Primary Hepatic Lymphoma After Lung Transplantation: A Report of 2 Cases

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ABSTRACT

Background. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non–Hodgkin lymphoma in the posttransplant setting. Treatment is based on chemotherapy; surgery is still debated and should be performed in very select cases.

Methods. We observed 2 patients out of 300 who underwent lung transplantation in the Nouvel Hopital Civil between 2013 and 2019 with primary hepatic lymphoma. Chemotherapy with a rituximab-cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone protocol was performed in all patients. Mycophenolate mofetil was interrupted before treatment, and everolimus was introduced after chemotherapy by associating tacrolimus withdrawal.

Results. One patient showed complete remission; after 7 years, no recurrence has been noticed. The second is still undergoing chemotherapy with no signs of disease progression.

Conclusions. DLBCL risk is higher in solid organ transplant recipients than in the general population. Primary hepatic lymphoma diagnosis is often difficult and based on histologic findings after initial clinical and radiological suspicion of primary or secondary liver neoplasia. Diagnosis is challenging because no clinical, radiological, or biological features exist. Biopsy is always indicated for histologic confirmation. Chemotherapy is the mainstay of therapy, but surgery may be indicated in very select patients.

POSTTRANSPLANT lymphoproliferative disorder is one of the most common forms of transplant-associated malignancies, with an incidence rate of 20.8% of all posttransplant neoplasia [1]. Diffuse large B-cell lymphoma (DLBCL) is the most common non–Hodgkin lymphoma (NHL) subtype in the posttransplant setting, involving approximately 73% of specified NHL subtypes [2]. DLBCL risk is 12 times higher in solid organ transplant recipients than in the general population, and risk is even higher in specific subgroups, including children and lung- or pancreas-transplanted patients [3,4]. DLBCL is also the most common cause of cancer-related deaths in transplanted patients [5,6]. Several factors contribute to the development of DLBCL in transplant recipients [7,8], most of them due to Epstein-Barr virus (EBV), which in absence of host immune control leads to lymphocyte proliferation. However, the occurrence of DLBCL in long-term transplant survivors appears to be caused by specific factors in addition to EBV [3,9,10]. DLBCL potentially arises within lymph nodes and in other areas such as in the gastrointestinal tract. As the liver is the largest reticuloendothelial organ, DLBCL can develop in it as well. Primary hepatic lymphoma (PHL)

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0041-1345/21
https://doi.org/10.1016/j.transproceed.2021.01.030

is a rare disease [11], reported as reaching approximately 0.016% of all cases of NHL. Its pathogenesis is linked to sequential adhesive interactions of human B cells with hepatic sinusoidal endothelial cells and subsequent proliferation within the liver [12]. Currently, some specific risk factors have been reported. Patients with hepatitis C virus infection or immunosuppressive disorders (systemic lupus erythematosus, acquired immune deficiency syndrome, those receiving immunosuppressive treatment, etc.) are more likely to present such diseases [13]. Late diagnosis often results in poor prognosis because of multifocal localization and disease progression. At present, chemotherapy is the mainstay of therapy, but the role of surgery and other treatments are debated with no clear guidelines [14]. We present the case of 2 patients diagnosed with primary hepatic lymphoma in a cohort of 300 patients who have undergone lung transplantation.

CASE DISCUSSION

The first patient is a 43-year-old man who underwent bipulmonary transplantation in June 2012 for mucoviscidosis (donor status of EBV negative). In his past medical history, Bouverie disease, congenital hydrocephalus, peripheric neuropathy, cortico-induced diabetes, and epilepsy were noticed. Six months after transplantation, the patient presented an inflammatory syndrome associated with acute renal failure. Contrast-enhanced abdominal computed tomography (CT) scan (Fig 1) and liver magnetic resonance imaging (MRI) showed multifocal bilobar liver lesions; the largest was 50 mm localized in the junction of segments 2 and 3. Initial clinical and radiological suspicion suggested an intrahepatic cholangiocarcinoma associated to synchronous bilobar liver metastases. Tumoral markers Ca 19.9, carcinoembryonic antigen (CEA), and alphafetoprotein were within limits. Liver biopsy was performed to confirm diagnosis, but the result showed an EBV positive B lymphoproliferation (EBV status of recipient positive). A positron emission tomography (PET) scan showed no extrahepatic localization of the disease. Serum creatinine was 110 μmol/L, C-reactive protein (CRP) 96.6mg/L, alkaline phosphatases 333 U/L, gamma glutamyltransferase (GGT) 374 U/L, lactate dehydrogenase (LDH) 380 U/L, hemoglobin 9.8 g/dL, platelets 274,000 mm/L, and white blood counts 3420 mm^3/L. Immunosuppressive regimen before diagnosis included tacrolimus, corticoids, and mycophenolate mofetil; before treatment, mycophenolate mofetil was interrupted to avoid strong immunosuppression. Histologic examination of the osteomedullary biopsy was also performed, and no anomalies were present. After a multidisciplinary discussion, an R-CHOP (rituximab-cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone) chemotherapy regimen was indicated. An fluorodeoxyglucose (FDG) positron emission tomography (PET) scan performed after treatment showed complete remission. After a 6-year follow-up, the patient is alive without recurrence.

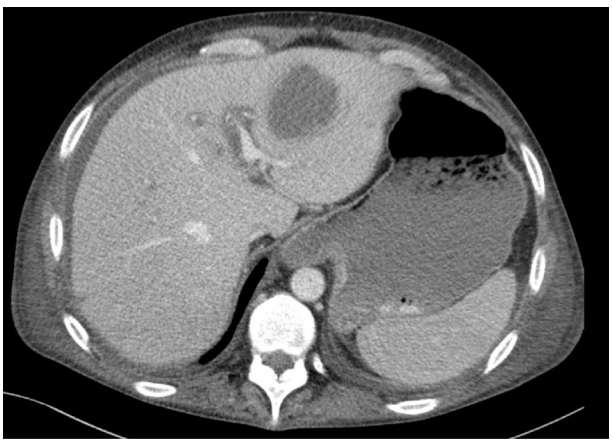

Fig 1. Computed tomography scan arterial phase. Hepatic hypodense mass. CT, computed tomography.

The second patient is a 68-year-old patient who underwent bipulmonary transplantation in February 2015 for severe obstructive bronchopneumopathy (donor status of EBV positive). In his past medical history, we found osteoporosis and diabetes. Four years later, the patient presented with diffuse abdominal pain and jaundice. An abdominal CT scan (Fig 2) showed a hypodense liver mass of 85 mm localized in segments 5 and 6. Biology revealed a cholestatic syndrome with hepatic cytolysis with aspartate aminotransferase (ASAT) 228 IU/L alanine transaminase (ALAT) 394 IU/L, gamma-glutamyltransferase (GGT) 1035 IU/L, total bilirubin 150 micromol/L. Ca 19.9 was 1666 kIU/L; carcinoembryonic antigen (CEA) and alphafetoprotein were within limits. Jaundice was secondary to a biliary confluence extrinsic compression by the lesion. A cholangio-MRI was performed, and it confirmed the mass with no biliary confluence infiltration. A percutaneous liver biopsy associated with biliary stenting was then performed for suspected intrahepatic cholangiocarcinoma. Histology showed a B-cell Lymphoma (EBV status of recipient negative). A PET-CT scan showed nodal involvement in the hepatic pedicle but no other extrahepatic disease. Immunosuppressive regimen before diagnosis was tacrolimus, prednisolone, and mycophenolate mofetil; after the diagnosis of lymphoma, administration of mycophenolate mofetil was stopped for the same reason as the first patient. After a multidisciplinary discussion, R-CHOP was indicated and started in September 2019. The patient, after the second cycle of chemotherapy, is in good general condition with excellent metabolic response to PET-CT scan control.

DISCUSSION

Posttransplant lymphoproliferative disorder is one of the most common forms of transplant associated malignancies, and diffuse large B-cell lymphoma (DLBCL) is the most common NHL subtype in the posttransplant setting, comprising approximately 73% of specified NHL subtypes. T-cell PHL is rarely reported. Other histologic subtypes are lymphoblastic and Burkitt lymphoma (17%), follicular lymphoma (4%), lymphoma of the mucosa-associated lymphoid

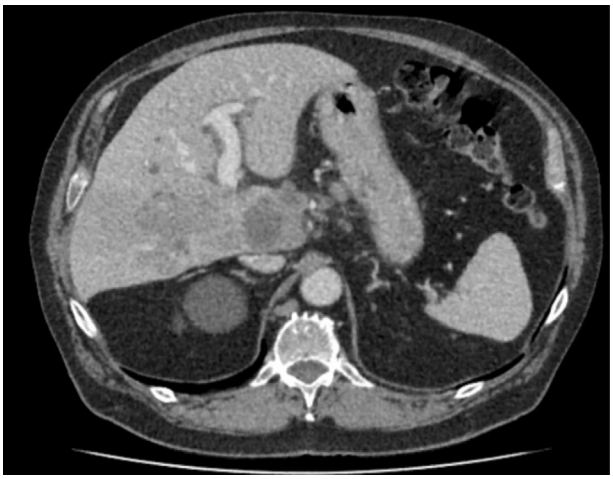

Fig 2. Computed tomography scan venous phase. Hepatic hypodense mass. CT, computed tomography.

tissue type, T-cell-rich B-cell lymphoma, anaplastic large-cell lymphoma, hepatosplenic T-cell lymphoma, and mantle cell lymphoma [14].

PHL is a rare disease [11], reaching approximately 0.016% of all cases of NHL. The rarity of the disease and the absence of specific radiological findings make the diagnosis challenging. In fact, it is often a diagnosis of exclusion, and the first clinical hypothesis often is oriented to primary liver neoplasia, such as intrahepatic cholangiocarcinoma or liver metastases. Histology is the only way to determine the exact diagnosis and characterize the type of lymphoma. Common but aspecific symptoms are abdominal pain, fever, fatigue, jaundice, and vomiting. Incidental diagnosis in asymptomatic patients may be present in about 8% of patients [14]. Primary NHL of the liver appears most often as a solitary mass or, more rarely, as multiple lesions showing different types of radiological features [15,16]. Some echographic features might be suggestive [17], but their actual sensitivity and specificity have not been closely evaluated. Ultrasound studies showed that the majority of the hepatic lymphomas are hypoechogenic lesions, in agreement with a previous study on liver lymphomas [18]. On a contrast-enhanced CT scan, primary hepatic lymphoma has been described as a low-density mass, usually not enhanced after contrast injection or faint enhanced.

Peripheral enhancement in the early arterial phase is sometimes present. MRI is characterized by low signal intensity on T1-weighted images and moderately high signal intensity on T2-weighted images; the enhancement pattern is similar to that of CT [18–20]. Radiological features of PHL, especially the nodular type, could be very similar to other primary or secondary liver neoplasia such as cholangiocarcinoma, hepatocellular carcinoma, or colorectal metastases. There are no biological elements that help in the diagnosis. As far as the cases of these 2 patients are concerned, diagnosis was always made on histology and not suspected until the biopsy analysis was performed. Treatment is still debated, and chemotherapy is very often performed. Several other treatments have been proposed, including surgery, radiotherapy, or combined therapies. At present, it is widely accepted that chemotherapy should be the first-line treatment once a diagnosis has been made. The conventional treatment for DLBCL is an anthracycline-based regimen (CHOP and nowadays R-CHOP with rituximab, an anti-CD20 monoclonal antibody), associated with a better disease-free survival. In our series, the administration of mycophenolate mofetil has been discontinued to avoid excessive immunosuppression.

In fact, decreasing the degree of immunosuppression, in association with chemotherapy—and surgery in some select cases—is the most successful treatment. Everolimus introduction after chemotherapy has been performed in our experience, with the double goal of completing immunosuppression and associating the antiproliferative characteristics of the molecule. The role of surgery has not been fully clarified yet. Some PHL may be eligible for liver resection in case of no extrahepatic disease and no signs of progression after chemotherapy. In a recent review [14], factors associated with favorable prognosis were localized single PHL without right lobe localization, young age, and no secondary lymphoproliferative lesions. An important consideration that can be drawn by the presented series is that in cases of immunosuppressed patients, the presence of a solitary liver mass without classical radiological features of primary or secondary liver tumors should always arouse suspicion of an intrahepatic lymphoma. Multidisciplinary discussion is fundamental to take into account all the relevant and specific aspects of the patient's disease and plan the best possible treatment strategy.

CONCLUSION

PHL is a rare disease. Diagnosis is often challenging because no clinical, radiological, or biological features exist. Biopsy is always indicated for histologic confirmation and to distinguish the type of lymphoma and plan the best medical strategy. Chemotherapy and decreasing immunosuppression is the mainstay of therapy. Surgery may be indicated in very select patients with confined and solitary liver disease in the case of partial response or stable disease after chemotherapy. Although the percentage of primary hepatic lymphoma in the normal population is very low, in transplant recipients the possibility of the onset of this disease becomes much more frequent; therefore, it should be considered in the presence of liver masses found in the follow-up of transplanted patients, with regard to the different treatments and the evolution of the pathology according to the kind of liver disease.

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