the transplant due to immunosuppressive treatments. The prolonged use of the immunosuppressive treatments was complicated by high blood pressure in 2009, hemorrhagic cerebrovascular accident in 2014 with sequelae paraplegia, sphincter disorders that need an indwelling bladder catheter, ophthalmic zoster in 2015, and diabetes in 2016. He was receiving prednisolone 5 mg daily and orally administered Mycophenolate Mofetil 500 mg twice daily, until he presented in January 2019 to emergency with aphasia and

then partial seizure. The cerebral CT demonstrated left temporal hypodensities. The brain MRI without gadolinium injection demonstrated an expansive cortical mass in the left temporal lobe with some hemorrhagic reshuffles and significant perilesional edema. A surgical biopsy was performed. Pathologic examination revealed a predominantly angiocentric lymphoproliferative lesion characterized by large atypical lymphocytes with prominent nucleoli, moderate amounts of cytoplasm, few mitoses, and zones of necrosis. The tumor cells were positive for CD20 and negative for CD3 and GFAP. The Ki-67 proliferation index was 40%. So, he was diagnosed with brain diffuse large B-cell lymphoma (DLBL). The lumbar puncture was not performed due to the significant mass effect. Bone marrow biopsy, cervical-chest-abdominal and pelvic CT, ophthalmologic examination, and testicular echography were performed. They didn't show any extra CNS lesions and the diagnosis of PT-PCNSL was retained. Hepatitis B, C, and HIV serologies were negative. At the time of diagnosis, the serum creatinine level was 146 µmol/L and the complete blood count showed anemia (hemoglobin = 10 g/dl). The rest of the blood tests were correct.

He received preventive treatment with valaciclovir to prevent the reactivation of the varicella-zoster virus. . In view of his renal allograft, he was not suitable for Methotrexate caused by the risk of toxicity. A treatment based on Rituximab 375 mg/m^2 on day 1, Cytarabine 200 0mg/m^2 on days 2 and 3 with G-CSF for 4 to 6 cycles was decided. In April 2019, he underwent one cycle of cytarabine-only chemotherapy while awaiting treatment with rituximab. Fifteen days after the treatment, he developed a fever. The complete blood count showed a WHO grade 4 neutropenia. The cytobacteriological examination of the urine revealed a multiresistant Klebsiella pneumoniae urinary tract. Although he received adapted antibiotic therapy, he died of septic shock.

Discussion

PTLD is a well-recognized complication that occurs in up to 10% of all solid organ transplantations (SOT) [14]. It is the second most common form of post-transplant malignancies with a much lower incidence than skin cancers [15,16]. Kidney transplantation was described as the most frequent type of SOT among PTLD patients, as was our patient [17,18]. It can be explained by the commonality of this transplantation and possibly longer survival compared with other SOT. The first year after SOT is associated with a high risk of PTLD but the period of greatest incidence is in the late post-transplant period, especially for PCNS-PTLD [19]. The time from SOT to PTLD is generally over 3-5 years [10,20-22]. In our case, the interval was of 22 years. PTLD showed the highest cancer-related mortality in transplanted patients with reported overall mortality for PTLD that exceeds 50% [5,23-25].

CNS is involved in approximately 7% - 15% of all these PTLD cases, mostly as primary CNS PTLD (PCNS-PTLD) [7-12,26,27]. High-level immunosuppression and the absence of EBV infection are considered the most important risk factors for the development of PCNS-PTLD [28-30]. The association of these two factors exposes the recipient to EBV infection and then the development of PCNS-PTLD. Over the last decade, there has been a rise in EBV negative PTLDs, especially in cases occurring late after SOT [31,32]. Their pathogenesis remains unknown. Other infections such as CMV or hepatitis C may be also incriminated [33]. In our reported case, only Hepatitis B, C, and HIV serologies were performed and were negative. The patient was using immunosuppression since transplantation for 22 years. He subsequently developed a PCNS-PTLD. The incrimination or not of EBV infection remained unknown.

The clinical presentation of PCNS-PTLD is non-specific, similar to other CNS lesions. MRI is more sensitive than CT for detecting these lesions. The imaging findings with MRI reflect hypercellular tumors, which are prone to hemorrhage, have cystic and necrotic changes, and surrounding edema. The cases reported in the literature showed that the lesions are generally supratentorial, with lobar location and ring enhancement [34]. Similar findings were found in our case but imaging with gadolinium injection was not performed. These lesions are predominantly multifocal in 61% to 88% of cases [10,15,34-36]. However, some series such as the 84 cases reported by Evens, et al. showed predominant single lesions (63%) as was our patient [37].

Histopathological examination is the gold standard in the diagnosis of PCNS-PTLD [38]. The commonly used and last version of the classification system of PTLD is the WHO classification 2017 [39]. It classifies PTLD lesions into four subtypes which are early lesions, polymorphic PTLD, monomorphic, and Hodgkin's PTLD. The monomorphic subtype is more frequent in PCNS-PTLD compared to non-CNS PTLD patients [37]. It consists of DLBLs, as was our case, in approximately 90% of the PCNS cases [39].

There was only limited data reported in the literature regarding the optimal treatment modalities of PCNS-PTLD which are not standardized. It generally includes reducing immunosuppressive therapy with what is used in immunocompetent patients such as radiotherapy, chemo-therapy, and rituximab. Reduction in immunosuppression has been a mainstay for PTLD that aims at restoring an immune response to EBV [10,40-42]. Tumor regression in up to 50% of cases can be obtained without any additional therapies, especially in polymorphic forms of PTLD [10]. This reduction seems to be less effective in late monomorphic PTLDs which are usually EBV negative and have not been evaluated extensively in the management of PCNS-PTLD [10,43]. The increase in the risk of graft rejection should not be ignored and the reduction must be made with caution. Another challenge in the treatment of PCNS-lymphomas is to use chemotherapy agents that can cross the blood-

brain barrier. Regimens usually used in non-CNS-DLBL, such as cyclophosphamide, doxorubicin, vincristine, and prednisone, were ineffective in PCNS-lymphoma partly due to their inadequate penetration of this barrier [44,45]. Then, Methotrexate is an effective treatment in two case series when administered at high doses (> 1.5 g/m^2) (HD-MTX) [10,46]. Ferreri, et al. demonstrated that the addition of cytarabine to HD-MTX improved ORR from 40% to 69% and prolonged progression-free survival from 3 to 18 months, suggesting that polychemotherapy is more effective than single-agent HD-MTX in PCNS-lymphomas [47]. Other induction chemotherapy regimens, especially other combinations with HD-MTX, are currently under study in randomized, multicenter trials [48]. however, the use of HD-MTX in itself is concerning in renal transplantation recipients given that the main toxicity of methotrexate is nephrotoxicity [46]. Rituximab, an anti-CD20 monoclonal antibody, is an active component for the treatment of non-CNS-PTLD, whether used alone or in combination with chemotherapy [5,27,37,49]. But its use has been restricted in PCNS-PTLD as it does not cross the blood-brain barrier. However, Patrick et al. showed the effectiveness of using high dose intravenous rituximab given in dose escalation protocol in these patients, leading to complete remission [50]. Another study looked at the efficacy of intrathecal rituximab in 8 children with PCNS-PTLD and showed that 7/8 patients responded well [51]. Further studies are needed to confirm these results. In our case, we did not reduce the immunosuppression since he was under a minimal dose according to his nephrologist. So, Cytarabine-based chemotherapy awaiting treatment with rituximab was administered. The patient died on day 15 due to a sepsis choc secondary to febrile neutropenia and the evaluation of the treatment couldn't be done.

Despite treatment, PTLD is associated with a poor prognosis due to either graft rejection from the reduction of immunosuppression, disease progression, or toxicity from therapy [32,52]. Registry series have published overall response rates of 60% and survival rates of 54% at 3 years and 45% survival at 10 years with treatment-related mortality causing 13% [32,37,53]. French registry data analyzing 500 adult kidney transplant patients with PTLD between 1998-2007 showed that CNS localization was one of the independent prognostic indicators of poor survival, with an adjusted hazard ratio of 2.65 on multivariable analysis. Age > 55 years at diagnosis, late-onset PTLD, high LDH and creatinine levels (> 33 µmol/L), widespread PTLD, T cell lymphoma, and monomorphic histology are associated with a poor prognosis [53]. Our patient showed enough prognostic factors to be considered for a poor prognosis (CNS localization, late PTLD, high creatinine level, and monomorphic histology). He died 3 months after diagnosis due to the toxicity of chemotherapy.

Conclusion

PCNS-PTLD is a rare complication occurring in post-transplantation patients. It can develop within months to years after transplantation. Because of its rarity, the optimal treatment remains poorly codified. Despite the treatment options currently available, the prognosis remains poor for PCNS-PTLD and further studies are necessary to improve the management of this disease.

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