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Primary hepatic lymphoma after lung transplantation : a report of two cases.

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EMM, EF, participated in research design, drafting the article, TD, MC, RM, BRP, SH, participated in research design and critical revision of article, AO, EFP data collection, RK and GB participated in research design, PP participated in research design and approval of the article.

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Abbreviations: (DLBCL), Diffuse large B-cell lymphoma, (EBV) Epstein–Barr virus, (HCV) Hepatitis C virus, (HSECs) Hepatic sinusoidal endothelial cells, (NHL) Non Hodgkin Lymphoma, (PTLD) Post-transplant lymphoproliferative disorder, (NHL) Non Hodgkin Lymphoma, (PHL) Primary hepatic lymphoma.

Introduction:

Post-transplant lymphoproliferative disorder (PTLD) is one of the most common forms of transplant associated malignancies, with an incidence rate of 20.8% of all post-transplant neoplasia¹. Diffuse large B-cell lymphoma (DLBCL) is the most common Non Hodgkin Lymphoma(NHL) subtype in the post-transplant setting involving approximately 73% of specified NHL subtypes². 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 patients³⁻⁴. DLBCL is also the most common cause of cancer-related deaths in transplanted patients⁵⁻⁶. Several factors contribute to the development of DLBCL in transplant recipients⁷⁻⁸, 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 EBV³⁻⁹⁻¹⁰. DLBCL potentially arises within lymph nodes and in other different areas such as in the gastro-intestinal tract. As the liver is the largest reticulo-endothelial organ, DLBCL can develop in it as well. Primary hepatic lymphoma (PHL) is a rare disease¹¹, reported as reaching approximately 0.016% of all cases of Non-Hodgkin Lymphoma (NHL). Its pathogenesis is linked to sequential adhesive interactions of human B cells with hepatic sinusoidal endothelial cells (HSECs) and subsequent proliferation within the liver¹². Currently, some specific risk factors have been reported. Patients with hepatitis C virus (HCV) infection or immunosuppressive disorders (systemic lupus erythematosus, acquired immune deficiency syndrome, those receiving immunosuppressive treatment, etc.) are more likely to present such disease¹³. Late diagnosis often results in poor prognosis because of multifocal localisation and disease progression. At present, chemotherapy is the mainstay of therapy, but the role of surgery and other treatments are debated with no clear guidelines¹⁴. We present the case of two patients diagnosed with primary hepatic lymphoma, in a cohort of 300 patients who have undergone lung transplantation.

Cases Discussion:

The first patient, is a **forty-three** years-old man who underwent bipulmonary transplantation in June 2012 for mucoviscidosis (**donor status of EBV negative**). In his past medical history Bouveret disease, congenital hydrocephalus, periferic neurophaty, 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 CT scan (figure 1) and liver MRI showed multifocal bilobar liver lesions, the largest one of 50mm localized in the segments 2-3 junction. Initial clinical and radiological suspicion suggested an intrahepatic cholangiocarcinoma associated to synchronous bilobar liver metastases. Tumoral markers Ca 19.9, 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 PET-scan showed no extrahepatic localization of the disease. Serum creatinine was 110 μ mol/l, CRP 96.6mg/l, alkaline phosphatases 333U/L, gamma GT 374 U/L, LDH 380U/L, hemoglobin 9.8 g/dl, platelets 274000 mm/l, white blood counts 3420mm³/L. Immunosuppressive regimen before diagnosis included tacrolimus, corticoids and mycophenolate mofetil; before treatment mycophenolate mofetil was interrupted to avoid strong immunosuppression. Histological examination of the osteomedullary biopsy was also performed and no anomalies were presents. After multidisciplinary discussion an R-CHOP (Rituximab-Cyclophosphamide-Hydroxy-doxorubicine-Vincristine-Prednsione) chemotherapy regimen was indicated. [F18] FDG PET scan performed after treatment showed complete remission. After a 6 years follow up the patient is alive without recurrence.

The second patient is a **sixty-eight** years-old patient who underwent bipulmonary transplantation in February 2015 for severe **obstructive bronchopneumopathy (donor status of EBV positive)**. In his past medical history **osteoporosis** and diabetes. Four years later the patient presented diffuse abdominal pain and jaundice. Abdominal CT scan (figure 2) showed an hypodense liver mass of 85mm localized in segments 5 and 6. Biology revealed a cholestatic syndrome with hepatic cytolysis with ASAT 228, IU/l ALAT 394 IU/l

,GGT1035 IU/l, total bilirubine was 150micromol/l. Ca 19.9 was 1666 kIU/l, CEA and alphafetoprotein were within limits. Jaundice was secondary to a biliary confluence extrinsic compression by the lesion. A cholangio-MRI was performed, and confirmed the mass with no biliary confluence infiltration. A percutaneous liver biospy associated to biliary stenting was then performed for suspected intrahepatic cholangiocarcinoma. Hystology showed a B-cell Lymphoma (**EBV status of recipient negative**). PET-CTscan showed nodal involvement in the hepatic pedicle but no other extrahepatic disease. Immunosuppressive regimen before diagnosis was Tacrolimus,prednisolone and Mycophenolate Mofetil;after diagnosis of Lymphoma administration of Mycophenolate Mofetil was stopped for the same reason of the first patient.After 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-CTscan control.

DISCUSSION

Post-transplant lymphoproliferative disorder (PTLD) is one of the most common forms of transplant associated malignancies, and Diffuse large B-cell lymphoma (DLBCL) is the most common Non Hodgkin Lymphoma(NHL) subtype in the post-transplant 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 tissue type, T-cell-rich B-cell lymphoma, anaplastic large-cell lymphoma, hepatosplenic T-celllymphoma, and mantle cell lymphoma¹⁴.

Primary hepatic lymphoma (PHL) is a rare disease ¹¹, reaching approximately 0.016% of all cases of Non-Hodgkin Lymphoma (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 first clinical hypothesis often is oriented to primary liver neoplasia such as intrahepatic cholangiocarcinoma or liver metastases. Hystology is the only way to determine the exact diagnosis and caracterize 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 non- Hodgkin's lymphoma of the liver appears most of the times 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 lymphomas¹⁹. On contrast-enhanced CTscan, primary hepatic lymphoma has been described as a low density mass, usually not enhanced after contrast injection, or faint enhanced.

Periferal enhancement in the early arterial phase is sometime present. MRI is characterized by low signal intensity on T1-weighted images and moderately high signal intensity on T2-weighted images; the enhancement pattern similar to that one of CT¹⁸⁻¹⁹⁻²⁰. 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 element that hepls in the diagnosis.As far as the case of these two patients is concerned, diagnosis was always made on hystology 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 diagnosis hase been made. The conventional treatment for DLBCL is anthracycline based regimen (CHOP and nowadays R-CHOP with Rituximab – an anti-CD20 monoclonal antibody) , associated to 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 to chemotherapy – and surgery in some selected cases-, is the most succesful treatment. Everolimus introduction after chemotherapy has been

performed in our experience, with the double goal of completing immunosuppression 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 case of immunosuppressed patients, the presence of a solitary liver mass without classical radiological features of primary or secondary liver tumours should always arise the suspicion of an intrahepatic lymphoma. Multidisciplinary discussion is fundamental in order to take into account all the relevant and specific aspects of the patient's disease and plan the best possible treatment strategy.

CONCLUSION

Primary hepatic lymphoma (PHL) is a very 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 to plan the best medical strategy. Chemotherapy, and decreasing of immunosuppression is the mainstay of therapy. Surgery may be indicated in very selected patients with confined and solitary liver disease in 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, having regard to the different treatments and the evolution of the pathology according to the kind of liver disease.

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REFERENCES:

- 1.Sampaio MS, Cho YW, Qazi Y, et al. Posttransplant malignancies in solid organ adult recipients: an analysis of the National Transplant Database. *Transplantation*. 2012;94(10):990–8.8.
2. Clarke CA, Morton LM, Lynch C, et al. Risk of lymphoma subtypes after solid organ transplantation in the United States. *British Journal of Cancer*. Jul; 2013 109(1):280–288.
3. Gibson TM, Engels EA, Clarke CA, et al. Risk of diffuse large B-cell lymphoma after solid organ transplantation in the United States. *Am J Hematol*. 2014; 3(10):23726.
4. Fernberg P, Edgren G, Adami J, et al. Time Trends in Risk and Risk Determinants of Non-Hodgkin Lymphoma in Solid Organ Transplant Recipients. *American Journal of Transplantation*. Nov; (2011) 11(11):2472–2482.
5. Farrugia D, Mahboob S, Cheshire J, et al. Malignancy-related mortality following kidney transplantation is common. *Kidney International*. Jun; (2014) 85(6):1395–1403.
- 6.Na R, Grulich AE, Meagher NS, et al. De novo Cancer-Related Death in Australian Liver and Cardiothoracic Transplant Recipients. *American Journal of Transplantation*. May; (2013) 13(5):1296–1304.
7. Hussain SK, Makgoeng SB, Everly MJ, et al.HLA and risk of diffuse large B-cell lymphoma after solid organ transplantation *Transplantation*. (2016) November ; 100(11): 2453–2460.
- 8.Cheng J, Moore C.A. Iasella CJ, et al.Systematic review and meta-analysis of post-transplant lymphoproliferative disorder in lung transplant recipients . *Clin Transplant*. (2018) May ; 32(5): e13235.

9. Morscio J, Dierickx D, Tousseyn T. Molecular Pathogenesis of B-Cell Posttransplant Lymphoproliferative Disorder: What Do We Know So Far? *Clinical & Developmental Immunology*. 2013; :13. Article ID 150835.

10. Morscio J, Dierickx D, Ferreira JF, et al. Gene expression profiling reveals clear differences between EBV-positive and EBV-negative posttransplant lymphoproliferative disorders. *Am J Transplant*. (2013); 13(5):1305–1316.

11. Noronha, V., Shafi, N.Q., Obando, J.A., et al.. Primary non-Hodgkin's lymphoma of the liver. *Crit. Rev. Oncol. Hematol*. (2005) 53 (March (3)), 199–207

12. Shetty, S., Bruns, T., Weston, C.J., et al.. Recruitment mechanisms of primary and malignant B cells to the human liver. *Hepatology* (2012) (October (4)) 56, 1521–1531.

13. Page, R.D., Romaguera, J.E., Osborne, B., et al. Primary hepatic lymphoma: favorable outcome after combination chemotherapy. *Cancer* (2001) October 15 (92 (8)), 2023–2029

14. Cesaretti M., Loustau M., Robba C., et al. Reappraisal of primary hepatic lymphoma: Is surgical resection underestimated?, *Crit Rev Oncol Hematol*. (2018) Mar, 123:1-6

15. Honda H, Franken EA Jr, Barloon TJ, et al. Hepatic lymphoma in cyclosporine-treated transplant recipients: sono- graphic and CT findings. *Am J Roentgenol*, (1989);152:501-503.

16. Sanders LM, Botet JF, Straus DJ, et al. CT of primary lymphoma of the liver. *Am J Roentgenol* (1989); 152:977-983

17. Legmann P, Ollier P, Barge J, et al. Le lymphome primitif du foie, une affection exceptionnelle: aspects échographiques et tomodensitométriques - à propos d'un cas avec revue de la littérature. *J Radio1* (1985);66:599-602

18. Ueda G, Oka K, Matsumoto T, et al. Primary hepatic marginal zone Bcell lymphoma with mantle cell lymphoma phenotype. *Virchows Arch* (1996);428:311–4.

19. Mehra S, Schima W, Ba-Ssalamah A, et al. Primary MALT-lymphoma of the liver: multimodality imaging. *Crit Rev Comput Tomogr* (2003);44:347–55.

20. Murakami J, Fukushima N, Ueno H, et al. Primary hepatic low-grade Bcell lymphoma of the mucosa-associated lymphoid tissue type: a case report and review of the literature. *Int J Hematol* (2002);75:85–90.

Figure Legends

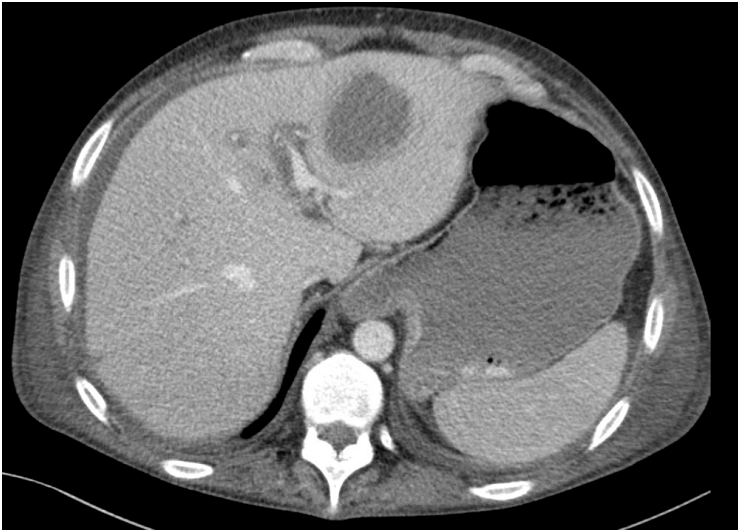


Figure 1.CT scan arterial phase. Hepatic hypodense mass.



Figure 2.CT scan venous phase. Hepatic hypodense mass .