Extrahepatic Conditions Related to Hepatitis C Virus (HCV)

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Disclosure Information

Dr Peters has reported the following financial relationships with commercial firms:

- Consultant: Merck & Co, Inc, Theravance, and Roche
- Data safety monitoring board: Biotron
- Scientific advisor: Clinical Care Options
- Her spouse is employed by Genentech (Roche)

Outline

- Hematologic manifestations (mixed cryoglobulinemia, monoclonal gammopathies, lymphoproliferative disorders)
- Dermatologic manifestations
- Rheumatologic manifestations
- Renal manifestations
- Endocrine manifestations

Hematologic and Rheumatologic Manifestations

Mixed Essential Cryoglobulinemia

- Mixed cryoglobulinemia (precipitate from cold serum)
  - 95% due to HCV infection
  - HCV antibody and HCV RNA found in immune complexes
  - Skin (leukocytoclastic vasculitis)
  - Neuropathy
  - Membranoproliferative glomerulonephritis (MPGN)
  - Arthropathy
- 19%-54% of HCV patients have detectable cryoglobulins in serum
  - Rheumatoid factor positive
  - 2%-3% have cryoglobulinemia

Himoto, 2012; Perico, *CJASN*, 2009.

Non-Hodgkin Lymphoma (NHL)

- 5%-10% of mixed cryoglobulinemic patients develop NHL (OR 2.5-10.8)
  - Marginal zone lymphoma
  - Diffuse large B-cell lymphoma
  - B-NHL regression after HCV eradication
- Monoclonal gammopathy of undetermined significance (MGUS)

Himoto, 2012; Peverling-Oberhag, 2013.

Hematologic Manifestations

- Autoimmune hemolytic anemia (AHA)
- Autoimmune thrombocytopenia
- Autoimmune neutropenia
- 66%–88% of patients with chronic HCV infection and thrombocytopenia have antiplatelet antibodies

Himoto, 2012.

Dermatologic Manifestations

Dermatologic Manifestations

- 15%-92% Porphyria cutanea tarda: blisters, vesicles after sun exposure, trauma
- Cryoglobulinemia: leukocytoclastic vasculitis
- 1%-6% lichen planus
- 1% CREST (calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome

Himoto, 2012; Caballo, 2012.

Endocrine Manifestations

Endocrine Manifestations in HCV

- 10%-25% of HCV patients have thyroid antibodies
  - More likely to get interferon alfa-induced disease
- Diabetes mellitus (DM; type 2)

Himoto, 2012.

HCV and Type 2 Diabetes Epidemiological Data

- In persons > 40 yrs, those with HCV infection have 4-fold higher risk of DM than those without HCV
- In persons with DM, prevalence of HCV 2.5-fold higher than in those without DM
- Odds ratio of having DM is 2 to 16 times higher in persons with chronic HCV than in those with other causes of chronic liver disease
- Odds ratio of having DM is 2.6 times higher in HCV-infected liver transplant recipients than in non-HCV-infected transplant recipients

Mehta SH, *Ann Intern Med*, 2000; Mason AL, *Hepatology*, 1999; Khalili M, *Liver Transplant*, 2004.

Proposed Mechanisms of Insulin Resistance

- High levels of tumor necrosis factor-alpha disturb phosphorylation of insulin receptor substrate-1 causing reduced hepatic insulin sensitivity
- High HCV viral levels related to insulin resistance
- Direct inhibition by HCV in transgenic mouse models
- Contribution from underlying liver disease, especially in those with cirrhosis

Shintani, *Hepatology*, 2004; Delgado-Borrego, *Transplantation*, 2004.

Renal Manifestations

HCV and Renal Disease

- HCV common in renal dialysis patients (5%-60%)
- 40% of renal transplant recipients have HCV
- Outcome after renal transplant worse in patients with HCV (all-cause mortality 13% vs 8.5%)
  - HCV can progress under immune suppression

Batty, *AJT*, 2001; Cacoub, 2000.

MPGN

- Usually asymptomatic with mixed cryoglobulinemia
- 30% have triad of purpura, asthenia, and arthralgia
- 10% cryoglobulinemic vasculitis affects small vessels
  - Skin, nerves, and kidney
- 1/3 of cryoglobulinemic patients have renal involvement
  - Proteinuria and microscopic hematuria with mild to moderate renal insufficiency
  - Hypertension
  - Renal biopsy shows a pattern of MPGN, with typical immune complex deposition in glomeruli. Inflammatory cells—both mononuclear cells and polymorphonuclear leukocytes—infiltrate the glomerular capillaries
  - 70% have increased ALT levels
  - Majority have low serum concentrations of complement components (C1q, C4, and C3)

Perico, 2009.

HCV-related Nephropathy

- Mixed cryoglobulinemia MPGN (precipitate from cold serum)
- Renal parenchyma expresses CD81 and SR-B1 receptors that allow HCV binding to the cell surface and endocytosis

Less common

- IgA nephropathy
- Postinfectious glomerulonephritis
- Membranous nephropathy
- Thrombotic microangiopathies
- Focal and segmental glomerulosclerosis
- Fibrillary glomerulopathy

Perico, 2009.

Outcome of Renal Disease in HCV

- Of 470,000 adult veterans, patients with HCV infection were more likely to develop End-Stage Renal Disease (ESRD) (4.3 per 1000 person-years) than HCV-seronegative patients (3.1 per 1000 person-years)
- Patients with an estimated glomerular filtration rate (GFR) ≤30 mL/min per 1.73 m^2, the presence of HCV was associated with a nearly 3-fold higher risk of ESRD

Tsui, 2007.

Summary

- Extrahepatic manifestations of HCV are common
- While cryoglobulins are common in serum, cryoglobulinemia is rare
- Renal disease is of particular concern
- Interferon alfa can induce extrahepatic manifestations
- Assessment of liver fibrosis stage is needed prior to renal transplantation

End

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