CLINICAL VIGNETTE

Primary Amyloidosis: A Case Report and Review

Nathan Cox, M.D., and Digish Shah, M.D.

Introduction

Amyloidosis is a syndrome involving extracellular fibril deposition in various tissues. Pathology stems from type, location, and amount of fibril deposition. There are at least 30 different human and 10 different animal precursors of amyloid fibrils known, leading to a wide variety of clinical disorders with significant variability of frequency, severity, and disease manifestation.[1] Clinical manifestations of amyloid deposition can involve essentially any organ system: patients can present with any combination of renal, cardiac, gastrointestinal, neurologic, pulmonary, hematologic, dermatologic, and/or musculoskeletal symptoms. We present a case of a previously healthy, middle-aged man presenting with vague generalized gastrointestinal and renal symptoms, who was ultimately discovered to have primary light chain amyloidosis with multi-organ involvement.

Case Report

A 49-year-old male with no significant past medical history presented with a 7-month history of unintentional weight loss, fatigue, diarrhea, nausea with vomiting, and anorexia. His symptoms began with unintentional weight loss of 45 pounds, beginning 7 months prior to presentation. A few weeks later, he began to note diarrhea occurring up to 6 times daily, for about 3-4 days weekly. He described the stool as loose and watery without visible blood or mucous. Around this time, he also developed intermittent postprandial nausea and vomiting. This occurred with increasing frequency over the next 7 months. Three months prior to presentation, the patient began to note generalized fatigue accompanied at times with vague myalgias involving his arms and shoulders most prominently. He also noted significant early satiety, and his oral intake gradually decreased.

The patient, who had regular physician for many years, sought evaluation with a new primary care physician 3 weeks prior to his hospital presentation. Initial workup was notable for a serum creatinine of 2.5 mg/dL. This finding, in combination with the ongoing and progressive symptoms, prompted him to present to the emergency department for further evaluation.

In the emergency department, the patient was afebrile and otherwise hemodynamically stable. Initial labs were notable for a serum creatinine of 3.1 mg/dL, blood urea nitrogen of 52 mg/dL, bicarbonate of 19 mg/dL, a normocytic anemia, and hemoglobin 10.0 g/dL.

The patient was admitted for further evaluation. The differential diagnosis was initially broad, including consideration for malignant, infiltrative, and infectious disorders. Gastroenterology and nephrology consultations were obtained. The patient was given intravenous hydration with improvement of serum creatinine to his baseline of 2.5 mg/dL. Extensive serologic workup was notable only for elevated kappa/lambda light chain ratio, but there was no monoclonal spike. The patient underwent upper endoscopy and colonoscopy with no gross abnormalities noted. Biopsies were taken. He was placed on a lactose-free diet with some marginal improvement of his diarrhea. Given his overall stability, he was discharged home to outpatient follow-up.

Shortly following discharge, pathology from endoscopy demonstrated diffuse amyloid involvement in the duodenum, cecum, descending colon, and rectum. He was promptly referred to hematology for further evaluation and treatment. He underwent bone marrow biopsy, which confirmed primary light chain amyloidosis. Over the next three months, the patient also began to note progressive dyspnea on exertion. Cardiac evaluation, ultimately including endomyocardial biopsy, revealed cardiac involvement with amyloid.

He was initiated on a regimen involving cyclophosphamide, bortezomib, and dexamethasone. On this regimen, his symptoms remained generally stable with some minimal weight gain. His serum creatinine slowly increased to a new baseline of 3 mg/dL. Given multi-organ involvement, he was not considered a candidate for bone marrow transplantation.

Discussion

Pathology: Amyloidosis is a general term referring to a syndrome involving the extracellular deposition of insoluble fibrils, which are polymers comprised of a variety of low molecular weight proteins often circulating within blood plasma. There are 30 known human and 10 animal precursors of amyloid fibrils, each with a different specific mechanism of amyloid formation.[1] Mechanism of amyloid formation is an area of extensive and active study, and many different causes for fibril formation have been discovered. Fibril formation appears to involve either destabilization of a “normal” protein (such as by exposure to abnormal proteolysis, as could occur in certain disease states), or by gradual fibrillization of an “abnormal” protein (made “abnormal” by point mutations, deletions, or other inherent structural abnormalities).[2,3]

Ultimately, amyloid fibrils themselves are polymers composed of these protein precursors. As a result of these varying mechanisms, some types of amyloidosis are primary pathologies (developing slowly over time, seemingly as a primary process), while others occur only when a patient is exposed to certain stressors such as in the setting of a specific disease states.

Despite the wide variety of precursor proteins known, the amyloid fibrils themselves classically adopt anti-parallel beta-pleated sheet configuration when viewed on x-ray diffraction once formed.[4] This similar ultimate configuration leads to the clinical ability to recognize amyloid via pathologic examination: on Congo red staining, amyloid tissue exhibits apple-green birefringence under polarized microscopy. Once recognized via pathology, serologic study in many cases can yield the underlying clinical diagnosis.

Classification: As noted above, there are 30 known human precursors of amyloid fibrils, each with distinct clinical manifestations. Despite this variety, however, certain types are noted to be significantly more common with a greater foundation for evidence-based management.

AL, or primary amyloidosis (also referred to as immunoglobulin light chain amyloidosis) is the most common type of amyloidosis recognized in the United States with incidence of approximately 6-10 cases per million person-years.[5] It involves deposition of amyloid protein polymers derived from immunoglobulin light chain fragments. It can occur alone or in combination with monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, more rarely with Waldenstrom's macroglobulinemia or non-Hodgkin's lymphoma.[6] It typically involves older patients, with a median age of 64 years at diagnosis and has male preponderance (65-70%).[7]

AA, or secondary amyloidosis, is the second most common form seen in the United States with incidence ranging from 0.5-0.86%.[8] It involves deposition of amyloid polymers derived from serum amyloid A (SAA), which is an acute phase reactant more prominent in the serum as a complication of chronic diseases with recurrent inflammation. It is typically seen as a complication of chronic inflammatory disorders, such as autoimmune disorders, chronic infections, or malignancy, though it can be seen idiopathically as well.[9] Due to its association with chronic infections, it is the most common type of amyloidosis in the developing world.

Less common amyloid diseases include dialysis-related amyloidosis (involving deposition of beta-2 microglobulin fibrils that accumulate in end-stage renal disease patients), age-related (senile) systemic amyloidosis (involving deposition of transthyretin protein), and various heritable amyloidoses, each with a unique fibril type and clinical presentation.[1,10,11] There are also multiple types of organ-specific amyloid diseases, most notably Alzheimer's disease, which is associated with deposition of amyloid composed of the beta protein (Ab) cleaved from the amyloid precursor protein (APP).[12]

Presentation and Diagnosis: Amyloidosis of varying types can present in a multitude of ways, depending upon the involved organ system. As noted above, clinical presentations can include renal, cardiac, gastrointestinal, neurologic, pulmonary, hematologic, dermatologic, musculoskeletal, and other organ systems. The system(s) involved depend upon the underlying pathophysiology. For instance, AA amyloidosis characteristically commonly involves the kidneys (in 80% of cases) with glomerular amyloid deposition most classically leading to nephrotic syndrome.[9] Additionally, dialysis-related amyloidosis typically involves bones and joints.[10]

AL amyloidosis is heterogenous with respect to organ involvement and can impact any organ system: renal involvement occurs in 70%, cardiomyopathy in 60%, peripheral neuropathy in 20%, and gastrointestinal in 70% of cases.[7] Renal involvement typically involves asymptomatic proteinuria or the nephrotic syndrome.[13] Cardiac involvement presents most commonly as congestive heart failure (systolic or diastolic) but can also involve arrhythmia and infarction.[14] Gastrointestinal disease commonly includes hepatomegaly, but gastroparesis, constipation, malabsorption with diarrhea, and pseudo-obstruction from dysmotility are also seen.[15]

The diagnosis of amyloidosis depends first upon high clinical suspicion, given the multitude of ways in which it can present. Once suspected, tissue biopsy is required to make the diagnosis. The site of biopsy depends upon clinical context. Kidney or liver biopsy is positive in over 90% of cases, but potential sites for less-invasive diagnosis include: abdominal fat pad aspiration (60-80%), rectal biopsy (50-70%), bone marrow biopsy (50-55%), or skin (50%).[16-18] As such, unless clinical context dictates otherwise, for suspected AL amyloidosis, a combination of abdominal fat pad and bone marrow biopsy is often used to make the diagnosis – either or both will be positive in 90% of cases.[16]

As noted above, tissue specimens are stained with Congo red – amyloid fibrils will demonstrate apple-green birefringence under polarized light. Thereafter, immunohistochemical staining in combination with serologic and other clinical data are used to identify the type of amyloid.[19]

Treatment: Treatment for the different types of amyloidosis depends upon the precipitant of the disease. For example, treatment for AA (secondary) amyloidosis involves control of the underlying inflammatory condition, whether it be a rheumatologic disease, chronic infection, etc. Treatment of dialysis-related amyloidosis involves adjusting the mode of dialysis or consideration of renal transplant.

Similarly, AL amyloidosis treatment is also aimed at the underlying cause: formation of excessive light chain fragments. Initial treatment considerations surround a patient's suitability for possible hematopoietic cell transplantation. As such, once a diagnosis of AL amyloidosis is made, the patient must have a thorough evaluation of the extent of organ involvement. Specifically, investigation for kidney (biopsy and/or urine protein), heart (biopsy and/or echocardiography and BNP measurement), liver (biopsy and/or size assessment and alkaline phosphatase measurement), nerve (by history),

gastrointestinal tract (biopsy or history), lung (imaging), and soft tissue (history and physical) must be undertaken.[20]

Patients are considered to be candidates for autologous hematopoietic cell transplantation when: age ≤70 years, troponin <0.06 ng/mL, NT-proBNP <5000 ng/L, creatinine clearance ≥30 mL/min, Eastern Cooperative Oncology Group performance status ≤2, New York Heart Association functional status class I or II, ≤2 organ systems are significantly involved, no large pleural effusions, and no dependency on oxygen therapy.[21] Those patients who are candidates are typically treated with high-dose melphalan followed by autologous hematopoietic cell transplant. A retrospective matched-pair case control study showed that this approach had a better 4-year survival rate than chemotherapy alone (71% vs. 42%).[22] A large university series examining 629 patients treated with transplantation showed hematologic response in 86% of patients and complete response in 40% of patients. Median overall survival was 7.6 years .[23]

Greater than 80% of newly-diagnosed patients will be ineligible for transplant. Consensus recommendations for treatment of these patients do not exist. These patients are typically either enrolled in clinical trials or initiated on a chemotherapy regimen. Typical regimens include: bortezomib with cyclophosphamide and dexamethasone or melphalan with dexamethasone. The largest study of the bortezomib-based regimen included 230 patients with overall response rate of 60% (23% complete) with 55% survival at 25 months of follow up.[24] Multiple small trials have investigated the melphalan-based regimen with response rates ranging from 51-76% (12-33% complete) and with median survival rates ranging between 20 months and 7.4 years (mainly depending upon initial risk level).[25-26]

Prognosis in AL amyloidosis depends heavily upon the extent of organ involvement at presentation. Risk models typically use measurements of serum BNP and troponin to quantify extent of cardiac involvement.[27-28] Patients with limited organ involvement (including no significant BNP or troponin elevation) have expected median survival over 5 years when treated with standard regimens. However when there is significant organ involvement at presentation, expected survival may be as short as 4-6 months. Typical causes of death include infection, renal failure, heart failure, and hepatic failure.[29]

REFERENCES

1. **Sipe JD, Benson MD, Buxbaum JN, Ikeda S, Merlini G, Saraiva MJ, Westermark P**. Nomenclature 2014: Amyloid fibril proteins and clinical classification of the amyloidosis. *Amyloid*. 2014 Dec;21(4):221-4. doi: 10.3109/13506129.2014.964858. Epub 2014 Sep 29. PubMed PMID: 25263598.
2. **Rochet JC, Lansbury PT Jr**. Amyloid fibrillogenesis: themes and variations. *Curr Opin Struct Biol*. 2000 Feb;10(1):60-8. Review. PubMed PMID: 10679462.
3. **Knowles TP, Vendruscolo M, Dobson CM.** The amyloid state and its association with protein misfolding diseases. *Nat Rev Mol Cell Biol*. 2014 Jun;15(6):384-96. doi: 10.1038/nrm3810. Review. Erratum in: Nat Rev Mol Cell Biol. 2014 Jul;15(7):496. PubMed PMID: 24854788.
4. **Bellotti V, Nuvolone M, Giorgetti S, Obici L, Palladini G, Russo P, Lavatelli F, Perfetti V, Merlini G**. The workings of the amyloid diseases. *Ann Med*. 2007;39(3):200-7. Review. PubMed PMID: 17457717.
5. **Kyle RA, Linos A, Beard CM, Linke RP, Gertz MA, O'Fallon WM, Kurland LT**. Incidence and natural history of primary systemic amyloidosis in Olmsted County, Minnesota, 1950 through 1989. *Blood*. 1992 Apr 1;79(7):1817-22. PubMed PMID:1558973.
6. **Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, Melton LJ 3rd**. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2002 Feb 21;346(8):564-9. PubMed PMID: 11856795.
7. **Kyle RA, Gertz MA**. Primary systemic amyloidosis: clinical and laboratory features in 474 cases. *Semin Hematol*. 1995 Jan;32(1):45-59. PubMed PMID: 7878478.
8. **Simms RW, Prout MN, Cohen AS**. The epidemiology of AL and AA amyloidosis. *Baillieres Clin Rheumatol*. 1994 Aug;8(3):627-34. Review. PubMed PMID: 7954866.
9. **Pinney JH, Lachmann HJ**. Systemic AA amyloidosis. Subcell Biochem. 2012;65:541-64. doi: 10.1007/978-94-007-5416-4_20. Review. PubMed PMID: 23225016.
10. **Stoppini M, Bellotti V**. Systemic amyloidosis: lessons from β2-microglobulin. *J Biol Chem*. 2015 Apr 17;290(16):9951-8. doi: 10.1074/jbc.R115.639799. Epub 2015 Mar 6. Review. PubMed PMID: 25750126; PubMed Central PMCID: PMC4400370.
11. **Westermark P, Bergström J, Solomon A, Murphy C, Sletten K**. Transthyretin-derived senile systemic amyloidosis: clinicopathologic and structural considerations. *Amyloid*. 2003 Aug;10 Suppl 1:48-54. PubMed PMID:14640042.
12. **Selkoe DJ**. Alzheimer's disease: genes, proteins, and therapy. Physiol Rev. 2001 Apr;81(2):741-66. Review. PubMed PMID: 11274343.
13. **Said SM, Sethi S, Valeri AM, Leung N, Cornell LD, Fidler ME, Herrera Hernandez L, Vrana JA, Theis JD, Quint PS, Dogan A, Nasr SH**. Renal amyloidosis: origin and clinicopathologic correlations of 474 recent cases. *Clin J Am Soc Nephrol*. 2013 Sep;8(9):1515-23. doi: 10.2215/CJN.10491012. Epub 2013 May 23. PubMed PMID: 23704299; PubMed Central PMCID: PMC3805078.
14. **Dubrey SW, Hawkins PN, Falk RH**. Amyloid diseases of the heart: assessment, diagnosis, and referral. *Heart*. 2011 Jan;97(1):75-84. doi:10.1136/hrt.2009.190405. Review. PubMed PMID: 21148582.
15. **Sattianayagam P, Hawkins P, Gillmore J**. Amyloid and the GI tract. *Expert Rev Gastroenterol Hepatol*. 2009 Dec;3(6):615-30. doi: 10.1586/egh.09.59. Review. PubMed PMID: 19929583.
16. **Duston MA, Skinner M, Meenan RF, Cohen AS**. Sensitivity, specificity, and predictive value of abdominal fat aspiration for the diagnosis of amyloidosis. *Arthritis Rheum*. 1989 Jan;32(1):82-5. PubMed PMID: 2912466.

17. **Sungur C, Sungur A, Ruacan S, Arik N, Yasavul U, Turgan C, Caglar S**. Diagnostic value of bone marrow biopsy in patients with renal disease secondary to familial Mediterranean fever. *Kidney Int*. 1993 Oct;44(4):834-6. PubMed PMID:7505040.
18. **Kyle RA, Greipp PR**. Amyloidosis (AL). Clinical and laboratory features in 229 cases. Mayo Clin Proc. 1983 Oct;58(10):665-83. Review. PubMed PMID: 6353084.
19. **Schönland SO, Hegenbart U, Bochtler T, Mangatter A, Hansberg M, Ho AD, Lohse P, Röcken C**. Immunohistochemistry in the classification of systemic forms of amyloidosis: a systematic investigation of 117 patients. *Blood*. 2012 Jan 12;119(2):488-93. doi: 10.1182/blood-2011-06-358507. Epub 2011 Nov 21. PubMed PMID: 22106346.
20. **Gertz MA, Comenzo R, Falk RH, Fermand JP, Hazenberg BP, Hawkins PN, Merlini G, Moreau P, Ronco P, Sanchorawala V, Sezer O, Solomon A, Grateau G**. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18-22 April 2004. *Am J Hematol*. 2005 Aug;79(4):319-28. Review. PubMed PMID: 16044444.
21. **Gertz MA**. How to manage primary amyloidosis. Leukemia. 2012 Feb;26(2):191-8. doi: 10.1038/leu.2011.219. Epub 2011 Aug 26. PubMed PMID: 21869840.
22. **Dispenzieri A, Kyle RA, Lacy MQ, Therneau TM, Larson DR, Plevak MF, Rajkumar SV, Fonseca R, Greipp PR, Witzig TE, Lust JA, Zeldenrust SR, Snow DS, Hayman SR, Litzow MR, Gastineau DA, Tefferi A, Inwards DJ, Micallef IN, Ansell SM, Porrata LF, Elliott MA, Gertz MA**. Superior survival in primary systemic amyloidosis patients undergoing peripheral blood stem cell transplantation: a case-control study. *Blood*. 2004 May 15;103(10):3960-3. Epub 2004 Jan 22. PubMed PMID:14739213.
23. **Sanchorawala V, Sun F, Quillen K, Sloan JM, Berk JL, Seldin DC**. Long-term outcome of patients with AL amyloidosis treated with high-dose melphalan and stem cell transplantation: 20-year experience. *Blood*. 2015 Nov 12;126(20):2345-7. doi:10.1182/blood-2015-08-662726. Epub 2015 Oct 6. PubMed PMID: 26443620.
24. **Palladini G, Sachchithanantham S, Milani P, Gillmore J, Foli A, Lachmann H, Basset M, Hawkins P, Merlini G, Wechalekar AD**. A European collaborative study of cyclophosphamide, bortezomib, and dexamethasone in upfront treatment of systemic AL amyloidosis. *Blood*. 2015 Jul 30;126(5):612-5. doi:10.1182/blood-2015-01-620302. Epub 2015 May 18. PubMed PMID: 25987656.
25. **Palladini G, Perfetti V, Obici L, Caccialanza R, Semino A, Adami F, Cavallero G, Rustichelli R, Virga G, Merlini G**. Association of melphalan and high-dose dexamethasone is effective and well tolerated in patients with AL (primary) amyloidosis who are ineligible for stem cell transplantation. *Blood*. 2004 Apr 15;103(8):2936-8. Epub 2003 Dec 18. PubMed PMID: 15070667.
26. **Palladini G, Milani P, Foli A, Obici L, Lavatelli F, Nuvolone M, Caccialanza R, Perlini S, Merlini G**. Oral melphalan and dexamethasone grants extended survival with minimal toxicity in AL amyloidosis: long-term results of a risk-adapted approach. *Haematologica*. 2014 Apr;99(4):743-50. doi:10.3324/haematol.2013.095463. Epub 2013 Nov 8. PubMed PMID: 24213149; PubMed Central PMCID: PMC3971085.
27. **Palladini G, Campana C, Klersy C, Balduini A, Vadacca G, Perfetti V, Perlini S, Obici L, Ascari E, d'Eril GM, Moratti R, Merlini G**. Serum N-terminal pro-brain natriuretic peptide is a sensitive marker of myocardial dysfunction in AL amyloidosis. *Circulation*. 2003 May 20;107(19):2440-5. Epub 2003 Apr 28. PubMed PMID: 12719281.
28. **Dispenzieri A, Kyle RA, Gertz MA, Therneau TM, Miller WL, Chandrasekaran K, McConnell JP, Burritt MF, Jaffe AS**. Survival in patients with primary systemic amyloidosis and raised serum cardiac troponins. *Lancet*. 2003 May 24;361(9371):1787-9. PubMed PMID: 12781539.
29. **Kyle RA, Gertz MA, Greipp PR, Witzig TE, Lust JA, Lacy MQ, Therneau TM**. A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine. *N Engl J Med*. 1997 Apr 24;336(17):1202-7. PubMed PMID: 9110907.

Submitted February 12, 2016