



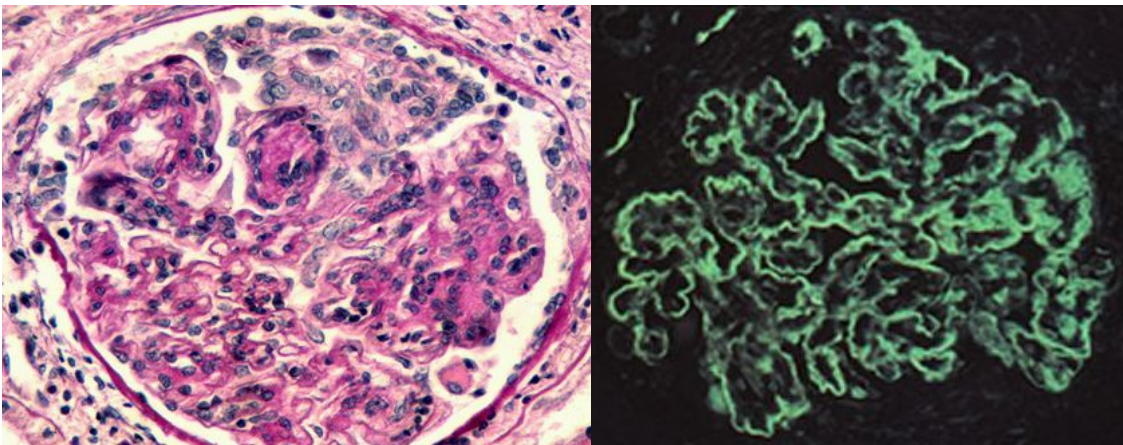
HOLY C.O.W.!

IT'S...

Clinical Question of the Week #27
January 12th, 2009 through January 19th,
2009

Please e-mail your answers to Kuo, Tim, Wendy, and Kevin (klian@mednet.ucla.edu; tprovias@mednet.ucla.edu; wsimon@mednet.ucla.edu; kbreger@mednet.ucla.edu) by 0800 on Monday, January 19th, 2009. The resident or intern with the most correct answers at the end of each month will receive a prize!

Case: A 57-year-old woman with a distant history of IV drug abuse presents for initial evaluation after recently moving to the area. She has been clean and sober for 25 years, does not drink, and smokes a half-pack per day of cigarettes. Her past medical history is notable for hypertension. Family history is unknown. She reports having a flu-like illness several weeks ago with diffuse aches and malaise (she's always catching "some bug or another" during winter), however this resolved after 1-2 weeks. Aside from this, the patient reports being in reasonably good health, although she reports occasional skin changes, which she attributes to her eczema. In addition to routine screening laboratory studies, a chemistry panel was obtained and revealed elevated creatinine. Urinalysis was obtained and revealed proteinuria and few RBCs. The patient later underwent renal biopsy, the results of which are shown below.



H&E staining (left) and immunofluorescence staining (right) from renal biopsy.

Questions:

- 1. What is the diagnosis? What is the likely pathophysiologic process in this case?**
Mixed essential cryoglobulinemia, referring to the presences of cryoglobulins (defined as immunoglobulins that precipitate in cold and dissolve on rewarming) in the patient's serum, is the result of a systemic inflammatory syndrome that involves small-to-medium vessel vasculitis due to circulating cryoglobulin-containing immune complexes. In this case, the antibodies are likely due to chronic hepatitis C, which the patient contracted from her history of distant IV drug abuse.

The Brouet classification separates cryoglobulinemia into three categories, roughly divided by clonality and RF binding activity:

- Type I – isolated monoclonal Ig (usually IgG/IgM, less commonly IgA or free light chains), typically associated with multiple myeloma or Waldenstrom's macroglobulinemia. Accounts for 5-25% of cases.
- Type II – a mixture of polyclonal Ig in association with a monoclonal Ig (usually IgM or IgA), also with RF activity. This accounts for 40-60% of cases, and is associated with chronic viral infections such as HCV and HIV.
- Type III – mixed cryoglobulins with polyclonal origin, accounting of 40-50% of cases, and is associated with connective tissue disease.

Clinically significant disease occurs in approximately 1:100,000 individuals, although detectable levels of cryoglobulins may be seen in patients with chronic inflammation/infection (15-25% in connective tissue diseases, 40-50% in chronic hepatitis C). Laboratory testing reveals elevated cryocrit and may reveal lowered CH50 and other early complement levels, such as C1q, C2, and C4. Other inflammatory or autoantibody markers may also be positive such as ESR, CRP, and RF. Finally, viral studies may reveal chronic viral infection or positive serology. (1)

2. Name two other manifestations of this condition.

In the setting of hematologic malignancies and monoclonal immunoglobulins, cryoprecipitation with hyperviscosity syndrome is the classical clinical syndrome. The other classic presentation of polyclonal cryoglobulinemia consists of Meltzer's triad, including palpable purpura, myalgia, and arthralgia. Additionally, patients may develop neuropathy, pulmonary small airways disease, and nephropathy (most commonly MPGN). (0.5)

3. Describe the findings shown in the images above.

Membranoproliferative glomerulonephritis is the most common nephropathy associated with cryoglobulinemia, and is associated with the depositions of immune complexes. Shown in the images above: right image with H&E stain showing increased cellularity and mesangial expansion, and left image with capillary wall deposits of IgG and IgM on immunofluorescence. Electron microscopy will Renal disease is seen most frequently in type II disease, affecting up to 35-60% of patients. Symptoms may range from asymptomatic hematuria to nephrotic syndrome to acute nephritis to acute and chronic renal failure. (1)

4. What is the treatment?

Mild disease such as fatigue, arthralgias, and myalgias are treated with conservative management including cold avoidance, NSAIDs, or analgesics. Moderate-to-severe type I disease warrants treatment of the underlying hematologic disorder, and in non-malignancy associated type I and type II/III disease, immunosuppression may be warranted. In life-threatening severe cases, plasmapheresis is indicated to reduce the cryoglobulin burden. (0.5)