Taxonomy and Imaging Manifestations of Systemic Amyloidosis

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KEYWORDS

• Amyloidosis • Heart • Lung • Urinary tract • Joint • Computed tomography • MR imaging

KEY POINTS

- Amyloid light-chain amyloidosis is the most common type of amyloidosis, and cardiac involvement is often a major determinant of prognosis.
- Global subendocardial to transmural cardiac wall enhancement is the most common pattern of cardiac amyloidosis on late gadolinium enhancement on MR images.
- The localized form of amyloidosis most commonly involves urinary tract or respiratory tract, and usually has a benign clinical course.
- Amyloid arthropathy is most commonly owing to Aβ2M (dialysis-related) amyloid deposition.
- Amyloid deposits commonly exhibit decreased T1- and T2-weighted signal on MR images.

INTRODUCTION

Amyloidosis is a heterogeneous group of multisystem disorders that are characterized by extracellular deposition of amyloid fibrils in β-pleated sheets resulting in organ dysfunction. Although approximately 25 different amyloid proteins have been identified, 5 types of amyloidosis account for 99% of all amyloidosis. Amyloid of all types shares the same physical properties: apple-green birefringence after Congo red staining. Amyloid deposits produce diverse clinical syndromes depending on their type, location, and the amount of deposition.

AMYLOID TYPES AND MANAGEMENT

There are several forms of amyloidosis. The 2 most common types of amyloidosis are amyloid light-chain (AL) amyloidosis (previously referred to as primary amyloidosis) and amyloid A (AA) amyloidosis (previously referred to as secondary amyloidosis).[1] AL amyloidosis is owing to deposition of protein derived from immunoglobulin light chain fragments. Patients with AL amyloidosis have monoclonal B-cell dyscrasia, which generally has low-level activity. However, 10% to 50% of patients are associated with multiple myeloma or other plasma cell neoplasia, such as B-cell lymphoma and Waldenström macroglobulinemia.[2] Similar to other plasma cell dyscrasias, AL amyloidosis is a disease of older adults with a median age at diagnosis of 65 years old. AL amyloidosis is mostly a systemic disorder that can present with a variety of symptoms or signs depending on the predominant sites of involvement. Nonspecific systemic symptoms include fatigue and weight loss. Other common clinical presentations of AL amyloidosis include proteinuria or nephrotic syndrome, heart failure, hepatosplenomegaly, and neuropathy. Without treatment, systemic AL amyloidosis is a fatal disease owing to uncontrolled organ damage. Treatment is aimed at control of plasma cell

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dyscrasia in the form of chemotherapy and/or hematopoietic stem cell transplantation.

In AL amyloidosis, amyloid deposition can be isolated to a single organ resulting in specific syndromes. Localized amyloidosis is attributed to a local immunocyte dyscrasia and resulting in deposition of immunoglobulin light chain. The location of the amyloid deposits can be a clue to its localized nature. Respiratory tract, skin, and urinary tract are common sites of localized amyloidosis. Patients with localized amyloidosis do not have monoclonal protein in the serum or urine or bone marrow plasmacytosis. Patients with localized amyloidosis do not require systemic therapy, and surgical excision may be the only treatment needed.

AA amyloidosis is a result of chronic inflammatory conditions such as rheumatoid arthritis, Crohn's disease, tuberculosis, bronchiectasis, and chronic osteomyelitis. It may occur in association with other causes, including neoplasms (renal cell carcinoma and Hodgkin's disease). Amyloid is composed of fragments of the acute phase protein, serum AA. The most common organ involved is the kidney, leading to nephrotic syndrome. If untreated, secondary amyloidosis may be fatal owing to end-stage renal disease, infection, or heart failure. Treatment is aimed at control of the underlying inflammatory or infectious process. AA amyloidosis is more common in underdeveloped countries, whereas AL amyloidosis is the most common type of amyloidosis in the developed countries.

Two other major forms of amyloidosis are transthyretin-related amyloidosis (ATTR) and Aβ2M amyloidosis. ATTR amyloidosis is owing to deposition of wild-type transthyretin (TTR) or mutant TTR. Wild-type ATTR amyloidosis is commonly referred to as age-related or senile amyloidosis. The predominant site of involvement is heart and it almost exclusively affects older men; most patients are older than 70 years at diagnosis, with a 10-fold greater incidence in men. Autopsy series suggests asymptomatic amyloid deposition is common in heart and gastrointestinal tract.[3,4] Mutant ATTR amyloidosis is a hereditary disease, and commonly referred to as familial amyloid polyneuropathy. It has predilection for involvement of the peripheral and autonomic nerves. Inheritance is autosomal dominant with variable penetrance, and at least 120 point mutations of the TTR gene have been described. Aβ2M amyloidosis (dialysis related) occurs in patients undergoing long-term hemodialysis owing to deposition of β2 microalbumin. It has a predilection for deposition in the bones and joints.

Although amyloidosis may be suggested by the history and clinical manifestations (eg, nephrotic syndrome in patients with myeloma), tissue biopsy is often necessary to confirm the diagnosis. Biopsies can be obtained from either clinically uninvolved site, such as subcutaneous fat, or from dysfunctional organs. Abdominal fat pad biopsy is preferred in patients with suspected systemic amyloidosis because it is less invasive. Biopsy of an involved organ is often necessary when a limited number of organs is affected, such as in localized amyloidosis.

GENERAL IMAGING FEATURES OF AMYLOID DEPOSITION

On computed tomography (CT), amyloid deposition is commonly associated with calcification, and it is attributed to an affinity of amyloid fibrils for calcium.[5] On CT and MR imaging, the enhancement of the affected organs is often decreased in the parenchymal phase and increased in the delayed phase. This enhancement pattern is considered owing to expansion of the extracellular space by amyloid deposition causing delayed inflow and washout of contrast material.[6,7] Amyloid deposits often shows decreased T1 signal (T1 prolongation) and decreased T2 signal (T2 shortening) on MR imaging likely related to physical properties of amyloid fibrils, but the exact cause of these signal changes are unknown.[8]

HEART

Amyloid Variants Affecting the Heart

The heart can be affected by several amyloid types, and cardiac involvement is often a major determinant of prognosis. The 2 most common forms of cardiac amyloidosis are the AL and ATTR types. AL amyloid is the most commonly diagnosed form of cardiac amyloidosis. It may involve almost any organ in the body, with cardiac disease seen in 50% to 70% of patients.[9] The prevalence of wild-type ATTR amyloidosis is uncertain; although fewer cases are diagnosed annually in comparison with AL amyloidosis, autopsy series have noted ATTR deposits in up to 25% of individuals greater than 80 years of age in the heart,[3] suggesting that the disease is underdiagnosed, or that perhaps there is a spectrum of disease including asymptomatic or minimally symptomatic disease. Cardiac involvement is the predominant clinical feature of wild-type ATTR amyloidosis, although carpal tunnel syndrome is common and may precede development of cardiac symptoms by 10 to 15 years. Isolated atrial amyloidosis occurs when atrial natriuretic peptide serves as the precursor protein for amyloid