Post-transplant lymphoproliferative disease in liver transplant recipients

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ABSTRACT

Introduction: Post-transplant lymphoproliferative syndrome (PTLD) is a rare and potentially life-threatening complication after liver transplantation. The aim of this study was to analyze the clinicopathologic features related to PTLD in a single institution after liver transplantation.

Methods: Observational study where we have retrospectively analyzed 851 cases who underwent liver transplantation. Ten cases have developed PTLD. Their clinical-pathological characteristics and the treatment received have been analyzed.

Results: PTLD incidence was 1.2% (10/851). The mean time from liver transplantation to PTLD diagnosis was 36 months (range 1.2 to 144 months). PTLD localization was extranodal in all cases, the most frequent location being intestinal. Seven cases showed a monomorphic lymphoma which in all cases was differentiated B cell lymphomas. Fifty per cent of the series were seropositive for Epstein-Barr virus. Five patients were alive at the time of the review. Among these patients, we observed three cases of complete remission and two cases of disease stabilization. The death rate was higher in the first year after diagnosis of PTLD.

Conclusion: PTLD is a rare complication after liver transplantation, but it may pose a threat to the life of a liver transplant recipient. It is essential to identify patients at risk, to establish an early diagnosis and treatment that can change the outcome of the disease.

Key words: Post-transplant lymphoproliferative disease. Liver transplantation. Rituximab.

INTRODUCTION

During the past 20 years, liver transplantation programs have undergone a huge development. Advances in preoperative management, improvements in surgical techniques and progress in postoperative care have facilitated the improvement of liver transplant patient survival rates. The survival results published in European and American records exceed 85%, 75% and 60% at one, five and ten years respectively (1).

However, long-term complications are a major cause overshadowing the prognosis of these patients. It has been observed that patients with solid organ transplantation are at increased risk of developing malignancies (2). Several factors have been described to contribute to the development of tumors. The reduction of immune surveillance mechanisms in the recipient, the activation of latent virus with oncological potential and the chronic use of immunosuppressive agents are the main factors for the appearance of cancer after a solid organ transplantation. In our country, the incidence of malignancies in liver transplantation is about 8%. The most common are skin tumors, followed by lymphoproliferative disorders (3).

Post-transplant lymphoproliferative disease (PTLD) is a rare but also a serious complication in solid organ transplantation. In liver transplantation recipients, PTLD is reported in up to 1 to 2.8% of adults and 15% of children (4). It has been closely associated with exogenous immunosuppression and the Epstein-Barr virus (EBV); in fact, EBV is associated in up to 90% of cases. PTLD mortality has been estimated at around 50%, although progress in treatment and chemotherapy regimens appear to have improved these results (5-9). Despite these different treatment options, mortality rates remain high. For this reason, early diagnosis is essential to facilitate prompt treatment.

Relatively little is known about the incidence and outcome of PTLD in adults with a transplanted liver. The main objective of this study was to analyze the clinical-pathological characteristics of one of the most uncommon complications after liver transplantation.

MATERIAL AND METHODS

In this observational study, 851 cases who underwent liver transplantation in the Hospital Universitario Virgen del Rocío (Seville, Spain) from 1994 to 2011 were analyzed. Among the 851 cases ana-

lyzed, ten patients developed a PTLD that was diagnosed in all cases by biopsy of nodal or extranodal sites detected on imaging tests. Immunohistochemical markers were used to delineate the subtype of lymphoid proliferation, including CD20, CD79a, CD3, CD10 and bcl-6. Lymphomas were classified according to the World Health Organization (WHO) classification of PTLD (Table I).

Inclusion and exclusion criteria

We have included in this study all patients who received an isolated liver transplantation (not split or living donor) and developed PTLD. We have excluded from the study those who did not meet PTLD features according the WHO classification (Table I).

Variables analysed

The variables included in the study were as follows: age, gender, cause for liver transplantation, immunosuppressive agents used at the time of diagnosis, presence of acute rejection and need for treatment, lactate dehydrogenase (LDH) > 250 mg/dl before PTLD detection, PTLD histological classification, agents used after the PTLD diagnosis, chemotherapy used and use of rituximab.

EBV was diagnosed before the transplantation both in the donor and in the recipient by RNA *in situ* hybridization.

Hepatitis C virus (HCV) recurrence was diagnosed by biopsy on the new liver graft prior to the development of PTLD, and confirmed by the HCV RNA detection.

Immunosuppression was based on triple therapy, consisting of calcineurin inhibitor (tacrolimus [FK 506]/cyclosporin A [CyA]), steroids and mycophenolate mofetil/azathioprine. Corticosteroids were removed from the third month.

We collected the cases that had a history of treated acute cellular rejection episodes. These cases were treated with 6-methylprednisolone intravenous bolus. In the same way, we have also collected patients who received induction therapy with OKT3 or anti-CD25 antibodies.

Finally, we have analyzed those cases that converted from a calcineurin agent to mTOR inhibitors (sirolimus/everolimus) after diagnosis of PTLD.

Evaluation of response to treatment and survival

Treatment response was assessed using follow-up computed tomographic (CT) scans. Restaging was performed following treatment.

Complete remission was defined as the disappearance of all clinical evidence of active tumor for at least one month. Partial remission was defined as a minimum of 50% reduction in the measurement of detectable lesions for at least one month. Stable disease was considered when no objective modifications in the lesions were observed. Progressive disease was defined as the enlargement of tumor size or the occurrence of new lesions.

Survival was defined as days survived from the date of diagnosis of PTLD to date of death or until the date of last revision.

Statistical analysis

Demographic characteristics, clinical presentation, histology and survival data were collected retrospectively in July 2013 in a SPSS 15.0 database (Tables II and III). A descriptive analysis was performed.

Table II. Baseline characteristics

Characteristics	No. of cases (%)
Age (years)	50 (± 13,24)
Female gender	2 (20%)
Etiology of liver disease	
Hepatitis C	1 (10%)
Primary biliary cirrhosis	2 (20%)
Alcohol	4 (40%)
HCV + alcohol	2 (20%)
Other	1 (10%)
EBV serology recipient positive	5 (50%)
EBV serology donor positive	6 (60%)
Immunosuppression	
Cyclosporine-based	3 (30%)
Tacrolimus-based	7 (70%)
Corticosteroids	4 (40%)
Mycophenolate	3 (30%)
Sirolimus	3 (30%)
Azathioprine	6 (60%)
Induction monoclonal antibodies	3 (30%)
Acute rejection episode	4 (40%)

Table I. 2008 WHO classification of post-transplant lymphoproliferative disease

Category	Clonality	VEB status
Early lesions (plasmacytic hyperplasia, infectious mononucleosis)	Polyclonal	EBV positive
Polymorphic PTLD	Monoclonal	EBV positive
Monomorphic PTLD		
B-cell lymphomas	Monoclonal	Frequently EBV positive
T-cell lymphomas	Monoclonal	Rarely EBV positive
Classic Hodgkin lymphoma-like PTLD	Monoclonal	Frequently EBV positive

For quantitative variables, data were expressed using means ± standard derivation, and percentage and counts were used for qualitative variables. For the analysis of two qualitative variables in a sample of unequal size we used the Fisher's exact test. Statistical significance was considered if p < 0.05.

Finally, the Kaplan-Meier method was used to estimate survival following PTLD diagnosis.

RESULTS

During the study period (1994-2011), the incidence of proven PTLD was 1.2% (10/851). Of the ten patients with histological PTLD, eight were male (80%) and two were women (20%). All patients studied were adults over 18 years of age. The mean age at disease presentation was 50 years (range 20-67). The causes underlying the liver transplantation included four patients with alcoholic cirrhosis, one case with hepatitis C cirrhosis, one case with hepatitis B cirrhosis and two cases of primary biliary cirrhosis. In addition, two patients had mixed alcohol cirrhosis and hepatitis C cirrhosis (Tables II and III).

The timing from liver transplantation to first diagnosis of PTLD mean was two years and nine months (range 12 months to 12 years). In 50% of cases, PTLD was diagnosed during the first year after liver transplantation, whereas 30% presented a late onset, within three years after transplantation.

Regarding clinical presentation, although symptoms were varied, the most common manifestations were fever and epigastric pain (30%). Other presentations were one case of intestinal obstruction, two cases of skin lesions, two cases of anemia, and one patient had chylous ascites. One case presented as a graft acute cellular rejection (Tables II and III).

The most common manifestation in clinical examination and imaging tests was as a tumor mass. PTLD localization was extranodal in all cases, the most frequent location was intestinal. Among the four cases of intestinal localization, two were located in the stomach and two in the small intestine (one of these patients had both sites). Other sites include two retroperitoneal masses, one mediastinal mass and a cutaneous lymphoma. In two patients the PTLD was located on the liver graft, although no evidence of tumor mass in the previous image was detected.

Following the WHO classification of PTLD (Table I), one patient had early lesions showing plasmacytic hyperplasia features, two patients were polymorphic PTLD, whereas seven cases remained monomorphic. Among the latter, six patients were B cell lymphomas (five resembling diffuse large B cell lymphoma) and one patient was Hodgkin lymphoma. No patient had monomorphic T cell lymphoma.

The status for the Epstein-Barr virus (EBV) receptor was performed in all cases by *in situ* RNA hybridization for EBV. Fifty per cent of patients were EBV positive and the remain-

Table III. Clinicopathological features of the ten PTLD cases

Case	Sex/Age	Primary liver disease	Year of diagnosis	Immunosuppression Pre-PTLD	ACR*	Recurrence VHC	Duration* (months)	PTLD site	Histological classification	EBV donor	EBV receptor	Clinical outcome	Rituximab	mTOR (sirolimus)
1	M/48	Alcoholic cirrhosis	1994	Cyclosporine	Yes	No	1,22	Hepatic graft	Polymorphic	-	+	Died	No	No
2	M/49	HCV cirrhosis	1998	FK506	Yes	No	1,30	Hepatic graft	Monomorphic, B cell	-	-	Died	No	No
3	M/58	Alcoholic cirrhosis	2011	FK 506 + MMF	No	No	144	Stomach + ocular nerve	Monomorphic, B cell	+	+	Stabilization	Yes	Yes
4	F/46	Alcoholic and HCV cirrhosis	2001	FK506	No	Yes	17	Retroperitoneum	Monomorphic, B cell	-	-	Died	Yes	No
5	M/44	HBV cirrhosis	2001	Cyclosporine	No	No	16	Cutaneous	Polymorphic	+	+	Stabilization	No	No
6	M/20	Primary biliary cirrhosis	2008	FK506 + MMF	Yes	No	105,21	Intestinal	Early lesions	+	+	Complete remission	No	No
7	F/67	Primary biliary cirrhosis	2006	FK506 + MMF	No	No	47	Mediastinum	Hodking lymphoma	+	+	Complete remission	No	No
8	M/64	Alcoholic cirrhosis	2009	FK506	No	No	7	Intestinal	Monomorphic, B cell	+	-	Died, complete remission	Yes	Yes
9	M/58	Alcoholic cirrhosis	2009	FK506 + MMF	No	No	7	Stomach + intestinal	Monomorphic, B cell	+	-	Complete remission	Yes	Yes
10	M/47	Alcoholic and HCV cirrhosis	1996	Cyclosporine	Yes	Yes	9,27	Retroperitoneum	Monomorphic, B cell	-	-	Died	No	No

ACR* acute cellular rejection. Duration*: Duration from liver transplantation to first diagnosis of PTLD.

ing 50% were negative. All patients who had negative serology for EBV showed a monomorphic B cell lymphoma.

Regarding the EBV status in the donor liver, 60% presented seropositivity for EBV. Among them, two grafts with positivity for EBV were implanted in recipients with negative EBV. In our series we found no significant difference among patients with EBV seronegativity who received a liver from a seropositive donor from those who received a negative EBV graft (Fisher's exact test p = 1).

Concerning HCV recurrence in the graft after liver transplantation, two of the three patients transplanted for virus C cirrhosis had a recurrence of the disease in the graft. Lymphoma appearance was earlier in these cases. Both patients were monomorphic B cell lymphomas (Table III).

LDH levels were determined prior to diagnosis of PTLD in eight cases, observing an elevation above 250 mg/dl in seven of them.

Seven patients have been treated with tacrolimus as a basic immunosuppressive therapy. Among these cases, five patients developed a B cell lymphoma, one case was a Hodgkin lymphoma and another case was plasmocytic hyperplasia. Among the three patients who received cyclosporine, two developed a polymorphic lymphoma and one, a monomorphic B cell lymphoma.

Although there is a tendency to use lower immunosuppressive levels in the latter years of the study, we have not seen a lower number of cases in this period. Fifty percent of the cases were diagnosed in the latter half of the study (Table III).

Four patients required intravenous treatment with 6-methylprednisolone (6-MP) for acute rejection. Among them, three patients received OKT3. In these cases, PTLD developed earlier.

Three patients were diagnosed *post mortem* (30%) and they were not treated. The immunosuppression reduction without any other treatment allowed the achievement of complete remission of early lesions in one case and the stabilization of a cutaneous lymphoma in another. Three patients received rituximab as a first-line treatment and one patient as a second-line therapy. The latter received rituximab when current protocols for the administration of this drug were not established, thus receiving rituximab after chemotherapy. Immunosuppressive therapy of the three cases that received rituximab as first-line treatment was substituted for an mTOR inhibitor after diagnosis of PTLD. Specifically, these patients received rapamycin (Sirolimus®) plus mycophenolate mofetil, among which a complete cure has been observed in two cases and disease stabilization in the remaining case.

Two patients received chemotherapy. Among them, the patient who received rituximab as second-line treatment died. The other case was a Hodgkin lymphoma who received chemotherapy with ABVD regimen as first-line and CEP as second-line treatment with a resulting complete remission.

The mortality in our series was 50%. The overall complete cure rate was 40%. One of the patients that had a complete remission died due to another cause not related with PTLD, specifically, he died due to a heart attack. We also observed a recurrence of 10%, resulting in death and rates of disease stabilization of 20%. The minimum follow-up time of patients from diagnosis of SLPT to the present time has been three years.

It should be noted that since the use of rituximab (four patients) and calcineurin conversion to mTOR inhibitors (three patients) the cure rate has been 66%, with one case of stabilization (33%). The latter patient had at the time of diagnosis a primary tumor in the stomach and a metastasis in the ocular nerve. After he received rituximab, the primary tumor completely disappeared but the metastasis still persisted. For this reason, he is waiting to receive radiotherapy.

Survival mean was 71 ± 21 months and the actuarial survival at the time of the study was 50%. The overall survival at one, three and five years was 60%, 50% and 50%, respectively (Fig. 1). In three cases, the diagnosis of PTLD was made *post mortem.* In the remaining two cases, death occurred at eight and 25 months of diagnosis.

DISCUSION

The incidence of PTLD after liver transplantation has been reported to vary from 2% to 5% (3,4). In our series, incidence was largely in accordance with the reference range in the literature, specifically, it was in up to 1.2% of cases.

Although PTLD is a rare complication, it can be a threat to the patient's life due to its high mortality rate and rapid clini-
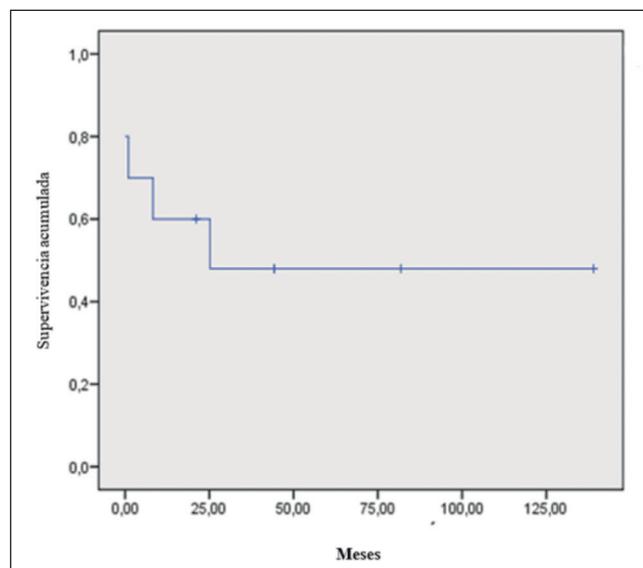
Fig. 1. Survival curve after PTLD diagnosis.

cal progression. It is estimated that the mortality of PTLD is around 50% (5-9). In our series, the survival mean from diagnosis of PTLD to death or the last contact with the patient was 71 ± 21 months. We have observed that the survival rate after the first year of PTLD diagnosis was 60%. The death rate has been higher in the first year after diagnosis of PTLD.

The median time for presentation was 36 months (range 1.2 to 144 months). In 70% of cases the diagnosis was made in the two years following liver transplantation. These findings are similar to those found in the literature, where the highest incidence of PTLD is observed at 18 months (10).

Risk factors for PTLD development

Risk factors for PTLD after liver transplant include EBV seronegativity, early age (especially children and adolescents), and high doses of immunosuppression and first year after transplant (11-13). In our case, 50% of recipients had EBV seronegativity prior to the liver transplant. Although multiple risk factors for the development of PTLD have been reported, the two main factors are EBV seronegativity of the recipient and the degree of immunosuppression. Recipients with EBV seronegativity who received a liver from a seropositive donor are at a particularly high risk due to the lack of specific immunity (cytotoxic T lymphocytes) to fight against infected B cells (14). In our series, no significant difference was observed, and this may be due to the limited number of receptors with seronegativity for EBV (Fisher's exact test p = 1).

In the same way, the administration of high doses of steroids as a result of acute graft rejection has also been associated with an increased risk of PTLD (15). Immunosuppression after transplantation, leading to a decrease of the specific response function of cytotoxic T lymphocytes against EBV generates an uncontrolled proliferation mediated by the virus which culminates with the appearance of PTLD. In our series, 40% of patients had acute liver graft rejection. As treatment, all patients received intravenous steroids. Among them three cases were also treated with OKT3. The latter may have had a greater predisposition to the development of PTLD due to the high degree of immunosuppression.

Other risk factors that have been associated with PTLD are HCV recurrence on the graft, age older than 50 years, alcoholic cirrhosis and hepatitis C cirrhosis (16). In our series, all patients were of legal age, with an average age of presentation of 50 years (range 20-67 years). The principal causes which motivated liver transplantation were alcohol and hepatitis C virus. Among patients with HCV, we have observed recurrence of hepatitis C virus on the graft in half of the cases. Immunosuppression received after liver transplantation suppress immunosurveillance mechanisms facilitating the activation of the virus with oncogenic potential that can lead to the development of tumors.

PTLD diagnosis

Clinical presentation often includes fever, lymphadenopathy, weight loss and splenomegaly. The disease can affect a single organ, graft or multiple organs. Bone marrow failure and central nervous system dysfunction is also common (6,17). Although in our series the most common clinical manifestations were fever along with epigastric pain (30%), in fact, the symptoms were varied.

As noted, the first manifestations of PTLD are widely variable; for this reason, a high index of suspicion for early detection of PTLD is required. To resolve this, the measurement of EBV load by quantitative polymerase chain reaction can be an important weapon for monitoring and diagnosing patients with PTLD risk factors. Although a high load of EBV has a high sensitivity to predict PTLD, specificity in the liver transplant recipient is only around 50%. Due to the low specificity of EBV load for detecting PTLD, new biomarkers such as CD30 are being sought.

In any case, an elevated EBV DNA in the peripheral blood should alert the physician to perform a physical examination and request imaging. If clinical suspicion is raised, an excisional biopsy should be done. Tissues should be submitted for EBV analysis and determination of CD20 expression, which are critical in determining treatment. If PTLD is confirmed, it is necessary to perform a complete staging, including CT of the neck, chest, abdomen and pelvis, evaluation of the transplanted liver graft, an echocardiogram, and glomerular filtration rate. SPECT-CT is also useful, since it can detect areas infiltrated by lymphoma that had previously gone unnoticed (17).

In our series, PTLD location was extranodal in all cases, the bowel being the most common site. These results do not agree with those obtained in other series where the most common localization were the lymph nodes followed by an intestinal location (18,19). On the other hand, the liver graft is a common site of presentation (up to 49% depending on the series) (19). In our case, although relatively frequent, the percentage is lower (20%).

Early diagnosis of PTLD is essential to initiate treatment and prevent progression to a more aggressive variant. Thus, in 2008 the WHO introduced the PTLD classification, which establishes four categories according to their mode of presentation (Table I).

Early lesions usually occur after the first year post-transplant. They have features of plasmocytic hyperplasia or mononucleosis primary infection (20). Lesions are usually polyclonal and they are more common in EBV seronegative recipients and in young patients. In our series, only one patient had early lesions such as plasmacytic hyperplasia. As in the literature, it occurred in the youngest patient in the series but this case was seropositive for EBV and debuted the first year after transplantation. Polymorphic PTLD, monomorphic PTLD and classic Hodgkin's lymphoma-type PTLD are usually monoclonal and they have a variable time of presentation after liver transplantation.

Monomorphic B cell PTLD is the most frequent variant, especially diffuse large B cell lymphomas (21,22). In our cases, 60% of patients had monomorphic B cell lymphoma, of which 50% were diffuse large B cell variant.

Lymphoproliferative syndromes are heterogeneous and EBV plays an important role in its pathogenesis. Eighty-five per cent of PTLD comes from the proliferation of B lymphocytes, and more than 80% of these are associated with EBV (21). Of the 15% that are of T-cell origin, 30% are associated with EBV (21). No monomorphic T cell PTLD was identified in our series; 100% of monomorphic lymphomas corresponded to B-cell lymphomas. These results are comparable with the revised data. However, in our series, only 20% of B cell lymphomas showed EBV seropositivity.

On the other hand, in our series, we observed a high mortality rate among patients who were EBV negative. Specifically, 80% of the deaths were EBV seronegative. The main prognostic factors for PTLD include high-grade lymphomas, EBV negativity on the recipient and an affected liver graft (6). This may explain the high mortality among patients with EBV negativity. As for the two patients who had liver involvement, both patients died and the diagnosis was made *post mortem*. PTLD located in the liver graft has a fulminant clinical course. Due to its similarity to acute rejection, it is essential to perform a liver biopsy to perform the diagnosis and start early treatment (23).

PTLD treatment

Current treatment for PTLD is based on an ascent therapy. It includes a reduction of immunosuppression, administration of monoclonal antibodies against specific biomarkers of B lymphocytes (anti-CD20) and chemotherapy. Surgery and radiation therapy may be useful when the disease is localized.

It is estimated that reduction of immunosuppression can lead to regression of PTLD in up to 23-50% of cases (17). Immunosuppression should be decreased to the lowest tolerated levels, considering the risk of graft rejection. The liver is a resistant organ to reduction of immunosuppression, with a low rate of graft loss due to rejection. Liver transplantation has a better tolerance to immunosuppression reduction than other solid organ transplants. In our series, in two cases, reducing immunosuppression alone was sufficient to produce complete remission in one patient and stabilization in the other. None of these cases showed signs of acute or chronic rejection after decreasing immunosuppression.

Although there is a tendency to use lower target levels of immunosuppressant in the second half of this study, this does not involves a trend towards a lower number of cases. Fifty percent of the cases were diagnosed in the latter half of the study (Table III).

It is thought that the use of both CsA and FK506 *per se* increases the incidence of neoplasia with respect to common guidelines of this medication. Although the primary risk factor is the overall degree of immunosuppression, there is evidence to suggest that CsA and FK506 can promote tumor growth in immunosuppressed animals through the release of tumor growth factor beta (24).

When we have a suspicion or confirmation of PTLD, the first step should be to reduce or withdraw immunosuppressive medication if possible, adding drugs with antitumor effect. The use of immunosuppressive regimens that include an mTOR inhibitor such as sirolimus or everolimus, which have an antitumor effect, could improve survival of these patients. However, although its effectiveness is recognized in patients with heart and kidney transplants, its efficacy in liver transplantation has not yet been established, so it is not advised as an initial immunosuppressive (25). In our series, immunosuppressive medication was replaced by an mTOR inhibitor (sirolimus) in three cases. Among them, complete cure of the disease was observed in two cases and stabilization in the remaining case.

New therapies with monoclonal antibodies against lymphocyte specific biomarkers have been a breakthrough in the treatment of lymphoproliferative syndrome. Rituximab therapy (an antibody against the CD20 receptor of B cells) seems to be effective in the management of PTLD cases, with a remission rate of 45-65% (17,26). In our study, 30% of patients received rituximab as first-line treatment, with a complete remission observed in 66% of these cases.

Chemotherapy should be reserved for patients with high-grade lymphomas, disease progression after exhausting other therapeutic options or the occurrence of any organ failure. Generally, chemotherapies are based on anthracycline, which results in longer survival and disease free survival, although its benefits are overshadowed by its toxic effects (23). In our series, we observed the progression of the disease in the two patients who received chemotherapy, resulting in one death.

CONCLUSION

In summary, patients with suggestive symptoms of PTLD should undergo a liver biopsy and complementary imaging tests that allow early diagnosis. Our first action in PTLD treatment should be to reduce immunosuppression, always assessing the risk of acute liver graft rejection. Patients may also benefit from the replacement of a calcineurin inhibitor for an mTOR inhibitor, specifically sirolimus.

Patient management should be based on histology, stage and location of the tumor. Patients with low-grade B cell lymphoma should be treated with rituximab monotherapy and the replacement of a calcineurin inhibitor for an mTOR inhibitor. In the event of therapy failure, high grade lymphomas or organ failure, chemotherapy should be used.

In conclusion, PTLD is a rare complication after liver transplantation that represents a threat to the patient's life.

Due to the high mortality and therapeutic limitations, it is essential to identify patients at risk to obtain an early diagnosis and treatment that can change the outcome of the disease.

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