AMR in Liver Transplantation: Incidence

- Primary AMR
  - 1/3 to 1/2 of ABO-incompatible transplants
  - Uncommon with ABO-compatible transplant

- Secondary AMR
  - Unknown incidence: rarely tested
Why is AMR uncommon in liver transplant?

- Dual blood supply
  - May dilute circulating immune complexes
  - Protects from ischemia
- Large vascular surface area along sinusoids
  - Preformed DSA absorbed and eliminated more easily
- Enhanced binding of preformed antibodies and removal of immune complexes
  - Kupffer cells
  - Soluble MHC class I antigens
Liver Histology

More oxygenated $\rightarrow$ $\rightarrow$ $\rightarrow$ $\rightarrow$ $\rightarrow$ Less oxygenated

http://php.med.unsw.edu.au
AMR in Liver Transplantation: Presentation

- Hyperacute rejection/ severe AMR
  - ABO-I graft

- Severe graft dysfunction within 2 wks
  - Initially normal LFT’s x 2-3d
  - Rapid rise in AST, ALT, bilirubin, PT
  - Signs of acute liver failure
Hyperacute rejection in Liver: Histologic Features

- Severe endothelial injury
- Microvascular fibrin thrombi
- Portal vein thrombosis
- Hemorrhage
- Hepatocyte necrosis (centrilobular/zone 3, midzonal/zone 2)
- Neutrophil infiltrate – portal and lobular
- Portal lymphocytes
- Bile duct injury +/-
- Often not biopsied due to coagulopathy
AMR in Liver Transplantation: Presentation

• Acute AMR
  • ABO-C graft + high DSA titers
  • ABO-I graft
  • Abnormal LFT’s on post-op screening

• Three phases
  • 1\textsuperscript{st} week
  • 1\textsuperscript{st} month
  • Late complications
Acute AMR in Liver – 1\textsuperscript{st} week: Histologic Features

- Ballooning and cholestasis of centrilobular hepatocytes
- Hepatocyte necrosis: patchy or confluent
  - ddx preservation-reperfusion injury
Liver Histology

Zone 1 = More oxygenated

Zone 3 = Less oxygenated
Acute AMR in Liver – 1st month: Histologic Features

- Bile ductular proliferation
- Portal tract edema
- Neutrophilic infiltrate
  - Neutrophilic portal venulitis +/-
  - Sinusoidal neutrophils +/-
- Centrilobular cholestasis +/-
- DDX: biliary obstruction
  - If you see biliary obstruction in liver txpl bx, and biliary disease can be excluded clinically, consider AMR
AMR in Liver Transplantation: Background

Breen et al., 2004 Dec;14(12):2249-60.
Late changes of AMR in Liver: Histologic Features

- Portal vein thrombosis
- Hepatic artery thrombosis
- Large bile duct ischemic necrosis
AMR in Liver Transplantation: Histologic Features with ACR

- Histologic features of ACR
  - Mixed portal inflammatory infiltrate
  - Bile duct injury
  - Endothelialitis
  - Arteritis, bile duct loss, *centrilobular hepatocyte ballooning or dropout*
AMR in Liver Transplantation: Role of C4d

- Not well-established in liver allograft
- Most studies have used IHC in FFPE
- Use known positive and negative renal or cardiac tissue as controls

AMR in Liver Transplantation: C4d positive IHC

- Positive IHC: Continuous linear staining of vascular endothelium, visible at low power
  - At high power, finely granular and may be on both luminal and basal surfaces of endothelial cells
C4d positive in portal vein
AMR in Liver Transplantation: C4d positive IHC

- Distribution: Not every vascular space will stain
  - Mostly positive in small portal venules or capillaries
  - Sinusoidal endothelium and hepatic venules are often not involved/don’t stain
- May see periportal sinusoidal staining along with portal venules/capillaries that are positive

More oxygenated (more staining) → → Less oxygenated (less staining)
AMR in Liver Transplantation: C4d positive IHC

- Positive IHC alternative pattern:
  - Diffuse portal stromal staining in >50% of portal tracts
    - Most specific pattern for AMR in ABO-I grafts
  - Also may see focal stromal staining around capillaries or around bile ducts
    - Damaged microvasculature
  - Portal stromal staining in ABO-C grafts:
    - Jury is out – may be nonspecific
Portal stromal staining          Capillary staining

AMR in Liver Transplantation: C4d Nonspecific Staining

- In arteries, nonspecific staining of internal elastic lamina makes interpretation difficult
- Sinusoidal staining alone may be nonspecific: described in the setting of lobular inflammation/necrosis
- Diffuse cytoplasmic staining of necrotic hepatocytes
Necrotic hepatocytes  
Arterial internal elastic lamina  

AMR in Liver Transplantation: C4d nonspecific staining

- Other post-transplant conditions where C4d has been identified
  - Acute cellular rejection (8-80% of cases)*
  - Chronic rejection (25%-100% of cases)
  - Recurrent disease
    - Hepatitis C and B, autoimmune hepatitis, primary biliary cirrhosis
  - Biliary obstruction
  - Vascular thrombosis
  - Preservation-reperfusion injury
Recurrent autoimmune hepatitis
Positive C4d portal & endothelial

AMR in Liver Transplantation: C4d IF vs IHC

• What about immunofluorescence?
  • Linear sinusoidal staining correlates with DSA and histology (these were nonspecific in IHC)
  • Portal vessel staining is infrequent and when present does not correlate with other parameters of AMR
  • Basically the opposite of IHC!... Needs further study
Linear sinusoidal C4d staining by IF

More oxygenated

IHC: More staining
IF: Less staining

Less oxygenated

IHC: Less staining
IF: More staining
AMR in Liver Transplantation: Role of C4d

• Problems with determining “the truth”
  • Lack of standardization of diagnostic criteria for positive C4d

• Lack of clinical correlation
  • Clinical and serologic (DSA) data not included in all studies
AMR in Liver Transplantation: Role of C4d

Can DSA and C4d be present when not clinically suspecting AMR?

- 43 patients with liver ABO-C
- Clinically indicated biopsy for allograft dysfunction
- DSA+/C4d+ found in ACR, ductopenic rejection, steroid-resistant ACR, AMR
- May respond to AMR therapy