



## An Unusual Cause of Liver Allograft Loss in a Poorly Compliant Young Adult

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### Abstract

Non-adherence to immunosuppressant therapy impairs long-term outcome after Liver Transplantation (LT), especially among pediatric recipients reaching adulthood. The main consequence is the development of chronic rejection. A young man underwent LT for biliary atresia. The follow-up was remarkable by poor adherence to immunosuppressant therapy. The last follow-up liver biopsy showed chronic rejection and one periportal non-necrotizing epithelioid granuloma that was neglected. The deterioration in the hepatic function due to presumed chronic rejection and the development of chronic kidney disease due to calcineurin inhibitor's toxicity led to a combined repeat LT and kidney transplantation at 21 years post-LT. Histologic examination of the explanted liver revealed granulomatous liver disease, unique by the surprising location of the granulomas, realizing « granulomatous endothelialitis » of veins responsible for their lumen narrowing. The extensive etiology work-up (including donor-specific anti-HLA antibodies and antibodies against the endothelin-1 receptor type A and the angiotensin II receptor type 1 two of the most potent vasoconstrictors reported to date) remained negative. This *de novo* case of granulomatous liver disease had unique presentation and adds further evidence that a careful search must be carried out for a cause when granuloma is seen on liver biopsy.

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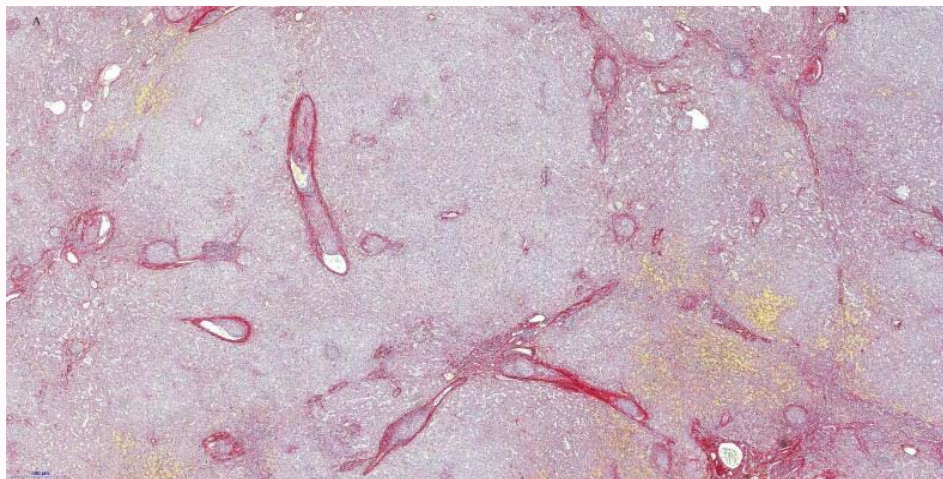
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### Introduction

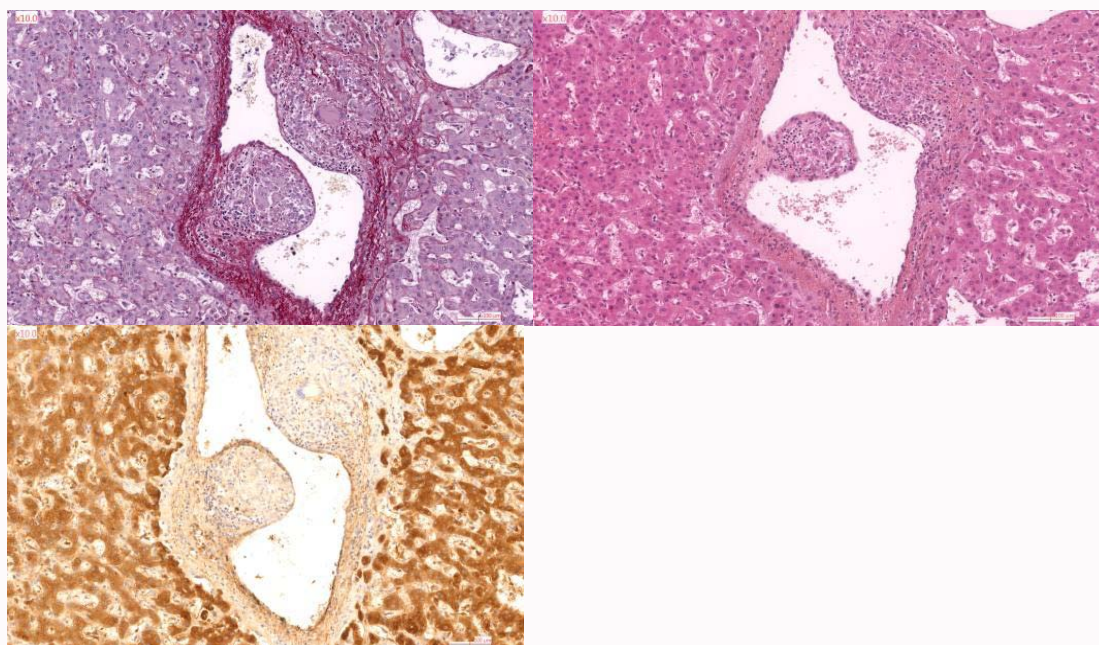
Liver transplantation is a life-saving procedure for most liver diseases developing in childhood. Patient and graft survival have improved significantly over time, with 10-year survival rates now reaching 75% and 63%, respectively [1]. However, non-adherence to medical prescriptions and immunosuppressant therapy with a prevalence up to 25% impairs long-term outcome after liver transplantation, especially among pediatric recipients reaching adulthood [1-3]. The main consequence is the development of chronic rejection leading to retransplantation in some cases. Here, we report a case of a young adult liver recipient, known to be non-adherent to immunosuppression and in whom the histological analysis of the explanted graft showed unexpected findings.

### Case Presentation

A 2-year-old male received a left liver transplant for biliary atresia. The donor, a 16 year-old male with no significant underlying medical history, deceased from a cranial traumatism. The recipient was maintained on a regimen of tacrolimus, mycophenolate mofetil, and prednisone. His post-transplant course was complicated by 2 episodes of acute cellular rejection at Day 14 and 7 years post-transplantation treated with pulse steroid therapy. He had then a hazardous follow-up including poor immunosuppression observance. At 18 years post-transplantation, he was admitted in the pediatric transplant center for pruritus, icterus, cytolytic and cholestatic. The liver biopsy showed an incomplete septal fibrosis and chronic rejection with 50% ductopenia. Tacrolimus dosage was increased and Ursodesoxycholic acid was introduced; liver enzymes progressively improved. At 21 years post-transplant, he was referred to our center for the management of general malaise and icterus. He denied recent travel and unprotected sex. On physical examination, he appeared jaundiced, had mild ascites but no hepatosplenomegaly. Laboratory study results showed a total bilirubin level of 160 mg/dL, alkaline phosphatase of 1050 IU/L, GGT of 300 IU/L, prothrombin time level of 46%, and normal levels of transaminases. Ultrasonography showed a liver without



**Figure 1:** Florid granulomatous involvement of the liver parenchyma, accompanied by irregular sclerosis at low magnification (Picrosirius staining).

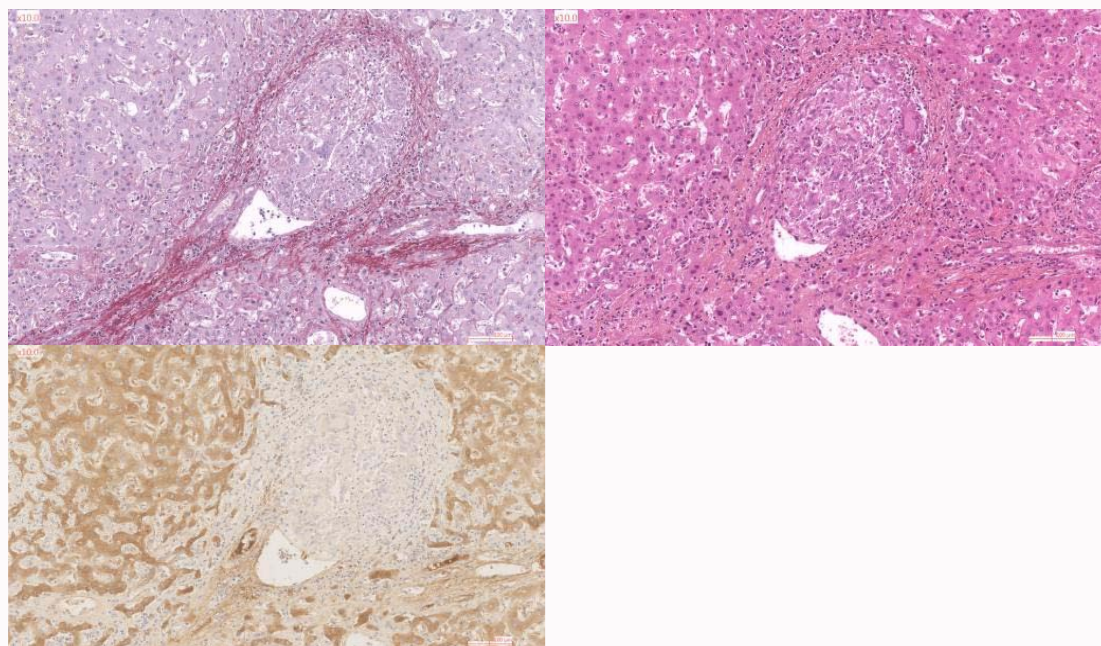


**Figure 2:** Granulomatous endothelialitis of a vein in a portal tract without bile duct (Picrosirius staining).

any focal hepatic lesions or biliary ductal dilatation. Hepatic vessels were patent. The liver biopsy showed a stable ductopenia of 50% and one small non-necrotizing epithelioid granuloma near a portal tract. Because of the worsening of the hepatic function due to presumed chronic rejection (MELD score =32) and the development of a stage 4 chronic kidney disease (creatinine 500  $\mu\text{mol/L}$ ) mainly due to calcineurin inhibitor's toxicity, he was listed for dual Liver-kidney transplant and underwent 4 months later a combined liver retransplantation and kidney transplantation. No Donor-Specific Antibodies (DSAs) directed against major histocompatibility antigens (Human Leukocyte Antigen [HLA]) were detected before and at the time of retransplantation. Histologic examination of the explanted liver revealed heterogeneous bridging fibrous septa (Figure 1), ductopenia, mild acute cellular rejection, and mainly numerous epithelioid and giant cell granulomas free from necrosis and fibrin ring. Granulomas were identified in portal and perivenular areas,

essentially distributed along venous route realizing « granulomatous » endothelialitis of portal (Figure 2) and centrilobular (Figure 3) veins. Granulomas did not show detectable foreign material microscopically under normal and polarized light. Negative special stains for bacteria, fungi, and parasites failed to show any microbiologic organism. C4d immunostaining was slightly positive in 10% of portal and centrilobular venules. An extensive search for infectious causes of liver granulomas, including imaging and serology for CMV, EBV, hepatitis A, B, C, and E, HIV, toxoplasmosis, *Bartonella henselae*, *Brucella*, *Mycoplasma*, stool examination for *Cryptosporidium*, tuberculin skin test, panbacterial PCR on blood and tissue, and atypical mycobacteria PCR on tissue, was entirely negative. Currently after the combined transplantation, the patient is doing well with standard triple immunosuppressive regimen. Liver and kidney function tests are normal. The 5-year protocol liver biopsy after retransplantation is normal without granuloma.





**Figure 3:** Granulomatous endothelialitis of a centrilobular vein (HES staining).

## Discussion

We describe a graft loss mainly due to idiopathic granulomatous liver disease in a young liver transplant adult known to be non-adherent to immunosuppression therapy. Like in the native liver, hepatic granulomas following liver transplantation can be caused by a multitude of infectious and non-infectious agents such as sarcoidosis, foreign body reaction and drug reaction [4]. Their presence requires an extensive etiology work-up, guided by histological evaluation [5]. This includes morphology of granulomas, accompanying inflammatory infiltrate, location of granulomas, nature of necrosis if present, foreign bodies in the granuloma and other associated morphologic changes, and the need for special stains although low threshold. Culture, molecular testing, and serologic studies are very useful diagnostic tools. Clinical history may be the diagnostic tool that is most helpful, cheapest, but not always easiest to get. Immune status of patient, exposure to animals, foreign travel, and medication/drug history are helpful questions to ask. Despite the extensive etiology work-up, the exact cause remains unclear in many cases like that of our patient [4]. Furthermore, we were particularly intrigued by the location of the granulomas, realizing « granulomatous endothelialitis » of the centrilobular and portal veins. Granulomas are a type of immune reaction, and their presence reflects hyperactivity of the immune system. Chronic Antibody-Mediated Rejection (cAMR) is now emerging from long-term of pediatric liver allograft recipients and suboptimally immunosuppressed recipients [6]. The worsening of our young patient's hepatic function occurred in the context of under-immunosuppression. As expected, he developed combined cellular and chronic rejection. An additional component of cAMR was searched for in our patient. C4d immunostaining was positive in only 10% of portal veins. No HLA DSAs were detected before and at the time of retransplantation. Clinical relevance of "vascular" antibodies targeting angiotensin type 1 receptor and endothelin type A receptor is now confirmed in acute and chronic immunologic complications in solid organ transplantation and systemic autoimmune vascular diseases [7,8]. These antibodies in the absence

of HLA DSAs involve different mechanisms of vasoconstriction [7,9]. Recently, O'Leary et al. [10] proposed portal venopathy as one of the histological criteria for cAMR. These observations encouraged us to extend immunological investigations to retrospectively evaluate the presence of such auto antibodies in the sera of our patient. Both were negative. AMR component definitely was excluded. After a negative extensive etiology work-up, we concluded to idiopathic granulomatous liver disease, or so-called hepatic sarcoidosis. To our knowledge, there were two cases of de novo sarcoidosis reported after liver transplantation [11,12]. Both were different from our case by the histological pattern and the course. Our case was histologically unique as he presented with « granulomatous endothelialitis » affecting the centrilobular and portal veins. Their luminal narrowing could explain the development of septal fibrosis and the architectural distortion. Usually, corticosteroids were first-line therapy in symptomatic patients. Unresponsiveness to corticosteroids indicated the need for second-line treatment with cytotoxic agents, such as methotrexate, azathioprine, cyclophosphamide, cyclosporine, thalidomide, or anti-tumor necrosis factor therapy. Patient general condition dramatically improved after corticotherapy in one case [11], and cyclosporine discontinuation and introduction of rapamune in the other [12], while our patient lost his allograft. Of course, it is impossible to know the counterfactual if we had not neglect the sole granuloma on previous liver biopsy and appropriately treated this patient.

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