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Amyloid: A Wolf in Sheep's Clothing



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Amyloidosis is a complex group of diseases associated with variable presentations characterized by excessive deposition of the misfolded, abnormal, and insoluble proteins in different organs of the body. The clinical findings depend on the organs involved i.e., kidney, heart, liver, and gastrointestinal (GI) tract, etc. The goal of management in amyloidosis is to inhibit the excessive production of amyloid fibrils and control symptoms. It includes treating underlying etiologies of acquired amyloidosis such as cancers, chronic infections as well as auto-immune diseases. The GI symptoms might result in nutritional deficiencies and malabsorption. Surgical management is needed in patients with uncontrolled GI bleeding and intestinal obstruction or symptoms refractory to medical therapy. This article highlights classification, etiologies, diagnosis, and management of amyloidosis, in particular, the management of GI symptoms and malnutrition.

INTRODUCTION

Amyloidosis is a complex and rare group of diseases associated with diverse etiologies and variable presentations. It is neither a malignancy nor an autoimmune disorder, but it can occur in response to, and along with, chronic infectious and inflammatory diseases. It is characterized by excessive deposition of misfolded, abnormal, and insoluble proteins in different organs of the body resulting in structural change and altered function.¹ The incidence or

prevalence is not well known due to the wide spectrum of presentations increasing the chance of under-diagnosis or even missing the diagnosis, resulting in confounding statistics of occurrence. In 1992, Kyle and colleagues reviewed a 40-year data set of primary amyloidosis in Minnesota and reported the overall prevalence of Amyloid light chain (AL) amyloidosis of about 6-10 cases per million person-years (MPY).² This corresponds to disease burden of approximately 2200 cases in the U.S. annually. The prevalence may have increased over the years due to newer diagnostic and therapeutic interventions for chronic infectious and inflammatory diseases contributing to increased

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morbidity. A recent cohort study of Latin America has reported incidence by describing the disease burden of 6.13 cases per MPY for AL and 1.21 cases per MPY for amyloid A (AA) amyloidosis.³ Given its complicated clinical course, amyloidosis poses diagnostic and therapeutic challenges for the clinicians. In this article, we aim to review the basic pathophysiology, clinical presentations, diagnostic dilemma and treatment hurdles, especially focusing on the management of gastrointestinal (GI) amyloidosis and nutritional implications.

Types of Amyloidosis

The group of diseases that fall under “amyloidosis” can be either genetic or acquired. Genetic/hereditary manifestations are due to mutations in specific genes. Acquired occurs in response to malignancies or chronic inflammatory and infectious states. Amyloid protein production starts in response to these conditions and has the propensity to deposit in certain organs or spread systemically and manifest with localized or systemic disease. The most common type of systemic amyloidosis is primary amyloidosis or, Amyloid light chain (AL).⁴ Other types include secondary amyloidosis (serum amyloid AA),^{2,5} dialysis-related (b-2 microglobulin),⁶ senile (Alzheimer's related apolipoprotein E), and familial amyloidotic polyneuropathy (transthyretin, apolipoprotein AL). Different types are described in Table 1. Primary amyloidosis AL has been described in association with plasma cell disorders like multiple myeloma.⁴ Secondary AA development occurs in the setting of chronic inflammatory/infectious disorders such as autoimmune diseases, persistent or longstanding microbial infections (leprosy, tuberculosis, bronchiectasis), and various cancers (carcinoma of the GI tract, kidneys, pulmonary, genitourinary system, or skin), etc. The proteolysis of serum amyloid A (acute phase reactant) results in the deposition of AA protein in various organs.⁶⁻⁸ In familial amyloid polyneuropathy, the mutated transthyretin and apolipoprotein can deposit in any tissue resulting in malfunction, but has a high predisposition towards the liver.^{4,9} Senile amyloidosis, commonly seen in the elderly, affects the heart, pancreas, prostate, and brain. Disease is confirmed with congo-red staining of biopsied specimens of above-mentioned organs.

The involvement of the brain is considered as one of the etiologies of Alzheimer's disease in the elderly.⁹ Familial amyloidosis is an autosomal dominant disease caused by abnormal deposition of serum amyloid P in mucosal or neuromuscular regions and results in disruption of tissue structure and function.^{6,10}

Pathophysiology

The amyloid protein develops in response to chronic inflammatory/infectious disorders including cancers and is deposited in various organs of the body most specifically, heart, kidneys, liver, bowel, skin, etc. depending on the type of amyloidosis. Tissue specimen can be obtained from any organ suspected/confirmed to have amyloidosis. In patients suspected of amyloidosis, subcutaneous (SC) fatty tissue biopsies (usually from the abdomen) are taken and can be stained with different stains like Congo red (appears green under polarizer), hematoxylin eosin (appears red) or thioflavin T (appears yellow green), but the Congo red staining is the most specific for diagnosis.^{4,11}

Clinical Presentation

The clinical findings of amyloidosis depend on the areas of involvement of the amyloid deposition. General symptoms include weight loss, fatigue, dizziness, and generalized or pedal edema.^{4,12}

Each type of amyloid has a predisposition to deposit in different organs and infiltration of the amyloid fibrils, commonly seen in kidney, heart, peripheral nerves, and GI tract, lead to the symptoms observed.¹³ Table 2 shows the percentage of organ involvement depending on the type of amyloidosis.

Initial findings of kidney involvement include proteinuria, followed by azotemia and renal failure depending on the underlying cause and severity of disease. Infiltration of the heart can manifest with symptomatology of restrictive cardiomyopathy, which can progress to heart failure or fatal cardiac arrhythmias.⁴

The amyloid deposition in the GI tract effect the myopathic and neuromuscular function by involving the muscularis mucosae, and gradually damaging blood vessels, nerves and nearby structures.¹⁴ The consequence of which is impaired GI motility leading to gastroparesis with nausea and vomiting, difficulty swallowing, gastric fullness,

Table 1. Types of Amyloidosis

General Classification	Subtypes	Amyloid Type	Associated Disorders	Mainly Involved Organs Causing Symptoms
Generalized Amyloidosis	Primary amyloidosis	AL	plasma cell proliferative diseases	Cardiac, renal, intestinal, cutaneous, neuropathy
	Secondary amyloidosis	AA	Chronic inflammatory conditions, autoimmune diseases, malignancies	Hepatic, splenic, renal, adrenals
	Hemodialysis associated amyloidosis	A β 2M	CKD	Musculoskeletal
	Genetic Types Familial amyloid polyneuropathies Familial Mediterranean fever Familial visceral amyloidosis	ATTR AL APOA/FGA/LYZ	Genetic mutations Genetic mutations Genetic mutations	Cardiac, peripheral and autonomic neuropathy Hepatic, splenic, renal, adrenals Renal, hepatic, splenic, Nonneuropathic symptoms
Localized Amyloidosis	Endocrine	Procalcitonin (ACal) Prolactin (APro) Proinsulin AIAPP	MCT Prolactinoma T2DM T2DM	Thyroid Pituitary gland Pancreas Pancreas
	Cerebral	A β APrP ACys	Alzheimer's disease CJD, BSE CAA	Brain, cerebral blood vessels, neurofibrillary tangles, plaques.
	Senile cardiac	ATTR AANF	Old age Senile	Cardiac Cardiac
	Cancer associated	AL	Pulmonary, cutaneous, urinary and head and neck malignancies	Pulmonary, cutaneous, urinary and head and neck

AL Amyloid light chain, **AA** Serum amyloid A protein, **A β 2M** β 2 amyloid microglobulin, **ATTR** Transthyretin, **CJD** Creutzfeldt-Jakob disease, **BSE** Bovine spongiform encephalopathy, **APrP** Prion proteins, **ACys** CST3 protein, **APOA1** apolipoprotein A1 gene, **FGA** fibrinogen alpha-chain gene, **LZA** lysozyme gene, **AANF** Atrial natriuretic peptide, **AIAPP** amylin, **CAA** Cerebral Amyloid angiopathy, **MCT** Medullary carcinoma of the thyroid, **T2DM** Type-II diabetes mellitus, **CKD** Chronic kidney disease

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heartburn, anorexia, and constipation; severe disease might lead to pseudo-intestinal paralysis. Diarrhea occurring in GI amyloidosis can be due to autonomic dysfunction, enteritis, or excessive bacterial overgrowth in the small bowel.¹⁵⁻¹⁷ GI bleeding is a fearsome presentation of systemic amyloidosis seen in 57% patients and can occur anywhere in the GI tract; the cause of which can be ulceration or erosion.¹⁸

Interestingly, AA amyloidosis exhibited the highest percentage of GI findings in the range of 10%-70%; AL amyloidosis is associated with fewer extrahepatic GI symptoms.⁴ The amyloid deposition in the liver occurs in stellate cells resulting in fibrogenesis¹⁹ and subsequently mechanical and functional tissue disruptions. It does not suddenly derange liver function, but initially causes symptoms like weight loss, abdominal pain, decreased appetite and fatigue. Jaundice is rare in amyloidosis, but if present, is associated with an increased mortality rate.^{20,21} Macroglossia and clinical splenomegaly have also been described in patients with systemic amyloidosis.²²

DIAGNOSIS

Patients with amyloidosis might undergo a battery of tests due to complex clinical presentations before the final diagnosis is made. Therefore, when suspected, relevant imaging and laboratory testing and appropriate tissue collection is necessary for the definitive diagnosis. It is ideal to biopsy the organ affected as it increases the diagnostic yield, but commonly SC fat tissue is biopsied usually from the abdominal wall, due to less risk of complications; however, any other site of adipose tissue can be biopsied depending on the availability of subcutaneous fatty tissue. Tissue biopsy is under local anesthesia with 2% solution of lidocaine subcutaneously; then using a scalpel, a cutaneous resection of 3-4mm length of skin is done; followed by clipping of subcutaneous fatty tissue with a Kocher and the material is separated with a scalpel. Biopsy site is wrapped with clean dressing for a couple of days. Some recent studies have reported a wide range (13-73%) of sensitivity of SC tissue biopsy, but specificity was 100%.²³⁻²⁴ The variable sensitivity is due to different types of amyloidosis. Rectum is the next common site of

biopsy with sensitivity of 75-85%.²⁵ Other organs may be biopsied when involved, but hepatic biopsy is usually not recommended given high risk of bleeding.^{4,26} In patients with systemic AA or AL amyloidosis, the diagnostic sensitivity of whole-body 123I-labeled serum amyloid P (SAP) scintigraphy was 90%. It showed the amount of amyloid infiltrated in all the affected organs except the heart.²⁷ It is very important to screen other organs such as heart, kidney, bone marrow, GI etc. for amyloidosis if the disease is suspected or confirmed anywhere in the body.^{11,12,28}

The radiological imaging is usually nonspecific, but can be helpful in leading towards diagnosis. Radiographs, barium studies, CT, and MRI are utilized to evaluate the abnormalities. The findings on imaging of the GI tract include mucosal irregularities, thickened mucosal folds, rough mucosal surface with multiple nodular densities, polyps, narrowed lumen, thickened intestinal wall, etc. They are most prevalent in the small intestine (SI).²⁹⁻³² Sometimes thickened and dilated SI can be visualized on the CT.³¹ Laboratory results revealing proteinuria, and abnormal serum protein electrophoresis may suggest the existence of amyloidosis in the patient.¹² These tests provide a clue for further assessment of a patient having an obscure diagnosis.

Alarming GI symptoms warrants endoscopy, which helps in revealing the site of involvement. In the GI tract, the small intestine is mostly affected.^{13,33} Studies have reported polypoid appearance and thickened intestinal folds in AL seen during endoscopy that can lead to intestinal obstruction and constipation. A diffuse granular appearance is seen endoscopically in AA and clinically manifests as bleeding, diarrhea, and malabsorption.^{12,30,34,35} Gastric findings include submucosal masses, erosions, ulcers, thickened rugae and hemorrhages.³⁶

Management

The goal of management in amyloidosis is to inhibit the excessive production of amyloid fibrils. It includes treating the underlying etiologies of acquired amyloidosis like cancers, chronic infections and auto-immune diseases.³⁷

Plasma cell proliferative disorders causing

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AL amyloidosis and affecting organ system warrant further investigation. This includes further evaluation by an oncologist for possible chemotherapy or stem cell transplantation (SCT).^{37,38} Similarly, patients suspected of having AA amyloidosis are managed by addressing the underlying etiology like chronic infectious or inflammatory disorders and/or malignancies. This is because targeting the underlying cause for AA amyloidosis will halt and prevent the progression of disease. Sometimes it can be difficult to elicit the cause of AA amyloidosis requiring frequent physician visits and extensive diagnostic work up. Studies have reported efficacy with the use of biologics³⁹ i.e., interleukin-6 inhibitors/anti-tumor necrosis factor agents (TNF) for the treatment of rheumatic diseases,⁴⁰ and anti-tumor necrosis factor agents (TNF) for management of inflammatory bowel disease.⁴¹

Symptoms

The GI symptoms can result in poor intake, nutritional deficiencies, and malabsorption. Initial management of patient requires control of symptoms such as persistent nausea and vomiting with anti-emetics. This includes treating symptomatic diarrhea with antidiarrheal or antisecretory agents, and diarrhea due to small bowel bacterial overgrowth with antibiotics.⁴² Prokinetics like metoclopramide or erythromycin may be tried for gastroparesis or dysmotility.^{13,43}

Nutritional Considerations

Malnourishment in amyloidosis is multifactorial

and requires regular nutrition assessment. Malnutrition should be corrected by managing symptoms and providing nutritional support, as well as vitamin and mineral supplementation when needed. Early nutritional referral and consultation is recommended.^{4,44} Patients with mild to moderate involvement of the bowel will benefit from enteral feeding if oral intake is inadequate. In patients with severe malnutrition, severe GI involvement with worsening GI symptoms or pseudo-obstruction, total parenteral nutrition (TPN) may be considered.⁴⁴ However, TPN is associated with increased risk of infections and edema in these patients, so caution is necessary.⁴⁴ These patients need to be closely monitored to decide if and when to start more aggressive management like TPN, but only after enteral feeding has failed. Intake of various supplements has shown to influence the disease activity in animals, but studies in humans are lacking.⁴⁵⁻⁴⁷

The response to treatments in AL amyloidosis can be assessed by monitoring the amount of amyloid deposits via serum amyloid P scintigraphy and functional status of organs via laboratory tests and imaging as required.⁴⁸

Prognosis

The survival in these patients depends on the type of amyloidosis and the severity of organ damage. AL amyloidosis has a poor prognosis due to its association with malignancy, even if the patient is undergoing chemotherapy alone. In patients undergoing chemotherapy and stem cell transplantation (SCT), the calculated 5 year survival is approximately 60%.³⁷ Treatment of underlying

Table 2. Different Types of Amyloidosis Affecting Internal Organs

Type of Amyloidosis	Organ Affected	Percentage
AL Amyloidosis	Kidneys	50%-80%
Systemic Amyloidosis	GI tract	79%
Systemic Amyloidosis	Liver	15%-25%
Systemic Amyloidosis	Nerves	15%-20%
Systemic Amyloidosis	Heart	50%

disorders in AA amyloidosis is associated with regression of amyloid deposits and improvement in mortality.⁴⁹ In addition, the survival of patients also coordinates serum amyloid P concentrations that can be monitored with SAP scintigraphy. This is of utmost importance in targeted management of serum amyloid P for the treatment of amyloidosis by monitoring SAP levels during therapy.⁵⁰ A recent study by Lim et al reported median overall survival of 15.84 months in AL amyloidosis patients without GI involvement and 7.95 months in patients with GI involvement. GI involvement is associated with poor prognosis.⁵¹

SUMMARY

Amyloidosis usually manifests in a discreet sequela, which include non-specific symptoms such as weight loss, autonomic dysfunction, fatigue, and GI symptoms. Patient with chronic diseases and cancers should be suspected to have amyloidosis if presenting with nonspecific symptoms. The evaluation includes laboratory testing and imaging, and if necessary, biopsy of the organ involved which is the gold standard for diagnosis. ■

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