CLINICAL VIGNETTE

Senile Amyloidosis

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An 85-year-old male presented with worsening shortness of breath. He had pneumonia with subsequent fatigue and dyspnea on exertion. Given persistent symptoms over the next six months, he saw a pulmonologist who ordered a Computed Tomography (CT) of the chest. The scan showed large and small subpleural irregular soft tissue masses with evidence of invasion into the surrounding pulmonary parenchyma and into the adjacent fat plane. The appearance was non-specific but active infection, granulomatous disease, or malignancy were all in the differential. Biopsy of one of the lung lesions demonstrated amyloidosis that stained prominently with the Congo red stain. There was scar tissue and patchy, chronic inflammation and foreign material resembling a prior suture. He underwent coronary artery bypass graft surgery many years prior and it was complicated by a bleeding vessel and required further cardiothoracic surgery. The amyloid stained focally for albumin suggesting transthyretin (TTR)- associated amyloidosis but given the lack of specificity the pathology was sent to Mayo Clinic. No amino acid sequence abnormality in the TTR protein was noted. This was consistent with age-related amyloidosis. Given the diagnosis of amyloidosis, the patient was referred for oncologic evaluation.

The patient was elderly appearing but otherwise in no distress. Vital signs and physical exam were unremarkable, including no organomegaly or lymphadenopathy. Beyond shortness of breath and dyspnea with exertion, he reported no other symptoms.

Amyloidosis has three important classifications: 1) light chain (AL) amyloidosis, 2) hereditary TTR amyloidosis, and 3) wild-type or senile amyloidosis. It is imperative to distinguish the subtype as treatment varies for each. Congo red staining will be seen in all. AL amyloidosis will note light chain deposition and is a plasma cell dyscrasia. Senile amyloidosis will have deposition of normal TTR. However, in hereditary TTR amyloidosis, genetic evaluation will note mutations in the TTR gene. In AL amyloidosis, treatment includes therapy similar to multiple myeloma. Hereditary amyloidosis may require aggressive management such as liver transplantation to reduce the risk of further deposition. In contrast, senile amyloidosis does not require further treatment and will be discussed in more depth below.

As the name suggests, the risk of senile amyloidosis increases with age.[1,2] Given the non-specific symptoms that can be confused with the aging process, the disease is likely underdiagnosed and usually noted post-mortem.[1,2] In the past, it was felt to have no clinical consequences, but further investigations suggest that it may be a factor in many elderly patients with heart failure.[2] However, with a growing elderly population and increasing studies addressing the disease process, it likely will be more commonly recognized going forward.[2] For example, patients with non-valvular atrial arrhythmias may warrant more aggressive evaluation since reports have noted up to two-thirds of senile amyloidosis patients with these arrhythmias at time of diagnosis.[2] There does seem to be a male preponderance for this disease.[1,2] It is a slowly progressive disease.[1,2] Deposition of wildtype TTR frequently occurs on the heart but has been noted in the carpal tunnel, lungs, bladder, kidneys, etc.[1] One report noted in their case series that almost half of patients presented with carpal tunnel syndrome years prior to any notation of heart failure.[1] Survival seems to be better in senile amyloidosis compared to cardiac AL amyloidosis, further emphasizing the slowly progressive disease process.[1] One group found that troponin and BNP values could help prognosticate for clinical outcomes.[2]

While cardiac imaging is improving, the diagnosis is best made by biopsy showing the transthyretin amyloid and wild-type TTR noted on gene sequencing.[1] Fat pad biopsy can be helpful to diagnosis other subtypes of amyloidosis, but data suggests that false negatives are not infrequent with senile amyloidosis.[1] Laboratory testing for a monoclonal gammopathy is often performed given familiarity with the plasma cell dyscrasia. However, this finding may be misleading in an elderly population that not uncommonly has a coincident diagnosis of monoclonal gammopathy of undetermined significance (MGUS).

On labs, the patient above had some evidence of chronic kidney disease (CKD) with a creatinine of 1.3. His blood counts showed a mild anemia of 13.2g/dL but no other cytopenias. Serum protein electrophoresis showed an Mspike of 1.0 g/dL and was IgM lambda on immunofixation. Immunoglobulin M was 1787mg/dL and immunoglobulin G (IgG) and immunoglobulin A were normal. Beta-2-microglobulin was unreliable given his CKD. His kappa and lambda light chains were mildly elevated but the ratio was normal. His 24-hour urine showed trace IgG kappa.

While the patient was noted to have a monoclonal gammopathy, it was most consistent with MGUS and not unexpected in this octogenarian. In fact, the monoclonal gammopathies on serum versus urine did not match. His lung biopsy indicated that he

had senile amyloidosis. Echocardiogram showed evidence of pulmonary hypertension, indicating likely cardiac involvement, but the patient was a poor candidate for cardiac biopsy. While amyloid deposition can still have clinical ramifications such as cardiopulmonary issues as seen in this patient, there are no current viable treatments.[1,2] Thus, the patient was referred to cardiology and pulmonary for supportive care of his pulmonary hypertension, worsening congestive heart failure, and shortness of breath. His labs on rechecks remained stable over the next year although clinically his shortness of breath progressed.

REFERENCES

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