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A rare case of very late onset post-transplant Burkitt lymphoma

Un raro caso de linfoma de Burkitt de aparición muy tardía post-rasplante

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RESUMEN

El trastorno linfoproliferativo postrasplante suele manifestarse en el primer año tras el trasplante de órganos sólidos, aunque raramente puede aparecer después de diez años. El linfoma de Burkitt postrasplante es infrecuente y agresivo. Su tratamiento incluye la reducción de inmunosupresores, rituximab y quimioterapia. Presentamos un caso raro de linfoma de Burkitt que se presentó18 años después de un trasplante renal. Tras el diagnóstico, el paciente fue tratado con everolimus, rituximab y quimioterapia, logrando una remisión completa, que se ha mantenido durante siete años sin tratamiento adicional. Este caso resalta la posibilidad de aparición tardía de estos trastornos, subrayando la importancia de una vigilancia a largo plazo. Además, el uso de sirolimus/everolimus combinado con rituximab y quimioterapia puede asegurar una respuesta completa y sostenida en el linfoma de Burkitt postrasplante.

Palabras clave: Linfoma de Burkitt; quimioterapia; trastorno linfoproliferativo postrasplante; trasplante renal; rituximab

ABSTRACT

Post-transplant lymphoproliferative disorder typically manifests within the first year after solid organ transplantation, though it can rarely occur ten years or more post-transplant. Post-transplant Burkitt lymphoma is seldom seen following solid organ transplantation and represents an aggressive subtype. Treatment involves reducing immunosuppressive therapy alongside rituximab and the use of multiple chemotherapy agents.Our case involves a rare occurrence of post-transplant Burkitt lymphoma 18 years after renal transplantation. Following diagnosis, the patient was switched to everolimus therapy and achieved a complete response after treatment with rituximab and chemotherapy. The patient has been in remission without further treatment for seven years. This case illustrates that post-transplant lymphoproliferative disorder can occur many years after transplantation, emphasizing the need for long-term vigilance in patients. The transition to sirolimus/everolimus, along with treatment protocols involving rituximab and multiple chemotherapy agents, can achieve a complete response and sustain it for extended periods for post-transplant Burkitt lymphoma.

Keywords: Burkitt lymphoma; chemotherapy; post-transplant lymphoproliferative disorder; renal transplantation; rituximab

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INTRODUCTION

Post-transplant lymphoproliferative disorder (PTLD) is one of the malignancies that can occur after solid organ transplantation. PTLD is closely related to immunosuppressive therapy and generally occurs due to the uncontrolled excessive proliferation of B lymphocytes [1]. In adult renal transplant recipients, the lifetime risk of developing PTLD is eight times higher than that of the general population [2]. Clinically, PTLD can be asymptomatic or present with severe manifestations such as organ failure and spontaneous tumor lysis syndrome. The incidence of PTLD has a bimodal peak within the first two years and between 5 to 10 years post-transplant [3]. In addition to reducing immunosuppression in treatment, rituximab and, if necessary, other chemotherapy agents are used [4].

Burkitt PTLD constitutes less than 10% of PTLD cases in adults. It is typically an aggressive, late-onset, and rare subtype. Studies indicate that Burkitt PTLD generally appears around five years post-transplant [5,6,7].

Contrary to the literature data, we present a case of Burkitt PTLD detected in the 18th year of follow-up after renal transplantation.

CASE REPORT

The 63-year-old female patient has a history of end-stage renal failure secondary to focal segmental sclerosis and underwent cadaveric renal transplantation in 1998. She was on low-dose prednisone, azathioprine, and tacrolimus, with creatinine levels stable at 0.6 mg/dL. A palpable mass approximately 8 cm in size was detected during physical examination in the suprapubic region. Laboratory tests revealed elevated LDH (1652 U/L) and uric acid (11.6 mg/dL), with no other abnormalities (**Table 1**).

Table 1: Laboratory Findings

Name of the Variable	Patient's Value	Normal Value
WBC	9900 mm3	4000-11000 mm3
Hemoglobin	12.1 g/dL	12-16 g/dL
Neutrophil	7500 mm3	2000-7000 mm3
Lymphocyte	1200 mm3	1000-4000 mm3
Platelet	256000 µL	150000-400000 µL
Tacrolimus	5 ng/mL	5-15 ng/mL
Glucose	88 mg/dL	70-99 mg/dL
BUN	10 mg/dL	7-18 mg/dL
Creatinine	0.6 mg/dL	0.5-1.2 mg/dL
Uric acid	**11.6 mg/dL**	3.5-7.2 mg/dL
Calcium	8.9 mg/dL	8.5-10.2 mg/dL
Phosphorus	3.4 mg/dL	2.5-4.5 mg/dL
Sodium	138 mmol/L	135-145 mmol/L
Potassium	4.7 mmol/L	3.5-5.0 mmol/L
Total Protein	6.87 g/dL	6-8 g/dL
Albumin	3.9 g/dL	3.5-5 g/dL
AST	32 U/L	10-40 U/L
ALT	14 U/L	7-56 U/L
Total Bilirubin	0.36 mg/dL	0.1-1.2 mg/dL
Direct Bilirubin	0.16 mg/dL	0.0-0.3 mg/dL
ALP	71 U/L	44-147 U/L
GGT	27 U/L	9-48 U/L
LDH	**1652 U/L**	135-225 U/L

***WBC**: white blood cell, **BUN**: blood urea nitrogen, **ALT**: alanine aminotransferase, **AST**: aspartate amino transferase, **ALP**: alkaline phosphatase, **GGT**: gamma glutamyl transferase, **LDH**: lactate dehydrogenase*

An abdominal ultrasound showed an 8 x 5 cm heterogeneous and hypoechoic solid mass in the anterior wall of the uterus. Advanced imaging with abdominal MRI revealed a 9 x 7 cm mass in the anterior uterine fundus with focal cystic-necrotic areas and several lymph nodes in the right iliac chain, the largest being 16 mm. An excisional iliac chain lymph node biopsy was performed, and the biopsy result was consistent with Burkitt lymphoma (**Figure 1**).

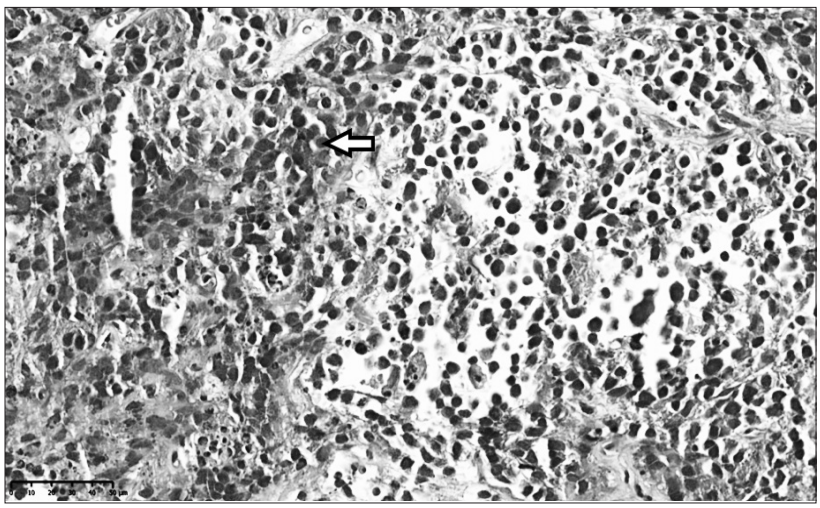

Figure 1: A lymph node infiltrated by lymphoblasts. Several lymphoblasts are visible (arrow)

The patient underwent bone marrow aspiration and biopsy, interpreted as normocellular bone marrow biopsy. Whole-body CT showed mass lesions causing 3.5 cm asymmetric thickening in the antrum of the stomach, nodular lesions measuring 4 x 5 cm in the inferior part of the stomach, and several lymph nodes, the largest being 11 mm in the paraaortic and paracaval areas. The Epstein-Barr Virus (EBV) polymerase chain reaction (PCR) result was negative, and the patient was started on R-HyperCVAD (rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) chemotherapy. We stopped her tacrolimus and azathioprine and started her on everolimus. A positron emission tomography (PET-CT) scan performed for response evaluation after chemotherapy showed no uptake. The patient completed chemotherapy in 2017 and has since been followed in remission. During chemotherapy, she developed avascular necrosis of the femoral head. Hence, corticosteroids were also stopped. Under single-agent everolimus, the patient's creatinine levels remained stable at 0.7 mg/dL without a sign of rejection.

DISCUSSION

Here, we present a rare case of very late-onset PTLD. PTLD that occurs after solid organ transplantation manifests generally within the first year, but cases appearing even after ten years exist due to prolonged immunosuppression [8]. Patients may present nonspecific symptoms such as fever, weight loss, and fatigue. Physical examination should be thorough for lymphadenopathy and hepatosplenomegaly, given the involvement of the reticuloendothelial system. Imaging modalities should be utilized for suspicious cases. Given the possibility of late-onset PTLD, patients should be carefully evaluated during each follow-up [9].

The majority of PTLD cases are associated with EBV. During the post-transplant period, latent EBV infection can become activated in transplant recipients due to immunosuppression, leading to viral oncogenesis and, ultimately, EBV-associated PTLD [10]. EBV-negative PTLD, however, is less common. In a study by Luskin et al., EBV-negative PTLD accounted for approximately 40% of PTLD cases. The same study demonstrated that EBV-negative PTLD cases were more frequent in renal transplant patients and tended to occur in the late posttransplant period [11]. The pathogenesis of EBV-negative PTLD is not well understood [10]. Similar molecular pathologies have been shown in cases of EBV-negative diffuse large B cell lymphoma developing after transplantation to

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those in non-immunosuppressed patients. This scenario suggests these cases may be de novo lymphomas [12]. Our case of a very late-onset PTLD is similar to literature data regarding EBV serology and features.

The treatment options for PTLD post-solid organ transplantation include reducing immunosuppression, rituximab, and chemotherapy. Early-stage lesions and indolent, non-aggressive subtypes may respond to immunosuppressive reduction alone; patients with advanced or bulky lesions are less likely to respond [8]. Reduction in immunosuppression for PTLD generally involves discontinuing calcineurin inhibitors and antimetabolite therapy and transitioning to sirolimus or everolimus [13,14,15]. For patients with advanced, late-onset, aggressive disease, adding rituximab and subsequent chemotherapy protocols like CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) or EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) has been shown to yield high treatment responses [8]. mTOR inhibitors, especially everolimus, may have single-agent anti-lymphoma activity; however, the doses used in lymphoma treatment are much higher than the doses we use in renal transplant recipients [16]. In addition, mTOR inhibition may also increase lymphoma response to chemotherapy [17]. All in all, switching the calcineurin inhibitor to an mTOR inhibitor seems wise for every case of PTLD.

Burkitt lymphoma is a rare subtype of lymphoma post-transplant. In immunocompetent individuals, Burkitt lymphoma is highly aggressive. Due to its rarity, the clinical course and treatment of Burkitt PTLD need to be better defined. In a retrospective study by Walczak et al. involving 55 Burkitt PTLD patients, the median time to diagnosis post-transplant was 5.4 years. Extranodal involvement was common (89.1%), with the gastrointestinal system being the most frequently affected site (52.7%) [5].

Contrary to literature data, our case is a rare Burkitt PTLD case presented 18 years post-transplant. This case emphasizes the need for vigilance regarding PTLD development even many years after solid organ transplantation.

The literature demonstrates the efficacy of sequential therapy in Burkitt PTLD cases, recommending the inclusion of rituximab and multi-agent chemotherapy protocols [5,6]. In our case, tacrolimus and azathioprine were discontinued, and everolimus therapy was initiated, which aligns with the literature approaches. The patient achieved a complete response with rituximab followed by HyperCVAD chemotherapy. This case supports transitioning to mTOR inhibitors in immunosuppressive therapy and incorporating rituximab and multi-agent chemotherapy protocols in treating advanced, late-onset Burkitt PTLD cases.

Data Availability

No data was used for the research described in the article.

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