Guidelines on post transplant management “think disease recurrence”
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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.

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
• Genetic testing
  – homozygous frameshift mutation in the \textit{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

\textbf{H&E of explant and IHC for BSEP}

\textbf{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
H&E of liver bx 20 months post OLT

• 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)

Clinical course post 2nd LT

• Immunosuppression induced by solumedrol, cyclosporine and mycophenolate mofetil
• 5-years post LT – developed allograft dysfunction (GGT 35 IU/L)
H&E of liver bx

IF of liver for BSEP

Western blot
**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.

**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.
• 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.

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 those 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.


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
• 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

• 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

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