Clinical vignette: Warm weather and plasmapheresis in the management of Hepatitis C cryoglobulinemia

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INTRODUCTION:

- Chronic infection with hepatitis C virus (HCV) is the main cause of mixed cryoglobulinemia (CG).
- Cryoglobulinemia is characterized by clonal expansion of rheumatoid factor expressing B-cells in the liver, lymph nodes and peripheral blood resulting in the presence of cryoglobulins in the circulation.
- Cryoglobulins are cold insoluble immune complexes containing RF, polyclonal IgG, and HCV RNA that precipitate and deposit on vascular endothelium. This can cause cryoglobulinemic vasculitis in organs such as the skin, kidneys, and peripheral nerves.
- It is unclear how B-cells become dysregulated during the course of chronic HCV infection.

CASE REPORT:

- A 51-year-old male with untreated chronic HCV presented to a rural hospital with a worsening bilateral lower extremity rash. He had recently been diagnosed with MPGN, severe anemia, and congestive heart failure. Cryoglobulinemic vasculitis was suspected, and the patient was referred to a larger regional hospital for further evaluation and plasmapheresis. On admission, the patient had pancytopenia and worsening renal function. Physical examination was consistent with painful palpable purpura involving both lower extremities. Initial testing showed Hep C viral load of 3.8 million, and serologic testing confirmed the presence of cryoglobulins. After a blood transfusion, plasmapheresis was initiated daily for 3 rounds then the frequency was decreased to every other day. After 6 rounds of plasmapheresis, renal function and the lower extremity rash had improved significantly. Hep C therapy was considered but was not possible due to the patient’s multiple contraindications including severe anemia and renal failure. CHF was a poor adherence to previous medication prescriptions.
- The patient was discharged and readmitted several times due to recurrence of painful lower extremity rash and fatigue. After each discharge, the patient returned to his hometown at a higher altitude and with a colder climate, likely exacerbating his CG. The patient was advised to move to a warmer climate and to continue plasmapheresis until he was a candidate for HCV therapy. He underwent a total of 30 sessions of plasmapheresis by the time of his last discharge.
- This case provides an example of the relative success of long term plasmapheresis for symptom management in patients with HCV-induced CG who are not candidates for HCV treatment.

EPIDEMIOLOGY:

- Prevalence of HCV-induced CG varies widely
- Though many HCV infected patient’s serum contain cryoglobulins, not all have cryoglobulinemic vasculitis. 30-50% of HCV positive patients have cryoglobulins.
- Between 2% and 15% of cryoglobulin positive patients develop cryoglobulinemic vasculitis.

MAJOR CLINICAL MANIFESTATIONS:

- Palpable purpura primarily of the lower legs occurs in more than 90% of patients with symptomatic HCV-induced CG.
- Membranoproliferative glomerulonephritis (MPGN) type I presents in 10-30% of patient with chronic HCV infection. Histology exhibits subendothelial deposition of cryoglobulin immune complexes.
- Myalgia, fatigue, and arthralgias are common manifestation in chronic HCV infection in general and noted in cryoglobulinemic patients.
- Neurologic manifestations include chronic sensory polyneuropathy, acute or subacute encephalopathy, “restless leg syndrome”, and Guillain-Barré syndrome.

TREATMENT:

- The treatment of HCV-induced CG vasculitis targets either HCV or associated clinical signs and symptoms of CG.
- The standard of care for HCV infection is pegylated interferon alpha 2a/2b (PEG-IFN) in combination with ribavirin (RBV).
- Rituximab shows good outcomes in treatment of HCV-CG but it increases HCV RNA, therefore recommended use is in combination with PEG-IFN and RBV.
- Contraindications for treatment include patients with:
  - Decompensated cirrhosis
  - Kidney/Liver/Heart or any other solid organ transplant
  - Severe depression
  - Pregnant females (contraception required in female)
  - Unstable cardiopulmonary disease
  - Erythropoietin-resistant anemia
  - Hemoglobinopathies
  - Current alcohol and IV drug use
  - Poor medication compliance
- Patients with severe disease may benefit from corticosteroids, cytotoxic medications and plasmapheresis.

PLASMAPHERESIS:

- Plasmapheresis is a technique that removes pathogenic cryoglobulins, immune complexes and autoantibodies from the circulation thereby improving symptomatology.
- In CG, plasmapheresis can be used as effective adjunctive therapy to minimize rapidly progressive disease or disease with severe cutaneous, renal and or neurologic involvement.
- Periodic plasmapheresis may control levels of cryoglobulins preventing renal deterioration and allowing a decrease in the dose of immunosuppressant drugs and side effects.
- The number and frequency of plasmapheresis sessions are not well established and depend upon the rate of cryoglobulin synthesis in each patient.

- Common mild side effects include chills, hypoglycemia, hypocalcemia, bronchospasm, urticaria, paresthesias, transient fever, nausea, vomiting, mild cytopenia and hypotension. Rarely side effects include arrhythmias and anaphylaxis.
- Small studies have shown that long term plasmapheresis exchange defined as >25 treatments have been successful in improving renal function and cutaneous manifestations of CG in patients who failed to respond to conventional therapy. Only minor side effects are usually observed, and the risk/benefit ratio for such therapy is excellent.

DISCUSSION:

- Plasmapheresis coupled with warm temperatures can alleviate symptoms in HCV-induced CG, providing a window of opportunity for patients to improve their overall health and become potential candidates for antiviral therapy. However, there is limited data and further research is needed to support the effectiveness of this management option.
- There is no specific guidelines for treatment of HCV-induced cryoglobulinemia and optimum treatment remains the subject of great debate.
- The general approach to treatment is based on patient specific signs, symptoms, and associated comorbidities.
- Specific needs for future research include improvement in knowledge of the mechanism by which HCV persists and the pathogenesis of sustained lymphoproliferation with aims to create improved therapies.
- Large clinical control trials to evaluate the long term outcomes of plasmapheresis as sole treatment in patient who are not candidates for antiviral are much needed.

Disclosure:
- The tissue images are not from the case presented as this were not available.
- Please e-mail me for a complete bibliography and image sources: sponce@unm.edu.