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Complete regression of generalized plasmacytoma of lymph nodes in a liver transplant recipient during the conversion of immunosuppressive therapy from tacrolimus to everolimus

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Abstract

Introduction. *One of the serious complications after transplantation of solid organs and bone marrow is the development of post-transplant lymphoproliferative diseases.*

Clinical case. *To evaluate the course of post-transplant lymphoproliferative diseases in the long-term in a liver transplant recipient after conversion of immunosuppressive therapy from tacrolimus to everolimus. We analyze a case of generalized primary plasmacytoma of lymph nodes with bone marrow involvement in a patient after liver transplantation.*

Results. *After conversion of immunosuppression we observed a rapid positive trend: decreasing size of lymph nodes and regression of the level of paraprotein down to its complete disappearance. There were neither adverse events associated with everolimus for four years, nor signs of immunosuppression insufficiency.*

Conclusion. *This Case Report is the first description of a long-term remission of nodal plasmacytoma that developed in a liver transplant recipient after complete withdrawal of calcineurin inhibitors and administration of everolimus. We suggest that the regression of post-transplant lymphoproliferative diseases after replacing calcineurin inhibitors with everolimus is associated not only with the minimization of calcineurin inhibitors exposure, but also with the antitumor effect of the everolimus itself, which prompts us to discuss the possibilities of expanding its clinical application.*

Keywords: liver transplantation, post-transplant lymphoproliferative diseases, proliferation signal inhibitors, everolimus

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CNI, calcineurin inhibitor

EBV, Epstein-Barr virus

PTLD, post-transplant lymphoproliferative disease

WHO, World Health Organization

Introduction

One of the most serious complications after solid organ and bone marrow transplantation is the development of post-transplant lymphoproliferative diseases (PTLDs). The first cases of PTLD were described in 1968 by P.B. Doak et al. in kidney transplant recipients [1]. The term PTLD was suggested by T.E. Starzl in 1984 [2]. The incidence of PTLD is about 1.5% in solid organ transplant recipients; 1% in bone marrow transplant recipients.

According to the 2017 World Health Organization (WHO) classification [3], there are four types of PTLD: non-destructive PTLD, polymorphic PTLD, monomorphic PTLD, and classical Hodgkin lymphoma. Different variants of non-Hodgkin's lymphoma tumors that can develop in patients after transplantation are classified as "monomorphic PTLD". A monomorphic PTLD is a potentially fatal complication of solid organ transplantation. Mortality in the development of PTLD reaches 50% [4].

In the immunocompetent population, plasmacytoma is a rare variant of a lymphoid tumor, which morphological substrate is represented by monoclonal plasma cells, and in the WHO classification (2017) it is referred to a group of plasma cell neoplasms. Solitary bone plasmacytoma and extramedullary plasmacytoma have been distinguished. In most cases, extramedullary plasmacytoma is located in the head and neck area, often involving the nasal cavity and nasopharynx. The second most frequent location of extramedullary plasmacytomas is the gastrointestinal tract [5]. In rare cases, the primary sites of extramedullary plasmacytoma are the central nervous system, thyroid, mammary glands, testicles, and the bladder wall [6]. The primary location in the lymph nodes is very rare and accounts for about 2% of all

extramedullary plasmacytomas. Meanwhile, in most cases, the primary plasmacytoma of the lymph nodes is of localized nature.

In most patients, PTLDs are of B-cell origin. In literature, there are few descriptions of clinical cases and series of cases of extramedullary plasmacytoma as a PTLD variant. According to the German Registry data from 2006 to 2010, of 182 patients with PTLD, only 8 patients (4%) with PTLD had plasmacytoma [7]. Investigators from Cleveland, Ohio, USA, reported 4 cases (6%) of plasmacytoma among 66 PTLD cases from 1987 to 2008 [8].

No bone marrow lesion is usually observed in patients with plasmacytoma within the framework of PTLD. In a series of 8 extramedullary post-transplantation plasmacytoma cases, no patient had a bone marrow involvement [7]. In another series of extramedullary post-transplantation plasmacytoma cases, the bone marrow involvement occurred only in 1 of 4 patients [8].

Clinical Case Report

We present a case of generalized primary lymph node plasmacytoma involving bone marrow in a patient after orthotopic liver transplantation and with a complete tumor regression after the immunosuppressive therapy conversion.

A female patient born in 1980 underwent orthotopic liver transplantation from a postmortem donor in October 2010 for liver cirrhosis in Wilson's disease. She received tacrolimus in a daily dose of 10 mg as a maintenance immunosuppressive therapy. Target baseline blood concentrations of tacrolimus were maintained in the range of 5-7 ng/mL.

From May 2016, the patient started noticing increased bleeding in the form of spontaneous occurrence of ecchymoses and heavy prolonged

menstrual bleeding. The examination revealed a generalized enlargement of the lymph nodes. The blood test revealed hypochromic microcytic anemia with a hemoglobin content of 92 g/L, moderate leukopenia (3.4 thousand/μL), the leukocyte formula without abnormalities, the platelet count being within the range of normal values, an accelerated erythrocyte sedimentation rate to 95 mm/h (tested by Westergren). There was an increase in the blood total protein content to 109 g/L, hypoalbuminemia (27 g/L). The bilirubin content, the activities of gamma-glutamyltransferase, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and blood levels of creatinine, uric acid, C-reactive protein, and calcium remained within the normal values. The iron content in the blood serum had reduced to 5.1 mmol/L. Beta-2 microglobulin level was 5 mg/L (the reference value being <2.4 mg/L.

Urinalysis showed minor proteinuria 0.2 g/L, erythrocyturia up to 10 in the field of vision (up to 55,000 cells/mL in the Nechiporenko sample). An immunochemical study of serum and urine proteins revealed monoclonal secretion of IgAλ (65 g/L) with a decrease in the content of polyclonal IgG in the blood serum and traces of type λ Bence-Jones protein (BJ) in urine.

The myelogram showed an increase in the count of monoclonal (λ light chain) plasmatic cells up to 19.6% without signs of the immunophenotype aberration (Fig. 1).

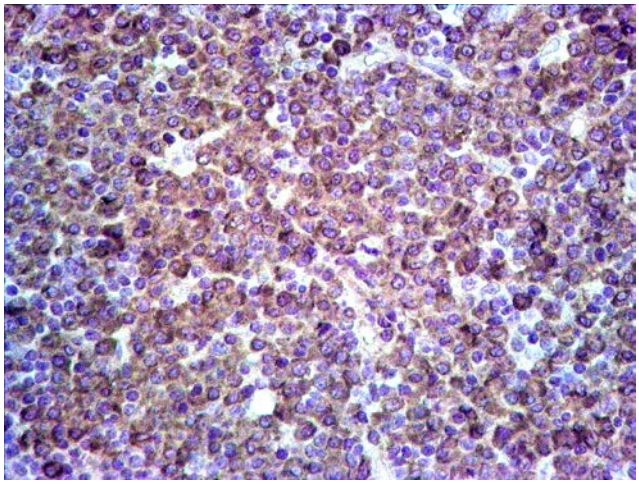

Fig. 1. Myelogram showing an increase in the number of monoclonal (λ light chain) plasma cells; stained with hematoxylin and eosin, magnification x 400

Computed tomography revealed an enlargement of the lymph nodes of the right lung root, retrocrural space, retroperitoneal lymph nodes (conglomerates up to 6.5 cm x 5.5 cm), and iliac areas (conglomerates up to 5.4 cm x 4.7 cm). No bone-destructive abnormalities were detected. The X-ray of the skull bones showed no foci of destruction.

A lymph node biopsy from the lower third of the neck and a pistol biopsy of the retroperitoneal lymph node were performed. Histological and immunohistochemical examination revealed a blurred lymph node structure due to the diffuse proliferation of plasma cells expressing CD138, VS3838c, CD79, MuM1, and IgAλ (Fig. 2).

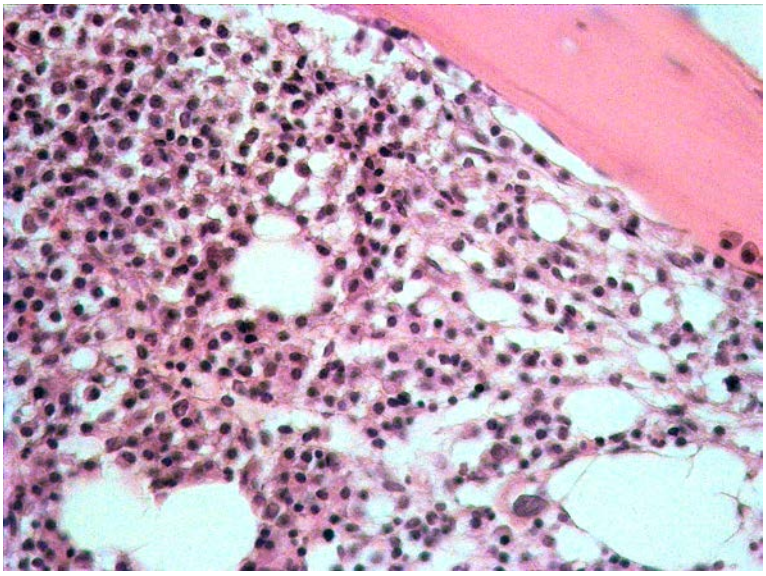

Fig. 2. Histological and immunohistochemical examination reveals the blurring of the lymph node structure due to diffuse proliferation of plasmatic cells expressing CD138, VS38c, CD79, MuM1, IgAλ, staining with hematoxylin and eosin, magnification x 400

Based on the examination results, the patient was diagnosed with primary plasmacytoma of the lymph nodes with the secretion of IgAλ paraprotein and BJ protein.

The immunosuppressive therapy was converted from tacrolimus to everolimus at a daily dose of 3 mg/day. The target baseline blood concentrations of everolimus were 2-4 ng/mL. After the immunosuppression conversion, rapid positive dynamics was observed in the form of a decrease in the size of lymph nodes and the regression of the paraprotein level until its complete resolution. No signs of insufficient immunosuppression or abnormalities in the results of functional liver tests were recorded. Repeated studies demonstrated the persisting microhematuria. No adverse events or signs of insufficient immunosuppression related to taking everolimus for 4 years were observed.

Discussion

The spectrum of post-transplant lymphoproliferative diseases varies from reactive (polyclonal) hyperplasia to highly aggressive lymphoid tumors. After liver transplantation, the incidence of PTLD is 2% in adults and up to 15% in children. The review of the very few cases of post-transplant plasmacytomas presented in the literature showed that they may develop many years after transplantation, while other forms of PTLD usually manifest themselves in the first year after surgery [8]. It is possible that a prolonged antigenic stimulation may play a role in the pathogenesis of this PTLD subtype. In the patient from the described case report, plasmacytoma also manifested itself only at 6 years after liver transplantation.

The diagnosis of primary lymph node plasmacytoma can be established only after excluding the terminal progression of multiple myeloma and upper respiratory tract plasmacytoma metastases to the lymph nodes. At examination, no upper respiratory tract plasmacytoma was seen in the patient. Besides, the lymph node involvement was of generalized nature, and the largest conglomerates were observed in the retroperitoneal and iliac regions. According to formal criteria, this case met the criteria for the diagnosis of "smoldering" (asymptomatic) myeloma: monoclonal plasma cells in the bone marrow accounted for more than 10%, the blood level of paraprotein A was over 30 g/L, and there were no organ lesions within the framework of symptomatic myeloma. However, lymphadenopathy is usually not observed in patients at the onset of multiple myeloma and can develop only in rare cases in the terminal phase of the disease. The generalized lymphadenopathy with the formation of conglomerates of lymph nodes the medical history, and the absence of bone-destructive lesions – all those indicated that the plasma cell tumor was primarily localized in the lymph nodes, and the bone

marrow lesion was secondary, metastatic by nature. In addition, the immunophenotype of plasma cells in the bone marrow of our patient did not show the aberrance characteristic of plasma cells in myeloma.

Hussong et al. (2007) suggested that extramedullary plasmacytoma in most cases is actually a lymphoma of marginal zone cells with pronounced plasmocytic differentiation, and, in particular, plasmacytoma of the lymph node represents a nodal variant of marginal zone lymphoma with a pronounced plasmocytic differentiation. In our case, we cannot rule out this variant of a lymphoid tumor with absolute certainty.

Since the earliest publications on PTLD, it has been obvious that minimization of an immunosuppressive therapy leads to an improvement in the course of the disease, and in some cases to a complete regression of PTLD [2, 4, 9]. The main component of the maintenance immunosuppressive therapy is usually calcineurin inhibitors (CNIs), and it is with a decreased exposure to these drugs that success in the PTLD treatment is usually attributed. In patients with nondestructive and polymorphic PTLD, a complete regression of the disease is possible without any specific therapy. Meantime, a prolonged reduction or a complete withdrawal of CNI is associated with an increased risk of the transplanted organ rejection.

The protein bound with mammalian rapamycin (mTOR) represents a ubiquitously expressed and highly conservative serine/threonine kinase that affects a number of key cell functions, including the protein synthesis and cell proliferation. Investigators from the United States demonstrated the activation of the mTOR signaling pathway in cells across the entire spectrum of PTLD subtypes. These data suggest that mTOR inhibitors may be effective in the treatment of PTLD [10]. The mTOR inhibitors represent a relatively new class of drugs used

for maintenance immunosuppression in solid organ transplantation. Drugs of this class are also called proliferation signal inhibitors, and they have both immunosuppressive and antiproliferative properties. Preclinical studies have shown that mTOR inhibitors (sirolimus and everolimus) have an inhibitory effect on the growth of PTLD cell lines [11, 13].

Since 2006, there have been reports about the possibility of a complete reverse development of monomorphic PTLD after replacing CNIs with sirolimus [14-16]. These reports mainly relate to non-plasmocytic PTLD in kidney recipients. Everolimus, a synthetic sirolimus analog, was registered for clinical use in liver recipients later than sirolimus. We were able to find only a few cases of an attempt to replace a CNI with everolimus in kidney recipients with PTLD [16-17]. It should be noted that the immunosuppression conversion per se was not always sufficient for the PTLD regression, but, as a rule, it did not lead to the development of the transplanted organ rejection.

The possibilities of using everolimus for the treatment of multiple myeloma are being actively studied [18, 19].

A possible shortage of the described case report is the lack of information about the Epstein–Barr virus (EBV) DNA in patient's blood at the time of plasmacytoma manifestation. Although more than 80% of post-transplant B-cell diseases and about 1/3 of post-transplant T-cell diseases are associated with EBV, current molecular studies have shown that this virus does not play an important pathogenetic role in the development of post-transplant plasmacytomas. Although mTOR inhibitors have a moderate antiviral activity against cytomegalovirus and EBV [20], there is no conclusive evidence for their role in reducing the risk of EBV infection after transplantation [21].

Conclusion

Apparently, this case report is the first description of a long-term remission of nodal plasmacytoma that developed in a liver transplant recipient after a complete withdrawal of calcineurin inhibitors and the administration of everolimus. We believe that both in our case and in the previously published reports, the regression of post-transplant lymphoproliferative diseases with the replacement of calcineurin inhibitors with mTOR inhibitors is associated both with minimizing the exposure to calcineurin inhibitors, and also with the antitumor effect of everolimus itself, which allows us to discuss the expansion of its clinical application.

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