Diagnosis and Management of Immunoglobulin Light Chain Amyloidosis

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QUESTIONS
1. A 67-year-old Caucasian woman who never smoked presents with a 3-week history of hoarseness of voice. Laryngoscopy reveals decreased mobility of the right vocal cord due to a 0.5-cm submucosal nodule. Biopsy of the lesion demonstrates extracellular amorphous material staining positive with Congo red with apple green birefringence under polarized light. Immunohistochemistry and laser capture mass spectrometry examination of the congophilic material confirm immunoglobulin lambda light chain as the precursor protein. She has no signs or symptoms of systemic disease, and the blood work does not demonstrate any evidence of clonal plasma cell dyscrasia. What is the next step in management?
   A. Referral for endoscopic laser treatment
   B. Bone marrow biopsy
   C. Fat pad biopsy
   D. Initiation of melphalan and dexamethasone
   E. Refer for high-dose melphalan therapy and autologous stem cell rescue

Questions 2 and 3 pertain to the following case:

A 58-year-old Caucasian man presents to the emergency department with a 1-week history of hematuria and epistaxis. For the past 3 months he has noticed fatigue and progressive swelling of his legs. Physical examination demonstrates a normotensive male with generalized purpura and ecchymoses, nondistended jugular veins, clear chest to auscultation, regular heart rhythm, mild hepatosplenomegaly, and 3+ pitting edema in both lower extremities extending up to the knees. The stool guaiac test is positive for occult blood. Having read a recent article on amyloidosis, you suspect the diagnosis and order the appropriate workup. The workup demonstrates mild anemia, serum creatinine of 1.3 mg/dL, severe hypoalbuminemia, and elevated lambda free light chains with abnormal kappa-lambda ratio. Protein electrophoresis and immunofixation of serum identifies a small IgG lambda and lambda light chain clonal gammopathy, and 24-hour urine studies demonstrate 6 g of proteinuria, with 85% of urinary protein being albumin. The coagulation profile demonstrates prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), and mixing studies show immediate correction of both PT and aPTT. You order a fat pad aspiration and biopsy that confirms the presence of amyloidosis.

2. What is the most likely cause of this patient’s bleeding diathesis?
   A. Acquired factor X deficiency
   B. Abnormal platelet aggregation
   C. Factor II deficiency
   D. Amyloid infiltration of blood vessels

3. The diagnosis of AL amyloidosis is confirmed and the patient is diagnosed with stage I cardiac disease. He elects to proceed with high-dose chemotherapy and autologous stem cell rescue. However, he continues to have mucocutaneous bleeding and requires frequent transfusion of fresh frozen plasma (FFP). What should be done next?
   A. Continue FFP transfusions, add aminocaproic acid, and proceed with the stem cell transplant
   B. Proceed with stem cell transplant as the bleeding will improve with chemotherapy
   C. Perform splenectomy and then proceed with stem cell transplant after coagulopathy improves
   D. Inform the patient that he is not a candidate for stem cell transplant

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4. A 55-year-old African-American man presents with increasing shortness of breath for the past 2 months. He has had multiple hospitalizations in the past 3 years for congestive heart failure, and previous workup including cardiac catheterization has been negative. Physical exam reveals increased jugular venous distension, S₄ gallop, bibasilar crackles, and 2+ pitting edema of the lower extremities. Cardiac evaluation includes an echocardiogram, which shows a restrictive cardiomyopathy and a “granular sparkling” appearance of the myocardium with an interventricular septum thickness of 2.2 cm. Laboratory tests reveal a troponin-T level of 0.05 µg/L, N-terminal pro-B-type natriuretic peptide (NT-proBNP) of 1000 pg/mL, an Ig kappa monoclonal gammopathy with M-spike of 0.3 g/dL, and elevated kappa free light chains in serum with elevated kappa-lambda ratio. Bone marrow biopsy reveals 5% atypical plasmacytosis. Fat pad biopsy reveals perivascular amyloid deposition. What is the next best step in management?

A. Management of congestive heart failure and then melphalan and dexamethasone therapy
B. Management of congestive heart failure and then autologous stem cell transplant
C. Proteomic analysis of the congophilic material with mass spectrometry
D. Referral for cardiac transplant

5. A 48-year-old African American man presents to the emergency department with new-onset slurred speech and weakness of the right upper extremity. A noncontrast computed tomography scan of the head is negative for intracranial bleed, and magnetic resonance imaging with stroke protocol demonstrates acute ischemic stroke in the left middle cerebral artery territory. The patient is started on systemic anticoagulation and aspirin. Four hours after starting anticoagulation, his stroke symptoms resolve. The patient has been previously healthy and works as a fitness trainer. Two-dimensional echocardiogram reveals severe left ventricular systolic dysfunction with an ejection fraction of 40% and sparkling appearance of thickened myocardium and an interventricular septum thickness of 1.6 cm. A transesophageal echocardiogram demonstrates absence of mechanical activity in the left atrium (atrial stand still) and a mural thrombus. Blood work demonstrates normal electrolytes, liver function tests, and complete blood count. Serum protein electrophoresis demonstrates a 1.0 g/dL M-spike identified as IgG lambda on immunofixation electrophoresis. Serum free light chain assay demonstrates lambda light chain levels of 38 mg/dL (normal, <2.6 mg/dL) and a skewed Kappa-lambda ratio. Fat pad aspirate biopsy demonstrates congophilic amyloid material. Bone marrow biopsy demonstrates 10% lambda restricted plasma cells. Cardiac biomarkers are indicative of stage III disease. Mass spectrometry confirms the amyloidosis as AL. Clinical and biochemical assessment indicates cardiac involvement only.

What is the best management plan for this patient?

A. Continue anticoagulation and proceed with high-dose therapy and stem cell transplant
B. Inform the patient about dismal prognosis and recommend hospice
C. Recommend standard chemotherapy with melphalan and dexamethasone
D. Recommend treatment with a bortezomib-based regimen as a bridge to cardiac transplant followed 6 months later by stem cell transplant

ANSWERS

1. The correct answer is (A), Referral for endoscopic laser treatment. This patient presented with vocal cord dysfunction due to localized amyloidoma. Localized amyloidosis is most commonly seen in the head and neck region and is most commonly of the immunoglobulin light chain (AL) type. It is characterized by local production of amyloidogenic light chains by the plasma cells. The diagnosis involves histologic confirmation by biopsy. Localized AL can also involve skin and mucosal surfaces of the genitourinary tract. It is treated by local interventions such as surgical resection, laser ablation, or localized radiation therapy. Patients can have localized recurrences that may require re-treatment, depending upon its location and symptoms. Localized AL almost never evolves into a systemic process and therefore does not require systemic therapy.¹²

References

2. **The correct answer is (A), Acquired factor X deficiency.** This patient presented with classic nephrotic syndrome, one of the most common manifestations of AL amyloidosis. Bleeding diathesis occurs in a significant number of patients with AL amyloidosis, with some series noting an abnormal coagulation profile in up to 50% of patients. It is pertinent to note that this patient has occult blood in his stool; gastrointestinal bleeding can be a major cause of morbidity and mortality in these patients. The bleeding diathesis in AL amyloidosis results from a multitude of factors, including loss of structural integrity of the vessel wall due to amyloid infiltration, resulting in poor vasoconstrictive response, as well as acquired coagulation defects, particularly deficiency of factor X as a result of binding to amyloid protein. This patient’s clinical picture is clearly consistent with factor deficiency, as mixing studies demonstrated correction of both PT and aPTT. Since factor X is part of the final common pathway in the coagulation cascade, its deficiency results in prolongation of both PT and aPTT. Abnormal platelet aggregation and factor II deficiency are not commonly seen in AL amyloidosis.

**Reference**

3. **The correct answer is (C), Perform splenectomy and then proceed with stem cell transplant after coagulopathy improves.** Because this patient has early-stage disease, high-dose chemotherapy can have a significant impact on his survival and quality of life and as such is a very important consideration. One of the main differences between stem cell transplantation for AL amyloidosis versus other diseases is the high incidence of bleeding complications, and in particular gastrointestinal bleeding, in the former. This patient is clearly at very high risk of bleeding complications, including significant risk of mortality. Clinical experience has suggested that AL amyloidosis patients with factor X deficiency can benefit from splenectomy because splenic amyloid deposits are thought to be the major site of consumption of factor X. In this case, splenectomy with full supportive care may significantly improve the bleeding diathesis and thereby allow stem cell transplantation to be done safely.

**References**

4. **The correct answer is (C), Proteomic analysis of the congophilic material with mass spectrometry.** This patient has a classic clinical presentation of congestive heart failure and evidence of diastolic dysfunction. Echocardiography findings are suggestive of infiltrative cardiomyopathy, possibly resulting from amyloidosis. The diagnosis of amyloidosis was confirmed on abdominal fat pad biopsy. Given the finding of IgG lambda monoclonal gammopathy, it is very tempting to make the diagnosis of primary systemic, or AL, amyloidosis. However, monoclonal gammopathy of undetermined significance can be seen in patients with non–AL amyloidosis. This particular patient is a relatively young African American male who has been having these symptoms for the past 3 years; these features go against the diagnosis of AL amyloidosis. Approximately 3.5% of African-Americans have the Val122Ile mutation in the trans-thyretin gene, which can give rise to late-onset amyloid cardiomyopathy. Therefore, it is imperative to be certain of the type of amyloid protein to plan the next step of management and inform the patient of the prognosis.

**References**

5. **The correct answer is (D), Recommend treatment with a bortezomib-based regimen as a bridge to cardiac transplant followed 6 months later by stem cell transplant.** This patient presented with acute embolic stroke from left atrial mural thrombus. Typically, systolic function is preserved in AL cardiomyopathy; however, in some cases toxic amyloidogenic light chains can cause significant myocardial dysfunction with decreased ejection fraction. This patient has acute stroke and advanced cardiac involvement, and therefore stem cell transplant is contraindicated. Almost all patients with AL amyloidosis benefit from systemic
therapy, with improvement in symptoms and quality and duration of life; therefore, it is not appropriate to recommend hospice at this stage. Given his young age and no significant extra-cardiac involvement, he is a potential candidate for cardiac transplantation. Cardiac transplantation in AL amyloidosis has a generally poor outcome unless it is followed by high-dose chemotherapy and stem cell transplant. The best option would be supporting him with anti-plasma cell therapy as a bridge to cardiac transplant, and then performing stem cell transplant after heart transplant. The choice of initial therapy is influenced by the decision to proceed with stem cell transplant because melphalan-containing regimens are toxic to stem cells and negatively impact the mobilization and collection of autologous stem cells.¹

Reference