Ductopenic rejection: immunosuppression and infections

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Introduction

- Ductopenia (intrahepatic bile ductular paucity) is a histological descriptive term that refers to bile duct loss in more than 50% of the portal tracts (often affecting the interlobular and septal bile ducts). [1]
- Etiologies: immune mediated processes or ischemic insult after liver transplantation.
- Chronic ductopenic rejection (CDR) is progressive and potentially irreversible and can lead to graft loss. [2,3]
- Chronic ductopenic rejection is managed with intensive immunosuppression,[3,5] but continues to be a leading cause of graft loss and re-transplantation.[2]
- Published literature about chronic ductopenic rejection is limited to case reports and case series. [2]

Objectives

- Describe a case of chronic ductopenic rejection that was treated successfully with quadruple immunosuppressive therapy.
- Highlight the risks associated with intense immunosuppressive therapy (i.e. infections).
- Shed light on the paucity of medical literature addressing the management and outcomes of CDR.

Case Report

- Two-year-old female transplanted at age 2 months for gestational alloimmune liver disease.
- 8 months post-transplant, developed an episode of moderate acute cellular rejection (ACR).
- Histology showed no interlobular bile duct in half of the portal tracts and no bile ductular proliferation--satisfying the histopathological definition of ductopenic rejection (Figure 1A). She subsequently received two courses of intravenous methylprednisolone and then one course of anti-thymocyte immunoglobulin.
- Patient developed chronic ductopenic rejection despite adequate ACR immunosuppressive therapy.
- Upon identification of chronic ductopenic rejection she was started on quadruple immunosuppressive therapy with tacrolimus, mycophenolate mofetil (MMF), prednisolone, and sirolimus.
- After the diagnosis of chronic ductopenic rejection, the peak direct bilirubin was 6.2 mg/dL, peak gamma glutamyl transferase (GGT) 2672 U/L, and peak alanine aminotransferase (ALT) 689 U/L. It took several months of intense immunosuppressive therapy for these values to approach normal.
- Immunosuppressive therapy was gradually weaned down to a single immunosuppressive agent (sirolimus). Liver biopsy at 18 months after the initial episode of ACR revealed resolution of ductopenia (Figure 1B).
- As a result of intense immunosuppression, the patient developed multiple infectious complications including recurrent central-line-associated-blood-stream-infections, disseminated varicella infection with associated encephalitis, and reactivation of Epstein–Barr virus (EBV). Of note the patient did not receive the varicella vaccine prior to transplantation.
- She failed to develop protective immunity against varicella, mandating long term prophylaxis with valacyclovir.

Biopsies

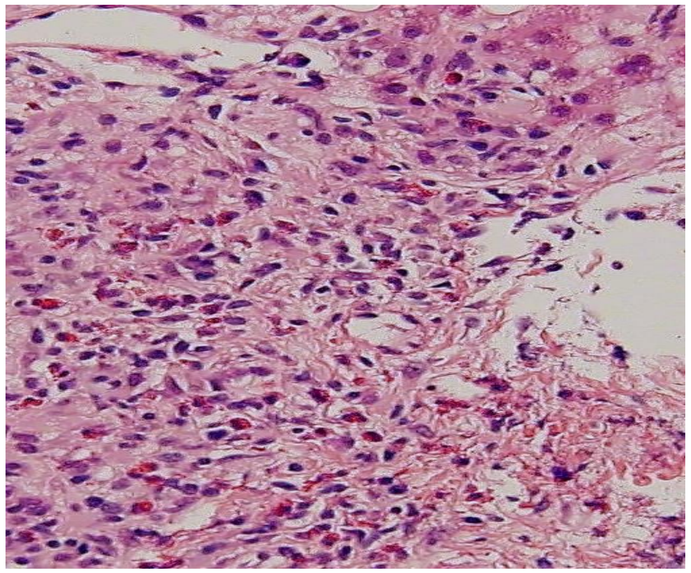

Figure 1A: 8 months following liver transplant at diagnosis of CDR. Note complete absence of bile ducts.

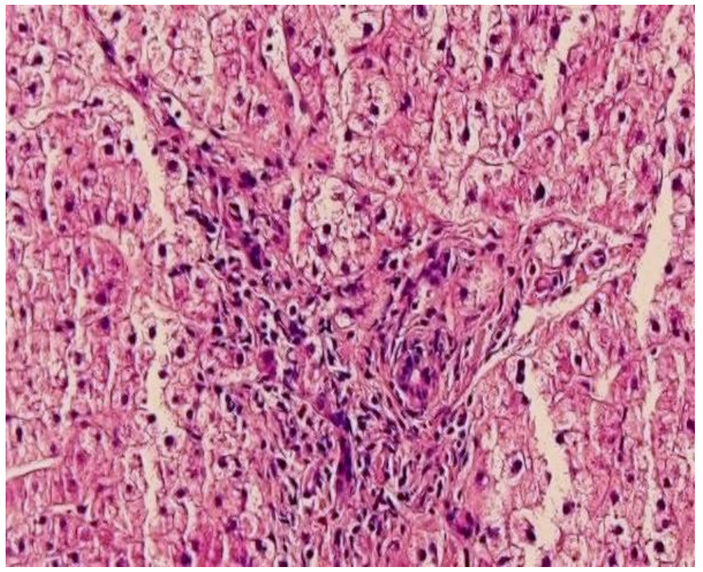

Figure 1B: 2 years following liver transplant. Note florid ductular proliferation.

Discussion & Conclusion

- Ductopenia is a key histological feature of chronic cellular rejection. [1]
- Salvage immunosuppressive therapy can halt progression and, in some cases, reverse this process. [3]
- Chronic rejection continues to be a leading etiology of graft loss. [2]
- More studies are needed to better understand drivers of chronic rejection and standardize immunosuppression therapy.
- Combination immunosuppressive regimen is a double-edged sword and can increase the risk of infection.

References

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