A 67-year-old woman presented to clinic with a 2-year history of diarrhea, nausea, vomiting, and unexplained weight loss of 50 pounds. She described 3 or 4 bowel movements per day, consisting of watery stools without identifiable triggers. She also noted an intermittent rash on her lower extremities bilaterally. She denied fever, abdominal pain, hematochezia, or melena. Her medical history was notable for lifestyle-controlled hypertension and nonerosive gastroesophageal reflux disease. Her medications included omeprazole 20 mg daily and a daily vitamin B12 supplement. She denied the use of any other over-the-counter supplements. She denied tobacco smoking, alcohol use, or recreational drug use.

On examination, she was overall well appearing, and vital signs were as follows: pulse, 86 beats/min; blood pressure, 130/75 mm Hg; and temperature, 36.3°C. Her abdomen was soft and nontender to palpation without masses or hepatosplenomegaly. Her bilateral lower extremities were noted to have mild pitting edema up to the shins with hyperpigmented macules and nonblanching erythematous papules overlying the distal parts of the legs bilaterally. Posterior tibial and dorsalis pedis pulses were normal bilaterally. Her toes were pale and distinctly cooler than the more proximal parts of the feet. However, by the end of the examination, the toes were pink and warm. The remainder of the examination was unremarkable.

Laboratory evaluation yielded the following (reference ranges provided parenthetically): hemoglobin, 8.5 g/dL (11.6 to 15.0 g/dL); leukocytes, 5.8 × 10⁹/L (3.4 to 9.6 × 10⁹/L); platelets, 169 × 10⁹/L (157 to 371 × 10⁹/L); creatinine, 1.81 mg/dL from a baseline of 0.80 mg/dL (0.59 to 1.04 mg/dL); C-reactive protein, 20.6 mg/L (≤8.0 mg/L); erythrocyte sedimentation rate, 27 mm/h (0 to 29 mm/h); rheumatoid factor, 100 IU/mL (<15 IU/mL); albumin, 3.4 g/dL (3.5 to 5.0 g/dL).

Urinalysis revealed proteinuria with a predicted 24-hour protein excretion of 2489 mg and hematuria with 51 to 100 red blood cells per high-power field (<3 per high-power field). Protein to creatinine ratio on a random urine sample was 1920 mg/g (<180 mg/g).

1. Which one of the following diagnoses is most likely, given these findings?
   a. Minimal change disease
   b. Membranous nephropathy
   c. Diabetic nephropathy
   d. Goodpasture disease
   e. Immune complex–mediated glomerulonephritis

When glomerular disease is suspected, the most common clinical classifications include nephritic and nephrotic syndromes. The predominant features of nephritic syndrome are hematuria and hypertension. Nephrotic syndrome is characterized by effacement of the podocyte foot processes, leading to proteinuria of more than 3.5 g/d, hypoalbuminemia, hyperlipidemia, and lower extremity edema. Some glomerular disorders can be manifested with either or both clinical syndromes.

Minimal change disease is the most common cause of nephrotic syndrome in children. In adults, membranous nephropathy is the most common cause of primary or idiopathic nephrotic syndrome, whereas the
most common secondary cause of nephrotic-range proteinuria is diabetes. Although diabetic nephropathy can be manifested with subnephrotic-range proteinuria, it is not usually associated with hematuria. Our patient’s estimated 24-hour urine protein level was below 3.5 g, and therefore diagnostic considerations commonly associated with nephrotic syndrome would be less likely to explain her presentation.

Nephritic syndrome is characterized by glomerular inflammation and basement membrane disruption; its clinical manifestations may include hematuria, variable proteinuria, and kidney injury. Causes of nephritic syndrome include IgA vasculitis (Henoch-Schönlein purpura), infection-related glomerulonephritis, and anti–glomerular basement membrane antibody disease (Goodpasture syndrome). Goodpasture syndrome is a reasonable diagnostic consideration; however, our patient did not show signs of pulmonary involvement at the time of presentation. Our patient’s clinical presentation with a purpuric rash, mild lower extremity edema, and hypertension in combination with laboratory findings of acute kidney injury, hematuria, and subnephrotic-range proteinuria is most consistent with an immune complex–mediated glomerulonephritis. This category of glomerulonephritis includes a variety of diagnoses that are mediated by glomerular deposition of immune complexes.

Results of additional laboratory testing were negative for myeloperoxidase antibodies, proteinase 3 antibodies, antinuclear antibodies, and human immunodeficiency virus (HIV) infection. The total complement level was 18 U/mL (30 to 75 U/mL), C3 level was 62 mg/dL (75 to 175 mg/dL), and C4 level was 5 mg/dL (14 to 40 mg/dL).

2. What is the most likely diagnosis?
   a. Infection-related glomerulonephritis
   b. IgA nephropathy
   c. IgA vasculitis (Henoch-Schönlein purpura)
   d. Cryoglobulinemia
   e. Hereditary nephritis

The differential diagnosis for nephritic syndrome includes infection-related glomerulonephritis, IgA nephropathy, cryoglobulinemia, lupus nephritis, and immune complex–mediated and complement-mediated membranoproliferative glomerulonephritis. Infection-related glomerulonephritis is an immune complex–mediated disease commonly associated with streptococcal and staphylococcal infections. There was no identifiable infectious process preceding our patient’s presentation. In addition, the degree of depression of C4 relative to C3 with rheumatoid factor positivity is more consistent with cryoglobulinemia.

IgA nephropathy is the most common cause of chronic glomerulonephritis and is often asymptomatic. The most common presentation in adults is microscopic hematuria, with or without proteinuria, and normal complement levels. The presentation may be preceded by an upper respiratory tract infection.

IgA vasculitis is also a reasonable diagnostic consideration because of the presence of kidney and skin involvement; however, complement levels are typically normal in this condition. Although IgA vasculitis may affect adults, it is more commonly seen in children.

Cryoglobulinemia is an immune complex–mediated disease characterized by depressed levels of both C3 and C4 in the context of the classical complement pathway. Notably, in cryoglobulinemic vasculitis, C4 levels are usually disproportionately depressed relative to C3. Although the renal manifestations of cryoglobulinemia vary, it commonly includes kidney injury with glomerulonephritis. Palpable purpura, which was present in our patient, is a characteristic dermatologic manifestation of cryoglobulinemic vasculitis.

Hereditary nephritis, or Alport syndrome, is a genetic disease that affects type IV collagen and is associated with sensorineural hearing loss. Although chronic kidney disease is common, complement levels are usually normal.
Cryoglobulin level was elevated at 11% (reference: negative). Immunofixation showed type II cryoglobulinemia with a monoclonal IgM kappa plus polyclonal IgG. She returned to clinic 1 week later to follow up on the results of testing. During her visit, she continued to describe severe fatigue and endorsed decreased urine output despite adequate fluid intake. Serum creatinine concentration was 2.48 mg/dL. She was admitted to the hospital, and renal biopsy showed an immune complex-mediated glomerulonephritis with numerous intracapillary immunoglobulin pseudothrombi. The glomeruli showed granular mesangial, capillary loop, and intraluminal capillary staining for IgM (2 to 3+), C3 (2 to 3+), IgA (1+), IgG (1 to 3+), C1q (1+), fibrinogen (1+), and kappa (1 to 3+) and lambda (1 to 2+) light chains. Electron microscopy showed diffuse effacement of the podocyte foot processes with subendothelial and capillary lumen electron-dense deposits, with a curvilinear substructure. The findings were typical of cryoglobulinemic glomerulonephritis and vasculitis.

3. Which one of the following is the most appropriate next step in testing?
   a. Hepatitis C antibodies
   b. Anti–citric citrullinated peptide antibodies
   c. Hepatitis B surface antigen
   d. Anti-myeloperoxidase (anti-MPO) antibodies
   e. Antineutrophil cytoplasmic antibodies (c-ANCA)

Cryoglobulinemia is divided into 2 main subgroups: type I cryoglobulinemia and mixed (type II/III) cryoglobulinemia. Mixed cryoglobulinemia is commonly seen in chronic hepatitis C, connective tissue diseases, and lymphoproliferative diseases. Given that our patient has type II cryoglobulinemia, checking hepatitis C antibodies is the most appropriate next step. This chronic viral infection provides the antigenic substrate for immune complex formation.

Whereas anti–citric citrullinated peptide antibodies have higher specificity than rheumatoid factor in the diagnosis of rheumatoid arthritis, our patient did not present with articular disease. The rheumatoid factor positivity reflects the presence of type II cryoglobulins as they have rheumatoid factor activity.

Although hepatitis B can cause a type II cryoglobulinemia, hepatitis C is more commonly implicated. Therefore, in this case, hepatitis C testing is of greater diagnostic yield.

Anti-MPO antibody–associated vasculitis typically involves the kidneys and commonly is manifested with palpable purpura; there is usually a paucity of immune deposits on immunofluorescence and electron microscopy. Our patient’s finding of immune complex–mediated glomerulonephritis is not typical of the renal involvement seen with anti-MPO antibodies.

Vasculitis associated with antineutrophil cytoplasmic antibodies (c-ANCA) and anti-proteinase 3 antibody usually affects the upper respiratory tract, ears, lungs, and kidneys. Our patient did not have sinus pain, rhinitis, epistaxis, hearing loss, or symptoms of pulmonary involvement.

On further investigation, the serum hepatitis C antibody assay was negative. Computed tomography of the abdomen and pelvis revealed mild mesenteric lymphadenopathy and mild splenomegaly with multiple confluent low-density splenic lesions. Asymmetric polypoid thickening of the gastric antrum was also noted. The next day, she was noted to make approximately 1000 mL of dark urine. Renal function panel showed the following values: potassium, 3.5 mmol/L (3.6 to 5.2 mmol/L); sodium, 137 mmol/L (135 to 145 mmol/L); chloride, 96 mmol/L (98 to 107 mmol/L); bicarbonate, 25 mmol/L (22 to 29 mmol/L); blood urea nitrogen, 55 mg/dL (6 to 21 mg/dL); and creatinine, 2.21 mg/dL (0.59 to 1.04 mg/dL).

4. Which one of the following is the most appropriate next step of this patient’s management strategy?
   a. Glucocorticoids and plasmapheresis
   b. Dialysis
   c. Captopril
   d. Observation
   e. Cyclophosphamide
The decline in kidney function and urine output was suggestive of rapidly progressive glomerulonephritis secondary to cryoglobulinemia. In most cases of cryoglobulinemia, treatment is aimed at the underlying cause. In rare cases of severe life- or organ-threatening presentations, treatment with plasmapheresis is indicated to rapidly remove the offending immune complexes from the bloodstream and to slow the inflammatory process. This is only a temporizing measure, and definitive treatment of the underlying condition must still be pursued. In the case of rapidly progressive glomerulonephritis, treatment with both glucocorticoids and plasmapheresis is suggested both to reduce the ongoing inflammatory response and to remove the causative agent.

The laboratory values and urine output do not indicate an urgent need for dialysis. Captopril is used in the treatment of scleroderma renal crisis and is not effective in the treatment of progressive glomerulonephritis due to cryoglobulinemia. Because of the progressive renal failure, this patient’s condition would not be suitable for observation alone. Cyclophosphamide therapy can be considered, depending on the specific cause of the immune complex–mediated glomerulonephritis, but glucocorticoids and plasmapheresis would be the most appropriate next step in this situation to avoid further imminent organ damage.

She received methylprednisolone 1 g intravenously and underwent urgent plasmapheresis. Slowly, creatinine concentration improved, and urine output increased. She underwent esophagastroduodenoscopy with biopsy to evaluate the gastric thickening seen on computed tomography scan. The pathologic examination returned a positive result for low-grade B-cell lymphoma, consistent with extranodal marginal zone lymphoma (EMZL) of mucosa-associated lymphoid tissue.

5. Which of the following infections is a risk factor associated with the patient’s condition?

- a. Human papillomavirus
- b. HIV
- c. Helicobacter pylori
- d. Human gammaherpesvirus 8 (human herpesvirus 8)
- e. Schistosomiasis

Human papillomavirus is associated with increased risk of cervical cancer. Infection with HIV is associated with an increased risk for Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer. Helicobacter pylori infection is associated with EMZL of mucosa-associated lymphoid tissue. Human herpesvirus 8 is associated with Kaposi sarcoma. Schistosomiasis is associated with bladder cancer.

She completed therapy with methylprednisolone 1 g for 3 days with 5 sessions of plasmapheresis. Testing for H. pylori returned a negative result. A plan was made for rituximab to treat the EMZL. She had a complicated hospital course but was ultimately discharged home after renal recovery.

**DISCUSSION**

Cryoglobulinemia is a condition characterized by the presence of cryoglobulins, which are abnormal monoclonal or polyclonal immunoglobulins that precipitate at temperatures below 37°C in vitro. Cryoglobulins can be deposited in medium and large blood vessels, causing endothelial injury and end-organ damage. This phenomenon was first described in the setting of multiple myeloma in 1933 by Wintrobe and Buell at Johns Hopkins Hospital. Cryoglobulinemia was then subcategorized into 3 types in 1974 by Brouet et al.

Type I cryoglobulinemia consists of monoclonal immunoglobulins, more commonly of the IgG or IgM isotypes and rarely IgA or free immunoglobulin light chains. Type I is most commonly associated with secretory monoclonal gammopathies, such as monoclonal gammapathy of undetermined significance, multiple myeloma, Waldenstrom macroglobulinemia, and other lymphoproliferative disorders.
Type II and type III cryoglobulinemia are collectively referred to as mixed cryoglobulinemia and are a result of B-cell lymphoproliferative processes with stimulated immune activation mediated by infection, inflammation, or an unknown cause. Type II is characterized by a mix of monoclonal IgM with rheumatoid factor activity and polyclonal IgG; 90% of patients with type II cryoglobulinemia have a concomitant hepatitis C virus infection. Type II can be associated with other infections (HIV infection and hepatitis B) and connective tissue diseases (systemic lupus erythematosus, Sjögren syndrome, and rheumatoid arthritis). As seen in our patient’s case, type II can be associated with lymphoproliferative disorders including EMZL. Type III is characterized by polyclonal IgM with rheumatoid factor activity and polyclonal IgG. Type III is usually associated with connective tissue disorders and infection, most commonly hepatitis C.

Cryoglobulinemia is often asymptomatic; however, symptoms can reflect sequelae of vascular occlusion and hyperviscosity. Hyperviscosity symptoms are occasionally seen with type I cryoglobulinemia but rarely encountered in type II. A constellation of symptoms including purpura, arthralgia, and weakness, called Meltzer triad, is seen in approximately one-third of patients with mixed cryoglobulinemia. The most common clinical sign of mixed cryoglobulinemia is purpura, seen in approximately 90% of cases. Other signs and symptoms include peripheral neuropathy, Raynaud syndrome, and renal disease.

Cryoglobulinemia is diagnosed through laboratory confirmation of elevated cryocrit, which is the relative volume of the precipitate as a percentage of the total serum volume, in the appropriate clinical setting. Cryocrit is collected in laboratory tubes pre-warmed to 37°C without anticoagulants. After cryoprecipitation, immuno fixation identifies the type of cryoglobulins. Mixed cryoglobulinemia (type II/III) is commonly associated with low C4 level and rheumatoid factor positivity. Rheumatoid factor activity results from the presence of a polyclonal IgG antibody with a monoclonal IgM that binds to other immunoglobulins. In cases in which diagnostic uncertainty persists despite the clinical and laboratory data, histopathologic examination of affected organs can provide evidence of cryoglobulinemia vasculitis.

After confirmation of the diagnosis, further work-up should be pursued to identify the underlying cause. This work-up is guided by the clinical picture and can include infections (hepatitis C, hepatitis B, and HIV infection), autoimmune disorders (antinuclear antibody test, double-stranded DNA, anti-Smith, Ro/SSA, La/SSB), and malignant disease (B-cell lymphoma, multiple myeloma). In asymptomatic or mild cases, treatment is targeted at the underlying disorder. In patients with monoclonal (type I) cryoglobulin associated with a lymphoproliferative disorder, the treatment is focused on the underlying malignant disease and the presence of complications, such as hyperviscosity syndrome. Patients treated with rituximab who have high levels of IgM (above 4 g/dL) with hyperviscosity may require treatment with plasma exchange combined with immunosuppressive therapy to prevent IgM flare.

Extranodal marginal zone lymphoma is a category of marginal zone B-cell lymphomas found outside the spleen and lymph nodes. It is commonly located in the stomach; however, it can also be found in the thyroid, skin, and lungs. It is suspected that chronic inflammation from infectious or autoimmune conditions leads to repetitive immune stimulation and the development of lymphoma. Important infectious associations include *H. pylori* in gastric EMZL, *Chlamydia psittaci* in ocular EMZL, *Achromobacter xylosoxidans* in lung EMZL, and *Borrelia burgdorferi* in skin EMZL. Autoimmune conditions encountered in association with EMZL include Sjögren syndrome in salivary gland EMZL and Hashimoto thyroiditis in thyroid EMZL.

Extranodal marginal zone lymphoma may be asymptomatic and incidentally diagnosed; however, it can be manifested with symptoms related to the area of presentation (ie, dyspepsia in gastric EMZL). In gastric EMZL, if *H. pylori* is not confirmed on...
biopsy, breath test or stool antigen should be pursued as infection is seen in 85% to 90% of gastric EMZL. In association with H. pylori, EMZL can be treated with antibiotics and proton pump inhibitors. Eradication of H. pylori should be confirmed 6 weeks after antibiotic treatment and 2 weeks after discontinuation of the proton pump inhibitor. After eradication of H. pylori, it can take up to 1 year to achieve remission of EMZL. If there is residual disease at 1 year after antibiotic treatment (or 3 to 6 months in H. pylori–negative cases), alternative treatment should be pursued. Radiation therapy is recommended for localized disease with a response rate of more than 90%, whereas chemotherapy, immunotherapy, or a combination is typically preferred for systemic disease. Proposed chemotherapy and immunotherapy regimens include bendamustine, chlorambucil, and rituximab, used as single agents or in various combinations. Outcomes in EMZL are favorable with an estimated 5-year overall survival of 86% to 95%.

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REFERENCES


CORRECT ANSWERS: 1. e, 2. d, 3. a, 4. a, 5. c.