

# Primary Systemic Amyloidosis: Review Questions

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## QUESTIONS

Choose the single best answer for each question.

All of the questions refer to the following case.

At his first visit with a hematologist, a 68-year-old Caucasian man states that he has been diagnosed with amyloidosis, but he is unsure of which type. The diagnosis was made after he developed peripheral sensory neuropathy, tongue enlargement, and intestinal malabsorption. He also reports recent onset of dyspnea and orthopnea.

- 1. Which of the following would be the best test to confirm whether this patient has primary systemic (AL) amyloidosis?**
  - (A) Congo red staining of fat pad aspirate
  - (B) Serum and urine protein electrophoresis with immunofixation
  - (C) Echocardiography
  - (D)  $\kappa/\lambda$  Immunostaining of tissue amyloid deposits
  - (E) Transthyretin mutation analysis
- 2. After the diagnosis of AL-amyloidosis is confirmed, the patient undergoes an echocardiogram, which reveals a thickened ventricular septal wall, impaired diastolic relaxation, and a left ventricular ejection fraction of 35%. Which of the following would be the best choice of initial therapy?**
  - (A) 5-Drug combination chemotherapy regimen (VBMCP)
  - (B) Melphalan and prednisone (MP)
  - (C) Colchicine
  - (D) MP and colchicine
  - (E) High-dose thalidomide
- 3. After initiating treatment, the patient returns for routine follow-up and states that several acquaintances from a local amyloidosis support group were treated with high-dose melphalan and autologous stem cell transplant (ASCT). He asks whether this therapy might be appropriate for him. Which of the following statements regarding ASCT for amyloidosis is correct?**
  - (A) There have been no randomized trials demonstrating improved survival following ASCT versus conventional nontransplant therapy
  - (B) Treatment-related mortality is similar to that in multiple myeloma
  - (C) This patient's amyloid-related cardiac dysfunction does not have prognostic significance in relation to ASCT as long as symptoms are well-controlled with medications
  - (D) Prior chemotherapy precludes further consideration of ASCT because stem cell collection will be problematic
  - (E) ASCT cannot be considered in this case because the patient is older than 65 years
- 4. The patient responds to initial therapy, but 8 months later develops progressive weight gain, lower extremity edema, anasarca, ascites, and hypotension. On examination, no jugular venous distention is observed, but the liver is enlarged. What is the most likely cause of these findings?**
  - (A) Hepatic amyloid deposition with resultant portal hypertension
  - (B) Renal amyloid deposition with resultant nephrotic syndrome
  - (C) Splenic amyloid deposition with capsular rupture and bleeding
  - (D) Cardiac amyloid deposition with resultant right-sided heart failure
  - (E) Vascular wall amyloid deposition with resultant deep vein thrombosis

(turn page for answers)

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## ANSWERS AND EXPLANATIONS

### 1. (D) $\kappa/\lambda$ Immunostaining of tissue amyloid deposits.

When AL-amyloidosis is suspected, a tissue biopsy is required to establish the diagnosis. Congo red staining of a fat pad aspirate would reveal amorphous tissue deposits that appear pink using standard light microscopy and apple green under polarized light, but this test does not distinguish between AL, acquired, and familial/inherited subtypes of amyloidosis. In AL-amyloidosis, a plasma cell dyscrasia, the amyloid fibrils are composed of monoclonal light chains (usually  $\lambda$ ). Performing both serum and urine protein electrophoresis with immunofixation reveals a monoclonal light chain in over 90% of patients with AL-amyloid but does not eliminate the need for  $\kappa/\lambda$  immunostaining of tissue amyloid deposits. Without confirming the Ig origin of the amyloid, one cannot rule out the possibility of another type of amyloidosis with an incidentally discovered monoclonal gammopathy of uncertain significance.<sup>1</sup> An inherited form of predominantly cardiac amyloidosis resulting from a specific transthyretin mutation has been described in older African Americans. In this Caucasian patient, this diagnosis is unlikely.

2. (B) **MP.** Oral MP is the best therapy choice for this patient. Colchicine alone is inferior to MP, and adding colchicine to MP does not improve efficacy.<sup>2</sup> Although hematologic improvement (ie, reduction in the monoclonal protein level) almost never results in immediate improvement in organ dysfunction caused by prior amyloid deposition, patients who have a sustained hematologic response are more likely to eventually have organ function improvement. VBMCP and other combination regimens do not improve response rates significantly but do add toxicity. Thalidomide is poorly tolerated at high doses because it can cause progressive edema, cognitive difficulties, and constipation as well as aggravate preexisting peripheral neuropathy.<sup>3</sup>

3. (A) **There have been no randomized trials demonstrating improved survival following ASCT versus conventional nontransplant therapy.** High-dose melphalan and ASCT, with its higher likelihood of inducing a hematologic response compared with conventional therapy, may be the treatment of choice in highly selected patients with good organ function. However, no randomized study has demonstrated that this results in improved survival. Two cycles of oral MP therapy do not significantly impact subsequent stem cell collection. Older age is not a contraindication to ASCT, but performance status should be carefully considered. Patients with cardiac dysfunction

from amyloidosis have inferior survival, regardless of treatment with ASCT or conventional regimens.<sup>4</sup> Treatment-associated mortality in patients undergoing ASCT for amyloidosis (even at the most experienced centers) is 10% to 15%, far in excess of what is reported for myeloma patients undergoing ASCT utilizing the same conditioning regimen.

### 4. (B) **Renal amyloid deposition with resultant nephrotic syndrome.**

Glomerular injury and resultant nephrotic syndrome is the most likely explanation for this patient's clinical deterioration. Hypoalbuminemia results in reduced serum oncotic pressure and subsequent fluid shifts into the extravascular space with associated orthostatic symptoms. Right-sided cardiac failure, if severe enough to cause this degree of edema, would likely be associated with jugular venous distention. A 24-hour urine collection to assess the degree of proteinuria and an echocardiogram should provide enough diagnostic information to distinguish between renal and cardiac causes of this patient's symptoms. Loop diuretics and midodrine can be used cautiously to treat symptoms related to edema and orthostatic hypotension, respectively. Because each of these medications has the potential to exacerbate symptoms being treated with the other drug, careful clinical monitoring is essential. Hepatic enlargement is likely to be caused by amyloid deposition rather than vascular congestion. Hepatic amyloidosis rarely causes portal hypertension, as patients typically succumb to other complications of their disease prior to reaching that point. Splenic amyloidosis typically results in splenomegaly but rarely capsular rupture (which would not explain the lower extremity edema). Amyloid deposition in the vasculature typically results in minor bleeding and bruising rather than thrombotic complications.

## REFERENCES

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