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Clinical Presentation of Amyloid A Amyloidosis

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1. Introduction

Amyloid is an eosinophilic substance which appears “apple-green birefringence” in Congo red stained tissue sections under polarized light. This standard histological analysis is supported with immunochemistry technic using specific antibodies directed against most of the common human amyloid proteins, and also amyloid proteins can be identified with characteristic fibrillar appearance by electron microscopy (1).

Amyloidosis is a name given to a heterogenous group diseases. It is caused by the extracellular amyloid deposition as insoluble fibrillar aggregates that destroy normal tissue architecture and interfere normal function of tissues and organs. The biochemical nature of the precursor protein forming the amyloid fibrils differs in the different clinical conditions such as chronic inflammatory infectious or non-infectious diseases, malignancies, hereditary diseases and other less common disorders. Identification of the type of amyloidosis is important to assess clinical management, prognosis and treatment. Amyloid fibril protein nomenclature “2010 recommendations of the nomenclature committee of the International Society of Amyloidosis” was reported and 27 human fibril proteins were described. In current nomenclature, a prefix “A” shows amyloid, followed by an abbreviation originated from the name of the precursor protein (for example, AL addresses amyloid derived from immunoglobulin light chain, AH shows amyloid derived from immunoglobulin heavy chain, AA indicates amyloid derived from serum amyloid A (SAA) protein, A β_2 M shows amyloid originated from β_2 microglobulin, ATTR describes amyloid derived from transthyretin, and others). The amyloidoses can be classified according to localized or systemic deposits along with its biochemical nature (2).

Localized amyloid depositions usually lead to mechanical interference and generally are considered to be benign. Alzheimer’s disease is the only form of localized amyloid fibril deposition which often leads to serious disorder.

Systemic amyloid forms include mainly immunoglobulin light chain (AL) amyloidosis, secondary, reactive (AA amyloidosis), hereditary familial form (for example, ATTR amyloidosis) and dialysis-related (A β_2 M) amyloidosis (3,4). AA, AL and ATTR amyloidosis involve more than 90% of systemic amyloidosis (5).

AL amyloidosis is the most common form of systemic amyloidosis in western world. The ratio AL/AA amyloidosis appears 2/1 in the Netherlands (6). A retrospective study from

France suggests a 3/1 AL/AA ratio (7). These ratios should be supported by prospective studies in the world. AL amyloidosis is caused by clonal plasma cells that produce misfolded light chains, associated with B cell lymphoproliferative diseases such as multiple myeloma, and rarely malignant lymphoma and macroglobulinemia. Cardiac involvement is main clinical characteristic of AL amyloidosis (8). Demonstration of a monoclonal immunoglobulin (Ig) protein in the blood, in urine, or in clonal plasma cells in the bone marrow is an important finding for the diagnosis.

AA amyloidosis is the second most common type of amyloidosis worldwide. Acquired and hereditary diseases can cause to AA amyloidosis, including chronic inflammatory diseases, such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), familial Mediterranean fever (FMF) or other periodic fever syndromes, bronchiectasis, tuberculosis, chronic osteomyelitis and rarely malignancies. The prevalence rates of AA amyloidosis in these disorders show the wide variations due in part to geographic differences, possibly genetic factors, and also according to the methods of the research performed by the native biopsies or postmortem studies. The underlying inflammatory disease is usually longstanding and characterized with persistent inflammation. Renal involvement is the major cause of morbidity and mortality in AA amyloidosis (9).

Hereditary amyloidosis occurs by deposition of genetically variant proteins and it is associated with mutations in the genes such as transthyretin, apolipoprotein AI, apolipoprotein AII, apolipoprotein AIV, lysozyme, fibrinogen A, gelsolin, cystatin C. The transthyretin amyloidosis is the most common form of hereditary amyloidosis, and consists in two varieties; as “senil” and hereditary. Clinic characteristics are polyneuropathy and cardiac involvement, and renal involvement may be clinically silent (10).

This review includes the following issues: (1) epidemiology and incidence of the underlying diseases related AA amyloidosis, (2) the clinical manifestations of the involved tissues/organs, and (3) diagnostic approach and treatment strategy in AA amyloidosis.

In AA amyloidosis (secondary, reactive), amyloid fibril proteins are composed of fragments of serum amyloid A (SAA) protein, a major acute-phase reactant protein, an apolipoprotein. Its serum concentration increases 100 to 1000-fold under inflammatory signals, predominantly interleukin (IL)-1 β , tumor necrosis factor (TNF)- α and IL-6. In chronic inflammatory diseases, persistent or intermittent elevated SAA concentrations are the basic factor promoting amyloidosis (9). Increased SAA levels were showed to be correlate to disease course in patients with amyloidosis. Also the increased amyloid load and deteriorated organ function were demonstrated to be associated with persistently high SAA concentration (>50m/L) (11). However, amyloidosis does not develop in every patient with chronic active inflammatory diseases, only a subset of patients with persistently increased SAA levels may develop AA amyloidosis. Several forms of SAA have been identified in human plasma, SAA1 seems a predominate factor in the formation AA deposits. The genetic factors may increase the risk of amyloidosis, but it is not fully clear. The main suspects focus on the genes of the SAA1 protein, however there are differences related to ethnicity (12-14). The frequency of the SAA1.3 allele is about 40% for Japanese, it is lower in whites (15). It was reported that the SAA1.3 allele is a risk factor for the association of AA amyloidosis and also a poor prognostic factor in survival for Japanese patients with RA (16).

Environment can affect onset of amyloidosis in chronic inflammatory disease. Toitou et al. suggested that country of recruitment is an important factor for the development of renal amyloidosis in FMF and authors suggested that the patient's country should be considered (17).

2. Epidemiology and incidence of underlying diseases due to AA Amyloidosis

AA amyloidosis occurs in association with chronic infectious (i.e. tuberculosis, bronchiectasis, osteomyelitis, leprosy) and chronic inflammatory diseases (i.e. RA, JIA, AS, IBD, psoriatic arthritis, Behçet's disease, adult Still's disease), malignancies (i.e. Hodgkin's disease, renal carcinoma, Castleman's tumor) and hereditary periodic fever (i.e. FMF, others). The prevalence rates of AA amyloidosis in these disorders show a wide variation due in part to geographic differences, possibly genetic factors, and also according to the study's material (i.e. biopsy or autopsy) and method (i.e. immunohistochemistry).

AA amyloidosis associated with chronic infections such as tuberculosis and osteomyelitis was common in early 20th century. These cases appear less frequent after the eradication of some infectious diseases and due to advances in the management of diseases. Von Hutten et al. reassessed renal amyloidosis in 233 renal biopsies and demonstrated that chronic non-infectious inflammatory diseases were more than chronic infectious diseases (73.8%, 24.6% respectively) (18). Similar results were found in the Western countries (19,20). Malignancy related AA amyloidosis is rare causes. Among malignities renal cancer, hepatocellular carcinoma and lymphoma are most frequently implicated in AA amyloidosis. Castleman's disease is one of the most recently recognized causes in case reports (21).

Rheumatoid arthritis is one of non-infectious, inflammatory, longstanding rheumatic diseases. It is generally an inflammatory disease in synovial joints, and also affects systemic organs including lungs, heart, kidneys, nervous system. A major factor responsible for the development of AA amyloidosis seems sustained overproduction of SAA under chronic inflammatory conditions. The prevalence of AA amyloidosis in RA is a range from 7% to 26% and it varies due to clinical severity of patients and duration of arthritis (22-24). In a Dutch series, RA was the most frequent cause of AA amyloidosis, followed by recurrent pulmonary infection (11%), Crohn's disease (5%), ankylosing spondylitis (5%), tuberculosis (3%), osteomyelitis (2%), FMF (2%) and Hodgkin's disease (2%) (25). A study from Finland (26) based on Finnish Registry for Kidney Diseases identified 264 patients suffering from amyloidosis associated with RA, AS or JIA over the period 1995-2008, most of cases were RA (n=229), followed JIA (n=20) and AS (n=15). A cohort study of patients with RA showed 16.3% AA fibril depositions in the abdominal fat samples of patients (27).

In general, the development of AA amyloidosis in RA takes a long time, often more than 15 years (28,29). Morigush et al. reported that secondary amyloidosis developed in a shorter period in Japanese RA patients with the γ/γ homozygotes in the SAAI gene (14).

Juvenile idiopathic arthritis is also a cause of AA amyloid which has been observed in systemic (Still disease) and polyarticular forms (30). However, the effective suppression of the disease activity with new immunosuppressive treatment agents (i.e. biologics) in early stages may change prognosis in both RA and JIA.

AA amyloidosis also complicates 4 hereditary diseases with varying frequencies: FMF, the tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Muckle-Wells syndrome (MWS) and hyperimmunoglobulinemia IgD with periodic fever (HIDS) (31).

Familial Mediterranean fever is well recognised among the hereditary periodic fever syndromes, also called as autoinflammatory syndromes. Autoinflammatory diseases are characterised by unprovoked inflammatory episodes without any recognizable pathogens. FMF mainly affects people of Mediterranean origin (Sephardic Jews, Turks, Armenians, Arabs). Its prevalence is between 1/500-1/1000 and carrier rate is very high in the Eastern

Mediterranean (32). It's a monogenic autoinflammatory disease associated with mutations in a gene called MEFV (Mediterranean FeVer) (33,34).

There are two phenotypes of FMF as types 1 and 2. Familial Mediterranean fever type 1 is characterised by recurrent short episodes of fever, peritonitis, synovitis, pleuritis, rarely pericarditis or erysipelas-like skin disease, along with increased acute phase reactants. Familial Mediterranean fever type 2 is probably quite rare characterized by amyloidosis as the first clinical manifestation of FMF without classical FMF attacks, but their family members have often characteristic FMF signs (35,36).

The symptoms and severity of FMF vary among affected individuals. During attacks, acute phase reactants such as C-reactive protein, fibrinogen, ceruloplasmin, serum amyloid A are elevated. After attacks, all these abnormal tests usually return to normal values. In 30-63% of patients, inflammation can persist in attack-free periods with elevated acute-phase proteins (37-39). Chronic subclinical inflammation can cause the risk of developing complications such as AA amyloidosis.

In a retrospective analysis of 287 patients with renal amyloidosis from Turkey, FMF appears most frequent among the causes of AA amyloidosis, the etiological distribution was found as follows; FMF 64%, tuberculosis 10%, bronchiectasis and chronic obstructive lung disease 6%, RA 4%, spondyloarthropathy 3%, chronic osteomyelitis 2%, miscellaneous 4%, unknown 7%. Oedema accompanied by proteinuria was the most prominent presenting finding in 88% of the cases. Hepatomegaly in 17%, and splenomegaly in 11% of the patients were found in this study (40). In pediatric FMF series, 29% of 110 cases developed AA amyloidosis (41). In Sephardic Jews, the incidence of FMF related amyloidosis was 37.2% (42). The frequency of amyloidosis varies among different ethnic groups and also due to regular the use of colchicine which is beneficial in preventing FMF amyloidosis by a reduction in the number and severity of attacks.

The mutations in exon 10, in the region between 680 and 694 and especially M694V homozygosity were demonstrated to be associated with AA amyloidosis (43-45), however the different mutations were also shown (46). M694V homozygosity and/or SAA alpha/alpha genotype, male gender, delay in diagnosis of FMF and the presence of secondary amyloidosis in the family has been suggested to be risk factors for the development of amyloidosis in FMF patients (43-47). The frequency of the main signs and symptoms of FMF were found fever 92.5%, peritonitis 93.7%, arthritis 47.4%, pleurisy 31.2%, amyloidosis 12.9% (44).

TRAPS is a rare autosomal-dominant disorder characterised by recurrent attacks of fever, abdominal pain, rash and periorbital edema. AA amyloidosis is more common among patients with cysteine mutations compared to non-cysteine ones (48).

MWS is also autosomal dominant disease, characterised by recurrent attacks of urticaria, fever, polyarthralgia. Amyloidosis may develop in later life (49). It was estimated that approximately one-third of patients suffer from amyloidosis and there is familial clustering (50).

Hyperimmunoglobulin D syndrome is an autosomal recessively inherited disease manifested by recurrent attacks of fever, arthralgia, abdominal pain, diarrhea, maculopapular rash, and lymphadenopathy lasting 3-7 days. The incidence of amyloidosis in hyper IgD syndrome is remarkably low compared to other periodic fever syndromes.

Secondary amyloidosis in ankylosing spondylitis is less frequent. Sing et al. detected that subclinical amyloid deposits by abdominal subcutaneous fat aspiration in 5 patients (7%) with ankylosing spondylitis (n=72) with disease duration longer than 5 years (51).

In other chronic rheumatic inflammatory diseases including systemic lupus erythematosus, polymyalgia rheumatica and Behçet's disease, AA amyloidosis has been rarely reported in case reports (52-59).

The development of AA amyloidosis was reported in 28 SLE patients (one of them overlapping with systemic sclerosis) between 1956-2011 (up to March, based on Pubmed). The lack of acute phase response in SLE compared to other inflammatory diseases has contributed to reduce the incidence (52-54). Most of patients presented proteinuria/nephrotic-range proteinuria or nephrotic syndrome or progressive renal insufficiency when the amyloidosis was diagnosed. Renal failure was a major cause of death of these patients. Cardiac presentations with arrhythmia and congestive heart failure in SLE related AA amyloidosis is not common. Hepatic, splenic, pulmonary, intestinal, adrenal involvement with amyloidosis and mononeuropathy were very rare in SLE patients (54).

Behçet's disease is a multisystem inflammatory disorder with a genetic background, characterised by oral and genital ulcers, uveitis, cutaneous pustular erythematous lesions, arthritis, central nervous system involvement and/or vascular manifestations such as venous thrombosis, arteritis and aneurysms. Behçet's disease is more frequent in the regions along the Mediterranean, Middle East and Far East countries. Amyloidosis is a rare complication, its frequency changes between 0.01 and 4.8 % in several clinical series (57). Major risk factors for the development of AA amyloidosis are peripheral or pulmonary arterial involvement and venous thrombosis, and the presence of arthritis has also been implicated as a predictor in Behçet's disease (58-59).

Secondary amyloidosis rarely occurs in long-lasting inflammatory bowel diseases. In the retrospective studies the prevalence is ranging from 0.5% to 3% among patients with Crohn's disease (60,61).

3. Clinical manifestations of AA Amyloidosis

Clinical amyloidosis is defined as the presence of symptoms or signs of visceral involvement by amyloid. General signs such as fatigue and weight loss are often. Clinical signs of amyloidosis generate according to its locations, and most of them are not specific. Kidney, liver, spleen, heart, intestinal and respiratory tract are the main involved organs or systems in AA amyloidosis (4,19,20,55,60-66). Adrenal and thyroid glands, testes, skin, synovial membrane and bone marrow are other sites of involvement and less common presentations (67-69). Most of clinical symptoms are caused by distortion of the normal tissue architecture. The patients can present with organ enlargement such as hepatomegaly, splenomegaly, renomegaly, enlarged thyroid, rarely hypertrophy of lymph nodes by massive amyloid deposition, easy bruising by weakening of the vascular walls (65,70), proteinuria, renal failure and malabsorption (4,19,20,61,65). Unexplained kidney, heart, or systemic disease, hepatomegaly and splenomegaly are among suspicious for amyloidosis.

In AA amyloidosis, kidney is the most affected organ (4). The first sign of renal amyloidosis is asymptomatic proteinuria, gradually progressing to nephrotic syndrome and /or renal dysfunction. Amyloidosis is one of the major differential diagnoses of proteinuria. The most common clinical manifestation is peripheral edema due to the development of nephrotic syndrome. Haematuria, renal vein thrombosis and tubular defects are very rare. Hematuria reflects amyloid deposition anywhere in the genitourinary tract. The blood pressure may often remain normal. It is not clear that development of hypertension in renal amyloidosis whether due to renal involvement or a coincidental finding. Persistent nephrotic syndrome

and advanced renal insufficiency and enlarged kidney suggest amyloidosis. Occasionally the kidneys are small and scarred. Rarely, a sudden onset of acute renal failure may occur due to renal vein thrombosis. It is very rare for the presenting symptoms to be those of chronic renal failure. AA amyloidosis usually progresses toward end-stage renal failure which is the main cause of mortality.

Amyloid deposits can occur in the mesangium, glomerular capillary loops, tubulointerstitium, and vasculature of the kidney. It was showed that the patients having glomerular amyloid deposition are more common and have a poor prognosis than patients having vascular and tubular amyloid deposition in secondary amyloidosis to RA (63).

Once the disease established, prognosis remains poor. Renal failure and low serum albumin levels are the most important predictors for poor prognosis (19). Survival of patients with AA amyloidosis appears greatly improved as compared to past decades. Torregrosa et al. reported in a group of patients a survival of 67% and 53% at 12 and 24 months without dialysis respectively (64). Amyloidosis without therapy usually progresses to end-stage kidney disease. Progression of renal amyloidosis can be delayed or slowed by treatments that reduce the production of amyloidogenic precursor proteins, deposits may also regress.

Hepatic involvement is usually expressed as hepatomegaly and increased in serum alkaline phosphatase levels. However, hepatic amyloidosis may remain asymptomatic for a long time or show only mild liver enzymes abnormalities. In the differential diagnosis in patients with long-standing inflammatory disease, hepatomegaly and liver function tests abnormalities hepatic amyloidosis should be considered. Some complications such as portal hypertension, jaundice, ascites are rare. Gioeva et al. retrieved all liver biopsies from a series of 588 cases with histologically confirmed amyloidosis and reported that hepatic amyloidosis is most commonly AL amyloid of lambda- and kappa-light chain origin (87%). Hepatic AA amyloidosis was found in a single patient (2%) in this study (71).

The spleen is affected and splenomegaly is seen in early periods, functional hyposplenism and splenic rupture rarely may develop (66).

Gastrointestinal amyloidosis manifestations such as abdominal pain, vomiting, dysphagia, diarrhea, malabsorption, obstruction, bleeding, perforation may occur in about 20% of patients (65), these symptoms are largely nonspecific. The rectum is a commonly affected site and rectal biopsy is the initial diagnostic tool. The hypoproteinemia may not only be due to proteinuria but also to a decreased rate of protein synthesis as a consequence of hepatic amyloidosis, and also to malabsorption of amino-acids because of amyloid infiltration in intestinal mucosa.

Heart disease in secondary amyloidosis is less common (<10%) than it is in other types of amyloidosis and is the main cause of death. Cardiac involvement has been associated with myopathic syndrome and coronary vascular syndrome. Arrhythmias may occur at any time. Cardiac amyloidosis should be suspected in any patient who presents with restrictive cardiomyopathy, prominent signs of right-sided heart failure or left sided heart failure in the absence of ischemia disease. Valvular disease, pericarditis, systemic arterial emboli are rare. The combination of clinical and echocardiographic findings suggest amyloidosis (9).

The involvement of adrenal glands may cause adrenal insufficiency. The involvement of thyroid may lead to hypothyroidism. Although microscopic amyloid deposition may be demonstrated in thyroid gland, a significant enlargement of thyroid and its dysfunction are not often, goiter as a first evidence of AA amyloidosis is rarely seen and thyroid function tests are usually in normal limits. Enlarged thyroid gland making pressure to the near tissues and leading operation is a rare condition in systemic amyloidosis associated with

inflammatory disease. Bleeding is an important complication in thyroid operation of patients with secondary amyloidosis (66,70).

Pulmonary amyloidosis is uncommon (72) and presents with cough, hemoptysis and dyspnea. Amyloid depositions may be found in bronchial, mediastinal and alveolar area and interfere with tumor mass.

Skin involvement can present with petechiae, purpura and ecchymoses. Rarely papules, nodules, plaques can be seen.

Arthritis is associated with febrile attacks in patients with FMF. The patients with MWS patients have polyarthralgias accompanying urticaria.

Spinal cord lesions and cranial nerve involvement are uncommon. Peripheral neuropathy or carpal tunnel syndrome occasionally may occur during the course of AA amyloidosis.

Urethral and bladder amyloidosis are rare and present with pain and hematuria. Amyloid deposits in the wall of blood vessel may lead to vascular fragility, impaired hemostasis, and bleeding (70). Amyloid fibrils can also accumulate in the bone marrow (68).

4. Diagnostic approach of AA Amyloidosis

The approach of the diagnosis based on clinical manifestations, clinical examination, biochemical nature of AA amyloidosis for differentiation with respect to other varieties, biochemical tests and genetic analysis. Clinical examination and evaluation of the various signs described above should be systematically performed. The diagnosis of amyloidosis should be confirmed by biopsy from suspicious tissue (s) such as kidney, intestine, liver, thyroid, skin, bone marrow and endomyocardium. If biopsy could not be taken from these tissues or clinical signs are not present, biopsy may be taken from intestinal mucosa (rectal), abdominal subcutaneous fat tissue, labial salivary gland samples. The results of gastrointestinal biopsy are highly correlated with those of renal biopsy but the results of abdominal fat samples are not (73).

Abdominal fat aspiration biopsy is easy to perform and repeatable. However, fat aspiration biopsy is less sensitive than kidney and rectal biopsy. Labial salivary gland biopsy is now replaced the old gingiva biopsy. Endomyocardial biopsy can be needed in cardiac involvement. The aim is to detect amyloid early and to type it correctly.

Congo red stain is the gold standard for amyloid detection. The amyloid type must be identified based on amyloid protein within the deposits by immunohistochemistry or immunoelectronmicroscopy and Western blotting. AA amyloidosis can also be diagnosed using serum amyloid P component scintigraphy (74).

5. Treatment strategy of AA Amyloidosis

The main therapeutic target of the chronic inflammatory diseases is to suppress the inflammatory activity of the underlying disease and to prevent the development of AA amyloidosis. The concentration or production of SAA is reduced by the treatment of underlying chronic inflammatory rheumatic diseases including anti-inflammatory drugs, immunosuppressants or biologics. Treatment with corticosteroids and immunosuppressive drugs in mainly RA and JIA have proved the suppression of the underlying inflammatory process (26). It is suggested that immunosuppressants can improve prognosis of patient with AA amyloidosis (75). Each patient requires systematic evaluation to determine their optimal treatment. Earlier and powerful treatments of underlying diseases should be aimed.

Colchicine is the most effective drug for prevention of acute inflammatory attacks and development of amyloidosis in most patients with FMF. Early treatment of amyloidosis is associated with much better prognosis and survival, but even reverse established deposits. Colchicine dose of 1.5-2 mg daily is necessary for prevention of the progression of amyloidosis (76). It was shown that colchicine can reduce proteinuria in patients with renal amyloidosis of FMF by case series (77,78).

Epradisate (anti-amyloid compounds) for treating with AA amyloidosis which leads a significant delay in the progression to dialysis or end-stage renal disease (79,80).

In recent years, new biological therapies were approved for the treatment, especially in patients with RA, JIA, spondyloarthritis, who is unresponsive to conventional treatment.

Several isolated cases and small series have demonstrated a marked clinical improvement and complete or partial resolution of AA amyloid deposits in patients with RA, JIA, hereditary periodic fever syndromes under these agents (81-90).

Anti-cytokine biologicals including TNF-alpha antagonists (infliximab, etanercept, adalimumab) (81-84) and a humanised IL-6 R antibodies (tocilizumab) suppress strongly SAA production by liver and also inflammatory process (85-87). These biologics have been reported to be highly effective in patients with AA amyloidosis secondary to RA and JIA. IL-1 receptor antagonist (anakinra) showed a persisted effect in patients with familial cold autoinflammatory syndrome (88-89).

The trial of rituximab (anti-CD 20 monoclonal antibody) was reported the efficacy for a few patients with AA amyloidosis secondary to RA (91).

A new class of anti-amyloid agents, currently in clinical trials, also appear to be amyloid type for AA and ATTR (92).

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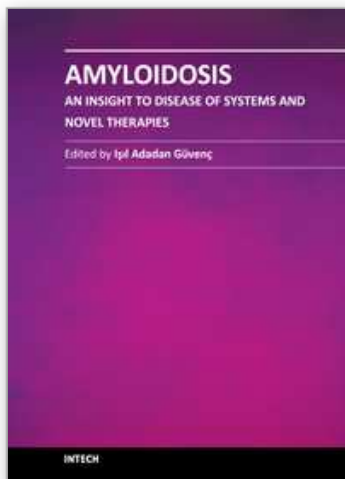
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Amyloidosis is a benign, slowly progressive condition characterized by the presence of extracellular fibrillar proteins in various organs and tissues. It has systemic or localized forms. Both systemic and localized amyloidosis have been a point of interest for many researchers and there have been a growing number of case reports in the literature for the last decade. The aim of this book is to help the reader become familiar with the presentation, diagnosis and treatment modalities of systemic and localized amyloidosis of specific organs or systems and also cover the latest advancements in therapy.

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