AMR in Liver Transplantation: Note on DSA

- Presence of DSA associated with increased risk of
  - Chronic rejection
  - Acute rejection with ductopenia
  - Unexplained graft fibrosis
  - Unexplained biliary complications
  - De-novo AIH (non-HLA DSA)
AMR in Liver Transplantation: Note on DSA

• Differences in class I vs class II DSA
  • Liver allograft in simultaneous liver-kidney transplant was thought to provide protection from DSA and decrease risk of kidney AMR, but high MFI HLA Class II DSA still at risk

• Likely higher MFI cut-off values than in other SOT

• DSA IgG subclass may be important
  • IgG3 strongly associated with graft loss

• DSA found in control patients with no other signs, symptoms, or risk factors
AMR in Liver Transplantation: Role of C4d

In studies that do include the full clinicopathologic correlation and clear diagnostic terms:

- Diffuse clearly positive C4d staining in >50% of portal tracts (IHC) or sinusoids (IF)
- Correlates with presence of DSA
- Correlates with histologic features of AMR
- Prevalence of reported cases of liver AMR meeting criteria of other solid-organ systems: 0.6-3.7%
AMR in Liver Transplantation: Role of C4d

• Take Home Message
  • Utility of looking for C4d not clearly established
  • No consensus diagnosis of AMR which includes C4d
  • IHC: small portal vessel staining is most specific
  • IF: sinusoidal staining is most specific
  • C4d staining may be seen in other conditions

• Banff 2011 liver group goal for 2013:
  • Better understanding of spectrum of AMR and consensus guidelines for C4d interpretation
AMR in Liver Transplantation: Differential Diagnosis

- Hyperacute rejection
  - Since not often biopsied, histologic features are derived from failed explanted allografts and are not specific
- Severe preservation-reperfusion injury
- Graft ischemia
- Idiopathic massive hemorrhagic graft necrosis
AMR in Liver Transplantation: Differential Diagnosis

- Acute antibody mediated rejection
  - Biliary obstruction/technical biliary complications
    - Histologic features overlap:
      - Bile ductular reaction
      - Portal tract neutrophils
      - Cholestasis
    - Preservation-reperfusion injury
  - Acute cellular rejection
  - Infection/Sepsis
    - Cholestasis
    - Acute ascending cholangitis
  - Ischemic injury
Take Home Message: AMR dx

- Due nonspecificity of histologic findings, AMR should only be suggested as an etiology of the findings

- Definitive diagnosis requires supportive clinical/serologic features and exclusion of the histologic mimics
AMR in Liver Transplantation: Pitfalls

• The four major diagnostic criteria for AMR dx in renal and cardiac allografts **have not been adopted for liver**
  – Clinical graft dysfunction
  – Compatible histologic features
  – Deposition of C4d
  – Serologic evidence of DSA
• No routine testing for DSA in liver recipients
• C4d immunostaining is less established/less reliable
AMR in Liver Transplantation: Clinical Aspects

• Prophylaxis
  • For ABO-incompatible grafts (living donor)
    • B-cell directed immunosuppression
      • Rituximab, IVIg, Plasma exchange, Splenectomy

• Treatment
  • B-cell directed immunosuppression
  • Bortezomib: proteasome inhibitor, depletes plasma cells → decreased Ab production
AMR in Intestinal Transplantation: Background

- Ileum
- Multiple vascular arcades
- Vasa recta
AMR in Intestinal Transplantation: Clinical Aspects

- Extremely limited literature
  - More common in patients undergoing retransplantation after failed graft/chronic rejection
- DSA alone associated with worse outcome
- DSA with histologic ACR – consider concurrent AMR
- High PRA is a risk factor for rejection
- DSA can persist asymptomatically after hyperacute rejection resolves
AMR in Intestinal Transplantation: Clinical Aspects

• Presentation
  • First 2 weeks post-transplant
    • Increased stoma output
    • ACR poorly responsive to standard therapy
    • Persistent mucosal ischemia/congestion/hemorrhage
  • Peri- and post-operative syndrome
AMR in Intestinal Transplantation: Clinical Aspects

Peri- and post-operative syndrome

- Patients with strong crossmatch (T-cell cytotoxicity test) and high PRA
  - Segmental graft spasm, cyanosis, petechial hemorrhage at reperfusion, lasting 45m
  - Blood-tinged ostomy content within a few hours
  - Ileostomy mucosal congestion for 1-2 weeks
  - Endoscopically, graft mucosa dusky with congestion, hemorrhagic

AMR in Intestinal Transplantation: Background

- Hyperacute rejection (hours)
  - Disseminated thrombosis
  - Total ischemic necrosis
- Associated with presensitization
  - high PRA, DSA
- Prophylaxis – desensitization
  - IVIg to reduce PRA
  - Protocols not standardized
AMR in Intestinal Transplantation: Histologic Features

- Capillary endothelial cell enlargement
- Fibrin thrombi
- Vascular congestion
- Hemorrhage
- Neutrophil margination
- Ulceration
- Crypt apoptosis +/-
AMR in Intestinal Transplantation: Histologic Features

- Features of ACR may be present
  - Crypt apoptosis
  - Crypt epithelial injury
  - Lamina propria mononuclear inflammatory infiltrate
  - Ulceration +/-
  - Architectural distortion +/-
  - Severe ACR with arteritis
Crypt apoptosis

Crypt injury & dropout
Denudation

AMR in Intestinal Transplantation: Role of C4d

• Nonspecific:
  • C4d + in 36% of intestinal allografts with rejection
  • And in 27% without rejection
  • May be positive in small arterioles of normal intestine

AMR in Intestinal Transplantation: Role of C4d

• Take Home message
  • C4d deposition is nonspecific and may be present independent of rejection or absent during hyperacute rejection
AMR in Intestinal Transplantation: Differential Diagnosis

• Vascular insufficiency/thrombosis
  • Ischemic change

• Preservation/Reperfusion injury
  • First few days post-op, resolves within 1 week
  • Ischemic change, regenerative epithelium, villous blunting, minimal inflammation

• Prior biopsy site
AMR in Intestinal Transplantation: Differential Diagnosis

• Chronic rejection
  • Arteriopathy: Mesenteric, serosal, and submucosal vessels
    • Luminal narrowing associated with intimal and medial hyperplasia
  • Associated mucosal changes
    • Mucin loss, submucosal fibrosis
    • Also paneth cell loss, neural hyperplasia
    • Nonspecific changes: crypt apoptosis and dropout, villous blunting, lamina propria fibrosis
AMR in Intestinal Transplantation: Chronic rejection

Does AMR have a role in chronic rejection?

- Intestinal allograft explants
  - Contracted mesentery with fibrosis and chronic arteriopathy

- Sampling mesenteric vessels for AMR before this stage is technically not feasible
AMR in Intestinal Transplantation: Diagnosis

Take Home message

• Suspect AMR with DSA, histologic evidence of vascular alteration, and early/severe/resistant clinical signs of rejection

• Treating a suspicion since no way to confirm AMR dx
AMR in Intestinal Transplantation: Clinical Aspects

- Treatment
  - OKT3
  - Steroids
  - Prostaglandin E
- Prognosis
  - May not be associated with chronic rejection
  - Does not contribute to overall mortality or graft loss
AMR in Pancreas Transplantation

- Pancreas allograft infrequently biopsied due to perceived risk
- AMR does occur in pancreas allograft
- Diagnosis requires 3 components (Banff 2011):
  - Histology
  - C4d IHC
  - DSA
- (Clinical graft dysfunction not required)

3/3 = acute AMR
2/3 = consistent with acute AMR
1/3 = clinical exclusion of AMR required
Acute AMR in Pancreas Transplantation

- Histology: evidence of tissue injury
  - Inflammation of interacinar capillaries (capillaritis)
  - Acinar cell damage (swelling, necrosis, apoptosis, dropout)
  - Vasculitis
  - Thrombosis
- C4d positive:
  - Diffuse C4d staining of interacinar capillaries (≥ 5% of acinar lobule surface)
Chronic Active AMR in Pancreas Transplantation

Diagnosis requires:

- Combined features of AMR and chronic allograft rejection/graft fibrosis
  - Fibrotic expansion of fibrous septae; exocrine atrophy
- Exclusion of features of acute T-cell-mediated rejection
  - Acinar inflammation→damage; also inflammation of septae, ducts, venules
Summary

• Liver
  • AMR can be suggested as dx, as histologic features overlap with other dx
  • C4d utility not clearly established
  • No consensus diagnostic criteria

• Small bowel
  • Histologic features and clinical syndrome described
  • C4d nonspecific

• Pancreas
  • Consensus dx criteria including histology, C4d IHC, and DSA
  • Infrequently biopsied
Summary

• Kidney
  • AMR very significant, acute and chronic forms, C4d done routinely (IF preferred)

• Heart
  • About 15% of patients, markedly increased risk of chronic rejection and death, C4d very helpful, IHC or IF

• Lung
  • Rare, diagnosis based on clinical graft dysfunction, circulating antibodies, absence of cellular rejection, non-specific C4d staining common, however strong endothelial staining reported
References