

IgM Gammopathy: Review Questions

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QUESTIONS

Choose the single best answer for each question.

Questions 1 to 3 refer to the following case.

A 60-year-old man presents to his physician for a routine physical examination. Laboratory testing reveals a total serum protein level of 8.7 g/dL (normal, 6.0–8.0 g/dL). Hemoglobin, white blood cell count, platelet count, and serum calcium level are normal. Serum protein electrophoresis with immunofixation confirms the presence of IgM- κ M-protein with a titer of 1.8 g/dL. The patient denies headaches, vision changes, early satiety, weight loss, or numbness/tingling in his fingers or toes. Physical examination reveals no lymphadenopathy or hepatosplenomegaly.

1. What is the next step in this patient's management?
 - (A) Bone marrow biopsy
 - (B) Close serial monitoring
 - (C) Computed tomography (CT) of the chest, abdomen, and pelvis
 - (D) Initiation of chemotherapy
2. Three years later, the patient develops normocytic anemia (hemoglobin, 9.2 g/dL), modest adenopathy, and uncomfortable splenomegaly. He has lost 14 lb over the past 5 months. The IgM level has increased to 4.8 g/dL. A bone marrow biopsy confirms 18% involvement by monoclonal lymphoplasmacytic lymphocytes. A direct Coombs' test is mildly positive. Which of the following is the most appropriate next step in this patient's management?
 - (A) Chlorambucil or another alkylating agent
 - (B) Combination chemotherapy
 - (C) Continued observation
 - (D) Fludarabine or another purine analogue
 - (E) Prednisone 1 mg/kg/day
3. The patient responds to initial therapy, but lymphadenopathy progresses 25 months later. The IgM level increases to 6.2 g/dL. Treatment with rituximab, an anti-CD20 antibody, is initiated. Four days after receiving therapy, the patient returns complaining of headache and blurry vision. Eye examination confirms the presence of small bilateral retinal hemorrhages. What is the most appropriate next step?
 - (A) Initiate purine analogue therapy
 - (B) Ophthalmology referral for retinal laser treatments
 - (C) Urgent CT scan of the brain
 - (D) Urgent initiation of plasmapheresis
4. A 77-year-old nonsmoking woman develops new-onset Raynaud's phenomenon. A thorough evaluation reveals no palpable peripheral lymphadenopathy or hepatosplenomegaly, mild anemia (hemoglobin, 10.1 g/dL), and a normal platelet count. Antinuclear antibody (ANA), rheumatoid factor (RF), and Coombs' tests are negative. A viral hepatitis panel is negative. Serum protein electrophoresis with immunofixation reveals a normal total serum protein level and a faint monoclonal IgM band (titer, 0.4 g/dL). What is this patient's most likely diagnosis?
 - (A) Hyperviscosity syndrome
 - (B) Mixed connective tissue disease
 - (C) Thromboangiitis obliterans (Buerger's disease)
 - (D) Type I cryoglobulinemia
 - (E) Type II (mixed) cryoglobulinemia
5. A 47-year-old woman presents with symmetrical numbness and tingling in her hands and feet, which has progressed over the last year. The patient works full-time as a dental hygienist, and her symptoms have led to difficulties at work. She denies associated pain or weakness and has not noticed unusual bruising or bleeding, rash, or back pain. There has been no change in her appetite or weight. Physical

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examination reveals subjective soft touch deficits in a stocking glove distribution, which are most severe distally. Strength and reflexes are normal. Her tongue, optic fundi, heart, and lungs are normal, and there is no peripheral adenopathy or organomegaly. Laboratory testing reveals a normal complete blood count, normal renal and liver function, a normal erythrocyte sedimentation rate, and a monoclonal IgM- κ level of 1.1 g/dL with normal levels of IgG and IgA. ANA and Coombs' tests are negative. A hepatitis panel and HIV test are negative. Radiographs of the spine do not reveal disc space narrowing or lytic or sclerotic lesions. What is the cause of this patient's symptoms?

- (A) Anti-myelin-associated glycoprotein (anti-MAG) antibodies
- (B) Guillain-Barré syndrome
- (C) Myeloma-associated amyloidosis
- (D) POEMS syndrome
- (E) Waldenström's macroglobulinemia (WM)

ANSWERS AND EXPLANATIONS

1. **(B) Close serial monitoring.** This patient almost certainly has IgM monoclonal gammopathy of uncertain significance (MGUS), defined as the presence of monoclonal IgM (< 3 g/dL); bone marrow with less than 10% involvement by CD10⁻, CD20⁺, CD23⁻, CD138⁻ lymphoplasmacytic lymphocytes; and no evidence of end-organ damage (eg, anemia, hepatosplenomegaly, serum hyperviscosity, B symptoms [fever, weight loss, night sweats], adenopathy). Patients with IgM MGUS have an approximate 46-fold increased risk of developing WM compared with the general population.¹ Although a bone marrow biopsy or CT scan may reveal greater than 10% marrow infiltration or modest enlargement of lymph nodes or the spleen, this would not change management if symptoms are absent. Patients with asymptomatic ("smoldering") WM may be followed for years in some cases without intervention. In patients with significant symptoms, systemic chemotherapy would not be started until the diagnosis was confirmed by immunohistologic testing or flow cytometry.
2. **(A) Chlorambucil or another alkylating agent.** This patient has developed symptomatic WM requiring therapy. Given the severity of this patient's symptoms, observation alone would be inappropriate. With anemia and a positive Coombs' test in this patient, cold agglutinin syndrome² or warm antibody-mediated autoimmune hemolytic anemia (AIHA) should be considered. Although fludarabine or other purine analogues are used to treat WM, a patient with a positive baseline Coombs' test may be at risk for a life-threatening exacerbation of AIHA following treatment with these agents, as has been described in patients with chronic lymphocytic leukemia.³ Chlorambucil would be a reasonable alternative, as up to 60% of patients with WM respond to this therapy.² Compared with chlorambucil monotherapy, treatment with multidrug combinations does not improve outcomes and may increase toxicity. Prednisone 1 mg/kg/day would likely be helpful for treatment of AIHA but would not adequately address the patient's other symptoms, such as splenomegaly.
3. **(D) Urgent initiation of plasmapheresis.** Symptomatic hyperviscosity is a medical emergency, and immediate initiation of appropriate therapy is critical. This patient has developed classic symptoms of hyperviscosity syndrome, which can include headache, mental status changes, dizziness, nystagmus, retinal hemorrhages, and, less commonly, congestive heart failure or respiratory compromise. Symptoms frequently develop when serum viscosity is greater than 5 centipoise, as may be observed following an acute increase of an already elevated IgM level. Urgent plasmapheresis is indicated to rapidly lower the IgM level (and thus serum viscosity). If the serum viscosity level is not immediately available, patients with strongly suggestive symptoms should be treated empirically. A relatively small decrease in serum IgM can result in a large change in viscosity and dramatic symptom improvement. An ophthalmologic consultation with retina-directed therapy would not treat the underlying problem. Although patients with WM can develop symptoms due to central nervous system involvement (Bing-Neel syndrome), this is sufficiently rare as to obviate the need for a head CT until the possibility of hyperviscosity has been addressed. This patient most likely developed symptomatic hyperviscosity due to a transient increase in the IgM level following therapy with rituximab. The IgM level may initially increase in approximately 40% of patients with WM treated with rituximab, but some patients will subsequently respond to therapy.⁴ Therefore, it is too early to conclude that this patient will not respond to rituximab, and therapy should not be changed.
4. **(D) Type I cryoglobulinemia.** This patient's cold-related vaso-occlusive symptoms and the presence of a monoclonal IgM strongly suggest cryoglobulinemia. Type I cryoglobulins can be either monoclonal IgG or

IgM and are commonly associated with lymphoproliferative disorders, and occult lymphoma needs to be considered even in the absence of palpable adenopathy or hepatosplenomegaly. The patient's IgM titer is relatively low, so there is no reason to suspect hyperviscosity as the cause of this patient's symptoms. Type II cryoglobulins, often seen in chronic hepatitis C infection, are IgM proteins with RF-like factor activity and immunoreactivity against polyclonal IgG. The negative RF test and negative viral hepatitis panel in this patient indicate that type I cryoglobulinemia is more likely.⁵ The negative ANA and RF tests essentially rule out a mixed connective tissue disorder as the underlying cause of this patient's Raynaud's. The patient's older age, female gender, lack of smoking history, and presence of Raynaud's phenomenon without claudication or digit ulcers effectively rule out thromboangiitis obliterans.

5. (A) **Anti-MAG antibodies.** This patient's symptoms of distal peripheral sensory neuropathy are strongly suggestive of the demyelinating condition caused by IgM MGUS with anti-MAG reactivity. Anti-MAG antibodies are the most common form of antineuronal autoantibodies. Other types include antisulfoglucuronyl paragloboside, antiganglioside (GM1 and GM2), and antidisialosyl ganglioside (GD1b and GT1b) antibodies.⁶ Although up to half of patients with WM may have some degree of peripheral neuropathy (occasionally due to anti-MAG specificity of the WM M-protein), only 10% of patients with an antineuronal antibody are subsequently found to have an underlying lymphoproliferative condition.⁶ The absence of lymphadenopathy, abnormal blood

counts, or organomegaly makes WM unlikely. There are also no findings to suggest myeloma, which is almost never associated with an IgM M-protein. Amyloidosis, a plasma cell dyscrasia usually associated with self-aggregating λ light chains, could be a consideration. If the patient had symptoms of congestive heart failure, tongue enlargement, renal dysfunction, or easy bruising often associated with amyloidosis, a fat pad aspirate with Congo red staining would be appropriate, but this is not the case in this patient. Guillain-Barré syndrome typically presents as an acute-onset, rapidly progressive, ascending motor neuropathy without significant sensory loss. The patient does not have findings to suggest POEMS syndrome (Polyneuropathy, Organomegaly, Endocrinopathy, M-protein [usually λ -restricted IgG or IgA, in contrast to the IgM- κ seen in this patient], and Skin changes/sclerotic bone lesions). At a minimum, a diagnosis of POEMS syndrome requires polyneuropathy, a plasmaproliferative process, and 1 other criterion included in the acronym "POEMS" or concurrent Castleman disease.

REFERENCES

1. Fonseca R, Hayman S. Waldenström macroglobulinaemia. *Br J Haematol* 2007;138:700-20.
2. Johnson SA, Birchall J, Luckie C, et al; Haemato-Oncology Task Force of the British Committee for Standards in Haematology. Guidelines on the management of Waldenström macroglobulinaemia. *Br J Haematol* 2006;132:683-97.
3. Weiss RB, Freiman J, Kweder SL, et al. Hemolytic anemia after fludarabine therapy for chronic lymphocytic leukemia. *J Clin Oncol* 1998;16:1885-9.
4. Treon SP, Branagan AR, Hunter Z, et al. Paradoxical increases in serum IgM and viscosity levels following rituximab in Waldenström's macroglobulinemia. *Ann Oncol* 2004;15:1481-3.
5. Tedeschi A, Barate C, Minola E, Morra E. Cryoglobulinemia. *Blood Rev* 2007;21:183-200.
6. Lozeron P, Adams D. Monoclonal gammopathy and neuropathy. *Curr Opin Neurol* 2007;20:536-41.

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