Guidelines on post transplant management "think disease recurrence"

Udeme D Ekong
Yale New Haven Hospital Transplantation Center
Yale University School of Medicine

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Disclosure

- In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.

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Case 1.

- An infant boy presented with a clinical and biochemical picture suspicious for intrahepatic cholestatic disease characterized by:
  - elevated serum bilirubin
  - normal gamma glutamyl transferase levels (GGT)
- Fast atom bombardment mass spectrometry of urine excluded an inborn error of bile acid synthesis

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- Genetic testing
  - homozygous frameshift mutation in the *ABCB11* gene: C.2787_2788insGAGAT
  - (which results in p.Lys930GlufsX79 predictive of PFIC-2).
- He developed end stage liver disease
- Deceased donor LT at 10-months of age

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H&E of explant and IHC for BSEP

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Post-transplant course

- Immunosuppression induced by Prednisone and Tacrolimus
- 15-months post LT - biopsy proven acute rejection
  - transiently responded to steroids
  - GGT 9 IU/L at time of rejection
- Serum bilirubin and aminotransferase levels fluctuated, but GGT remained normal

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H&E of liver bx 20 months post OLT

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- Medically managed with pulse steroids and change of immunosuppression to Sirolimus
- Progressive worsening of graft function
- Underwent a second liver transplant at 3.5-years of age (deceased donor)

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Clinical course post 2nd LT

- Immunosuppression induced by solumedrol, cyclosporine and mycophenolate mofetil
- 5-years post LT – developed allograft dysfunction (GGT 35 IU/L)

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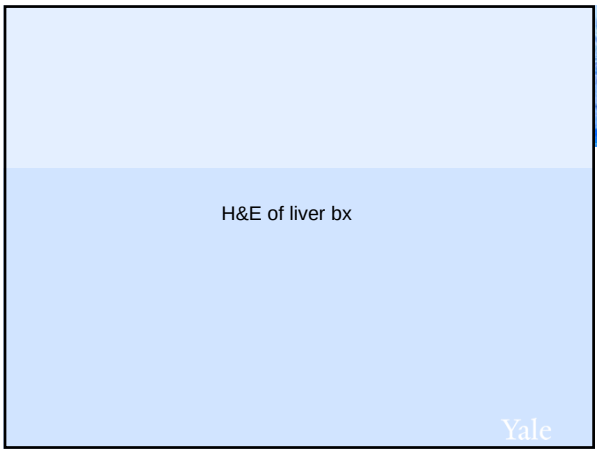
H&E of liver bx
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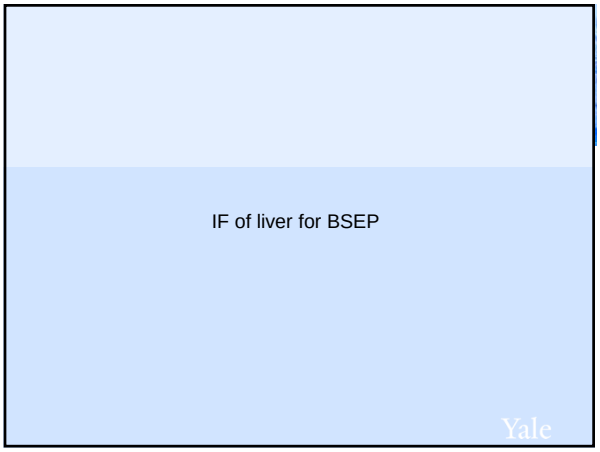
IF of liver for BSEP
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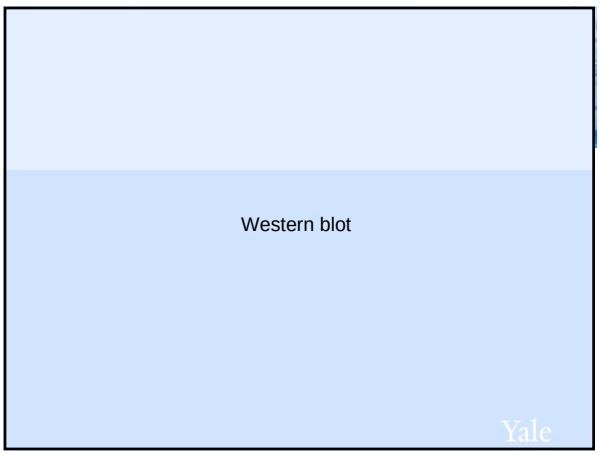
Western blot
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Disease course

- Plasmapheresis and three daily doses (1g/kg/dose) of intravenous immunoglobulin (IVIG)
- Monthly IVIG
- Symptoms of cholestasis continued, serum bile acids 296.6 µmol/L
- Cutaneous biliary diversion
- Cholestasis and mild coagulopathy persisted, serum bile acids 160.4 µmol/L.

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- Given the pathogenesis of recurrent PFIC-2 phenotype and that his disease remained refractory to Rx
  - Rituximab therapy initiated
  - weekly doses for 6-weeks
  - followed by doses q 6-weeks
- Cholestasis fully resolved and antibody titers 1:640
- Most recent antibody titer 1:80

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Discussion

- The mechanism for antibody mediated recurrence of PFIC-2 is not entirely clear.
- It is speculated that the domain against which BSEP antibodies develop is conditionally sequestered from the immune system.
- It is reasonable to assume that this domain must be exposed in some way to initiate an immune response.

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- Conditions needed for exposure:
  - ? bile duct injury
    - acute rejection
    - biliary obstruction
- This might explain the highly variable interval between LT and disease recurrence in those that develop antibodies.

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- In a review by Siebold et al:
  - 6 of 36 (16%) children with PFIC-2 who underwent LT developed recurrence.
  - mutation analysis suggested complete absence of BSEP protein in these 6.
  - it cannot be said with certainty that complete absence of BSEP is a necessary precondition for developing antibody after transplant, but available data suggest that may be the case.

Siebold, L., et al. Liver Transpl, 2010. 16(7): p. 856-63.

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Take home points

- Liver transplant for PFIC-2 should carry with it a heightened awareness of possibility of recurrent disease
  - differential diagnosis when cholestasis develops
- Special attention given to individuals with mutations expected to result in complete absence of BSEP protein
  - immunostaining for BSEP

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- Serum bile salts could serve as a potential screening tool
  - performed at regular intervals (2-4 X/year)
- Antibody measurements if there is concern for recurrent disease

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- Standard immunosuppression for liver transplantation appears not to be effective in preventing recurrent BSEP disease and only some cases respond to enhanced transplant immunosuppression
- Therapy directed against humoral immunity is required for satisfactory outcome
- If recurrent disease strongly suspected and not proven or other cause of cholestasis cannot be identified, Rx should be provided with plasmapheresis, IVIG and rituximab

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- Antibody-mediated recurrent BSEP likely to be progressive and require re-transplantation if not aggressively treated, which justifies this aggressive approach.

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