Immunosuppression Withdrawal After Liver Transplantation for Common Variable Immunodeficiency

TO THE EDITOR:

Common variable immunodeficiency (CVID) is a rare disease characterized by impaired B cell function with hypogammaglobulinemia, with or without impaired T cell function. CVID is often associated with hepatological complications that may lead to end-stage liver disease (ESLD).[1-3] Liver transplantation (LT) is the best available treatment for ESLD and has been carried out in selected patients with CVID-related ESLD, with variable outcomes. Two short reports published in 2018 confirmed that in the majority of transplanted CVID patients, the posttransplant evolution might be complicated by recurrent CVID liver disease and/or by severe infectious events that may be related to the necessity of adding immunosuppressive therapy in patients already suffering from an immunity deficiency. These severe complications often lead to early posttransplant death, and thereby, might produce questions about the indication of LT in CVID patients.[4,5]

A 59-year-old male patient suffering from CVID was evaluated for LT in 2016 because of cirrhosis with portal hypertension and ascites. The patient had been suffering from recurrent infections of the upper respiratory tract since the age of 20 years. A total absence of immunoglobulin G (IgG) was observed when he was 44 years old. In addition to the respiratory infections, he had developed alopecia areata, seronegative polyarthritis, and chronic liver disease with ductopenia. The workup performed in 2014 revealed agammaglobulinemia with IgG of <0.35 g/L, immunoglobulin A of <0.08 g/L, and immunoglobulin M of 0.07 g/L. Lymphocyte subset analysis showed T cells at 70% (1477 per μL), CD4 T cells at 18% (380 per μL), and CD8 at 52% (1097 per μL). B cells were totally absent. There was no familial history of immunodeficiency.

Genetic analysis ruled out Bruton's disease or other rare causes of monogenic agammaglobulinemia. Several missense variants of potential interest were nevertheless observed in a heterozygous fashion on the Sterile Alpha Motif Domain Containing 9 Like (SAMD9L) (c.854G>A), Sterile Alpha Motif Domain Containing 9 (SAMD9) (c.847T>C), and C-type lectin domain family 16 (CLEC16A) (c.1368G>C) genes. Also, notably, the patient had been receiving subcutaneous immunoglobulins (Hizentra, CSL Behring, Victoria, Australia) since 2014. Liver biopsy demonstrated cirrhosis and bile duct loss, and his Model for End-Stage Liver Disease score was 16. No other cause of ESLD, including alcohol abuse, viral infection, or other inherited disease, could be demonstrated. He underwent uncomplicated deceased donor LT in January 2017 and received immunosuppressive therapy, including low-dose tacrolimus (trough levels between 3 and 5 μg/L during the first year) and methylprednisolone 4 mg/day that was progressively reduced (4 mg once every 2 days from posttransplant week 5 to 8) to be withdrawn at month 2. Mycophenolate mofetil was not initiated due to granulocytopenia. Subcutaneous immunoglobulins were maintained after LT, and prophylactic antibiotherapy consisted in cotrimoxazole 800/160 mg once every 2 days for 3 months and valganciclovir 450 mg once daily for 6 months. Native liver pathology showed ductopenic granulomatous

Abbreviations: CVID, common variable immunodeficiency; ESLD, end-stage liver disease; IgG, immunoglobulin G; LT, liver transplantation; NRH, nodular regenerative hyperplasia.

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cholangiopathy with cirrhosis and focal nodular regenerative hyperplasia (NRH; Supporting Fig. 1).

During the first posttransplant year, the patient developed a progressive worsening of kidney function, and several episodes of infection, including pulmonary abscess, erysipelas, herpetic keratitis, and *Pneumocystis jiroveci* pneumonia. In January 2018, in view of the multiple complications and normal liver tests without any suspicion of rejection, tacrolimus was withdrawn. In the following 24 months after immunosuppression withdrawal, the patient did not suffer from any significant infectious episode, but he progressively developed end-stage kidney failure requiring peritoneal dialysis at posttransplant month 35. At the time of writing of this report in June 2020, immunosuppression had been interrupted for 28 months in total, and the liver tests had remained within the normal ranges. A liver graft biopsy was performed at 2 years after immunosuppression withdrawal. It demonstrated light portal chronic hepatitis without fibrosis (F0) and was scored 2/9 according to the Banff score classification (Fig. 1). There was no sign of cholangiopathy or chronic rejection, but some NRH areas were found (Supporting Fig. 2).

This report describes the case of a CVID patient who underwent LT and early (at posttransplant month 12) immunosuppression withdrawal, with more than 2 years of follow-up without alteration of the liver tests and without sign of acute or chronic rejection at graft biopsy. For this patient, withdrawal was attempted as a salvage therapy in an LT recipient who had developed severe infectious and renal complications during the first year after transplant. Tacrolimus withdrawal had no effect on kidney function recovery but resulted in a reduction of the incidence of severe infectious episodes. This patient's case might provide new insight into the management of CVID patients with ESLD, and the patient underwent LT in early 2017, before the publication of the 2 CVID reports.[4,5] Retrospectively, it is possible that the authors would not have considered LT in this patient because of the poor and complicated reported results of LT in CVID patients described in these 2 articles. Nevertheless, it was too late at that time, and in view of the complicated first posttransplant year of our patient (but without liver graft issues), tacrolimus withdrawal was attempted with success. According to the literature, 2 additional CVID patients have been withdrawn from immunosuppression. In a 2002 report, Gow and Mutimer described the case of a CVID patient in whom immunosuppression was interrupted due to hepatitis C virus recurrence causing fibrosing of the graft. The

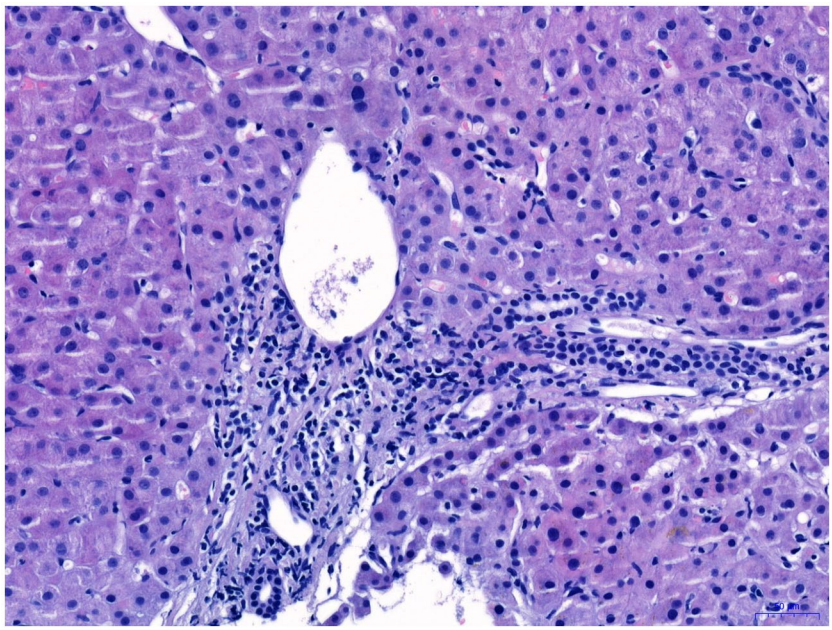

FIG. 1. Liver graft biopsy performed after 2 years of immunosuppression withdrawal showing light portal inflammation without bile duct injury.

patient developed some kind of chronic rejection and needed mycophenolate mofetil monotherapy.[6] Azzu et al. described another CVID patient with *Escherichia coli* sepsis, invasive aspergillosis and cytomegalovirus infections, in whom immunosuppression was withdrawn at 10 months after transplant. They did not describe rejection in the following 12 months.[4] On the other hand, liver graft rejection can occur in CVID patients[7] and may lead to graft loss in some severe cases.[8]

Because CVID patients not only suffer from impaired B cell differentiation but also from variable alteration of T cell function, it is possible that our patient has a specific CVID disease allowing early immunosuppression withdrawal. So far, the functional impact of heterozygous missense variants observed on the SAMD9L (c.854G>A), SAMD9 (c.847T>C), and CLEC16A (c.1368G>C) genes in this case has remained undefined. Diseases involving SAMD9L and SAMD9 mutations are classically associated with an increased risk of myeloid malignancies, but agammaglobulinemia has never been observed.[9] CLEC16A polymorphisms have been associated with multiple immunological disorders, including CVID, but they are usually considered "modifier mutations" that are not sufficient to induce disease by themselves.[10] Whatever the etiology of this patient's immunodeficiency, it also involved T cells because significant CD4 lymphopenia was present and opportunistic infections typical of T cell defects were also observed (recurrent herpetic infections and *P. jiroveci* pneumonia).

In the view of this patient and experiences in the literature, it is clear that the posttransplantation follow-up of CVID patients undergoing LT is usually marked by severe infectious complications. In CVID patients with life-threatening infections and normal liver graft function, minimization or withdrawal of immunosuppression might be attempted under close surveillance because rejection of the liver graft is possible. In our patient, regular protocol biopsies were not performed because of the presence of moderate ascites, which increases the risk of bleeding after biopsy. However, protocol graft biopsies are required in immunosuppression withdrawal because chronic rejection can manifest in LT recipients with normal liver tests even years after immunosuppression withdrawal.[11,12]

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