Erythropoietic Protoporphyria and liver complications.

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Discussant: Sioban Keel
Hematology Grand Rounds 11/9/12
Setting the Scene

Saturday 10/20/12:
55 yo woman with PMH of erythropoietic protoporphyria and breast cancer 2000 presents with 2 weeks of nausea, vomiting, painful “tightness” around her upper abdomen, and new jaundice transferred from Evergreen to UWMC for liver transplant..... Hematology is called.
SR

HPI:
-Patient had been “feeling unwell” for 2 weeks, decreased appetite, nausea, and a pain in her upper abdomen/lower ribs which was band like and woke her from sleep
-Pain so severe she went to an urgent care clinic near her home, was told it was muscle cramps and given ibuprofen.
-3 days later after an episode of near syncope, the patient’s husband brought her to OSH, husband did not see her jaundice until coming to the hospital (she usually lives in a darkened house)
-She has never had abnormal LFTs in the past

SH:
-Denies alcohol abuse, smoked 1ppd X25 yrs quitting in 1999, only used a occasional tylenol (1 pill at a time) for pain control, no history of drug abuse, no recent tattoos/piercings.
PMH

EPP:
- Adopted from Germany, reports as a baby she would scream whenever taken outside.
- Diagnosed with EPP in the 1960s at Johns Hopkins, remained in their porphyria clinic until she turned 18, took beta carotene for a few years which improved her photosensitivity but she discontinued it because of the number of pills involved.
- Her typical symptoms are severe burning pain and skin redness with sun exposure, if continued exposure then the exposed areas will become swollen, red, and painful for days.
- She had no recent sun exposure prior to admission.
PMH

Breast Cancer:
-dx 2000, ER +
-R lumpectomy 0/3 + sentinel nodes, Adriamycin/Cytoxan/Taxol and radiation
tamoxifen X1 year, she discontinued because she could not tolerate medication side effects.
she has not had regular mammograms since.
At OSH

Initial Labs:
CBC: WBC 20.2 Hct 42.4 plt 324
LFTS: T bili 24, AST and ALT ~400s
Ferritin 170.5, ceruloplasmin 32

Hepatitis A/B/C negative

US liver: No gallstones or dilated biliary ducts, mild hepatomegaly

MRCP: No dilated bile ducts or masses found

Liver Biopsy: showed no fibrosis/cirrhosis but deposits of birefringent protoporphyrin.
Porphyrias

- Caused by errors in one of the 8 specific enzymes in the heme biosynthetic pathway
- Heme is required for production of hemoproteins: hemoglobin, myoglobin, respiratory cytochromes, and cytochrome P450 enzymes
- 85% of the heme synthesis is in the erythroid precursor cells, 15-20% is in the hepatocytes
- Grouped by the primary site of overproduction and therefore primary symptoms (there are overlapping symptoms):

1. Acute hepatic porphyrias (neurovisceral): acute intermittent porphyria, hereditary coproporphyria, variegate porphyria, and ALA-dehydratase deficient porphyria
2. Hepatic cutaneous porphyria: porphyria cutanea tarda
3. Erythropoietic cutaneous porphyrias: erythropoietic protoporphyria, X-linked protoporphyria, and congenital erythropoietic porphyria

Balwani Blood 2012: Epub 22791288
Porphyrias:

- Acute Hepatic
- Hepatic Cutaneous
- Erythropoetic cutaneous

![Diagram of porphyria cycle]

http://rarediseasesnetwork.epi.usf.edu/porphyrias/images/clip_image002_0000.gif
Erythropoietic Porphyria -

Disorder of heme synthesis preventing correct heme production and therefore causing increased protoporphyrin IX. 1/75,000-200,000 of the general population.

Two genetic abnormalities cause EPP symptoms:

1. Autosomal recessive ferrochelatase (FECH- enzyme that inserts iron into protoporphyrin IX to make heme)
   - Most common “pseudo-dominant” FECH mutation (one copy mutated and second copy low expression normal variant) but also found homozygous for mutated gene.
   - <30% FECH expression causes EPP phenotype.
2. Over expression ALAS2 gain of function mutation (2% EPP)
   - ALAS2 gene is in erythroid tissue and on the X chromosome. Associated with increased risk of liver complications.

Lecha et al. Orphanet Journal of Rare Diseases 2009 (4) 19
Hemoglobin Production Pathway

ALAS2: X linked dominant
Ferrochelatase: aut recessive OR “pseudo-dominant”
Skin Disease of EPP

severe sun sensitivity caused by photoactivation of the excess protoporphyrin deposits in skin and in erythrocytes by ultraviolet light (400 nm) causing free radicals and skin injury

- burning pain on exposure to sun
- if exposure is prolonged, erythema and edema (rarely bullous lesions)
- pain from sun exposure can last hours to days depending on length of exposure
- repeated photosensitivity can alter skin causing thickening and hyperkeratosis
Skin Manifestations of EPP

Acute Manifestations

Chronic Skin Changes

The Lancet PIIS0140673605177447

Lecha et al Orphanet Journal of Rare Diseases 2009 (4) 19
A spectrum of liver disease can be seen in EPP

1. 10-20% cholelithiasis due to accumulation of free protoporphyrin in biliary system

2. Mild parenchymal disease: asymptomatic increase aminotransferases or cholestatic enzymes

3. Progressive hepatocellular disease leading to cirrhosis/fibrosis

4. ~5% rapidly progressing acute liver insufficiency
   • Caused by precipitation of the insoluble protoporphyrin in bile canaliculi and protoporphyrin oxidative stress
   • Protoporphyrin is insoluble so is not excreted in the urine, therefore all of the protoporphyrin is excreted in the stool through the bile (why CANNOT use urine tests in EPP!)
   • Patients homozygotes FECH mutation, rare FECH mutation heterozygotes, or ALAS2 mutants increased risk for liver disease.

Casanova-Gonzalez World J Gastroenterol 2010 16: 4526
Liver Pathology:

Protoporphyrin collections in hepatocytes

Polarized light- birefrinent pigments

Maltese cross

Courtesy of Dr Jen LaPointe
Treatments for EPP Cholestatic Liver failure in the literature

1. Reduce protoporphyrin XI production:
   - Hematin
   - Prevent anemia (hct goal 30-33)

2. Get rid of excess protoporphyrin XI in the body:
   - Plasmapheresis
   - Red cell exchange (red cells protoporphyrin sink)
   - Cholestyramine (removes protoporphyrin from GI tract)

3. Protect the liver from further damage:
   - N acetyl cysteine
   - Ursodiol
Case Report: Liver function/Protoporphyrin with plasma and red cell exchange

AST/ALT

Open arrows: plasma exchange
Filled arrows: red cell exchange

Total Bilirubin

Protoporphyrin levels

SR at UWMC

Labs on Admission:

134     100     7     11.87 [----------------------[ 131
---------|----------------|----------------< 89     25

3.5     27     0.59

AST (GOT):  219
ALT (GPT):  148
Alk Phos (Total):  249
Bilirubin (Total):  27.0
Albumin:  2.4

10/20: started cholestyramine, ursodiol, Hematin, hemoglobin >11
10/21: started N acetyl cysteine and placed apheresis catheter
10/22: First plasmapheresis
10/23: First red cell exchange
Response to therapy- LFTs

R = red cell exchange  P = Plasma Exchange
Response to therapy: Bilirubin

R = red cell exchange  P = Plasma Exchange
Response to therapy- Protoporphyrins

Graph showing the response to therapy with protoporphyrins over the period from October 18 to November 7. The graph includes dates such as 18-Oct, 20-Oct, 22-Oct, etc., with corresponding TP and RBC P values.
EPP and Liver Transplant

- Patients with rapid liver failure often do not respond to medical management alone.
- Even in patients for whom the liver disease is reversed with medical management, it usually recurs.
- Complications with EPP patient and liver transplant:
  a) burns from being under surgical lights
  b) prolonged ventilation from a motor neuropathy that develops after a long surgery
  c) recurrence of the disease in transplanted liver

Whalin et al Liver Transplantation (2011) 17: 1021
Liver Transplant Studies

- European (Whalin et al Liver Transplantation (2011) 17:1021)
  31 patients with EPP liver failure who had liver transplant 1983-2008
  -66% 5-10 yr survival (equivalent to non EPP liver transplant)
  -69% disease recurrence in the graft (from biopsy).
  20 patients with EPP liver failure liver transplant 1979-2004
  -69% survival 5 yrs and 47% at 10 yrs.
  -65% recurrence and 15% re-transplantation for graft failure
- UK (Dowman et al J Inherit Metab Dis (2011) 34:539)
  5 patients between 1987-2009
  -overall survival 60% (equivalent to non EPP liver transplant)
  -80% had recurrence in the transplanted liver within 2 yrs of transplant
EPP and Bone Marrow Transplant

• Rare case reports of bone marrow transplant in EPP patients, all in relation to liver failure as risk of BMT too high if uncomplicated EPP
• Concern is that EPP disease of liver and RBC so even if have bone marrow transplant alone may not resolve liver contribution
• Most cases BMT seen after liver transplant

Indications for BMT for EPP:
1. After reversal of liver failure in patients without fibrosis
2. After liver transplant in older patients with recurrent graft disease
3. After liver transplant in younger patients to preserve liver
4. In patients with progressive liver disease

Wahlin et al Bone Marrow Transplantation 2010 45: 393-394
Further Plans

• Ms SR has been presented to the liver transplant board, starting the process (she is uninsured) to prepare her for liver transplant

• She has had 18 days of intensive in-hospital treatment (9 plasmapheresis treatments and 3 red cell exchanges). She was discharged 11/6 after her LFTs held with every other to every 2 day plasmapheresis. She is continued on cholestyramine and ursodiol.

• If she gets a liver transplant, next would she need bone marrow transplant (she has no known siblings) ?
Thanks

- Dr Sioban Keel
- Dr Mike Linenberger
- Dr Bill Hobbs
- Dr James Kushner
- Medicine A team

BUT IF WE MOVE HIS LIVER HERE IT’S BETTER FENG SHUI
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