Secondary Amyloidosis in Patients with Rheumatoid Arthritis

**Key words:** amyloid A protein, serum amyloid A

The amyloidoses are a group of protein deposition diseases in which amyloid proteins composed of insoluble fibrils (diameter 80 to 100 Å) are deposited in various organs. They are classified according to the biochemical nature of the fibril-forming proteins. In addition to primary amyloidosis due to multiple myeloma in which AL amyloid derived from immunoglobulin light chain is deposited, Alzheimer’s disease (Aβ amyloid) and prion diseases are also classified as amyloidoses. A few decades ago, most cases of the secondary (reactive) amyloidosis were due to chronic infectious diseases such as tuberculosis. Recently the incidence of secondary amyloidosis (AA amyloidosis) in which amyloid A (AA) protein is deposited, is considered to be increasing. At present AA amyloidosis mainly followed by inflammatory diseases like rheumatoid arthritis (RA), Mediterranean fever, and adult onset Still’s disease causes the dysfunction of various vital organs. In addition, it has been revealed that the multi-organ dysfunction associated with AA amyloidosis causes the deterioration of RA prognosis. Since the mechanism of amyloid protein deposition is still unknown, the diagnosis of AA amyloidosis is difficult and there is no fundamental therapy for it; there are only supportive therapies for the malfunction of involved organs.

Most of AA amyloidosis is ascribed to uncontrolled, long term RA (disease duration 7 to 10 years). The clinical course of AA amyloidosis has not been clearly understood because the diagnosis in the early stage of disease is difficult. AA amyloidosis is diagnosed histologically and tissue biopsy is necessary to make the diagnosis. Biopsy of the upper gastrointestinal tract (GIT), especially the second portion of the duodenum is thought to be more useful and much safer than renal biopsy. AA protein deposition usually involves the arterial walls and interstitial tissues of the upper and lower GIT, kidney, heart, thymus, liver and sometimes urinary bladder. Therefore, most common symptoms are diarrhea, constipation, proteinuria, renal insufficiency, cachexia and arrhythmia. Serum amyloid A (SAA) is the precursor protein of AA protein. SAA and serum amyloid P component (SAP), heparan sulfate proteoglycan, apolipoprotein E, are coprecipitated in amyloid tissue. Therefore scintigraphy with 123I-labeled SAP might be helpful in the diagnosis (1). Although the SAA parallels that of serum CRP, the level of SAA is not useful in the diagnosis and it does not indicate of the severity of AA amyloidosis.

Recent advanced investigations in the pathogenesis of AA amyloidosis have clarified the mechanisms of synthesis and regulation of SAA. In humans, SAA consists of 104 amino acids and the AA protein deposits are derived from SAA by proteolytic cleavage and consist of 76 amino acids. Multiple forms of SAA have been identified. SAA1 and SAA2 proteins function as acute-phase reactants and both are also thought to be amyloidogenic. In animal studies, it was revealed that many factors account for the accumulation of amyloid deposition including the synthesis of SAA and the activity of macrophages in cleaving SAA to AA, etc. The overproduction of SAA is not the sole cause of AA amyloidosis. Baba et al reported that a novel allelic variant of SAA, designated SAA1γ (recently “SAA1.3”) should be used in place of “SAA1γ”), and hypothesized that this allele might be a risk factor for AA amyloidosis (2). Many reports (including ours) support that the allele SAA1γ renders RA patients susceptible to amyloidosis (3).

Once AA amyloidosis is diagnosed, the course of organ failure seems to exacerbate rapidly. The mainstay of therapy has not been confirmed yet, since it is not known whether or not the deposited fibrils can be dissolved. Neither DMSO (dimethyl sulfoxide) nor colchicine is able to dissolve the deposited AA protein from tissues. Thus, the main purpose of therapy for AA amyloidosis is merely supportive, to maintain the remaining function of kidney and heart. The causes of death in AA amyloidosis are renal and cardiac failure and infection. Therefore, earlier administration of hemodialysis is helpful for the improvement of the survival rate of kidney-involved patients. IVH (intravenous hyperalimentation) might be more effective than any medication against GI symptoms.

Immunosuppressive agents including cyclophosphamide might be useful to aggressively lower the level of serum SAA and the activity of underlying disease and to prevent accumulation of additive amyloid deposition, although there is a risk of infection (5). Corticosteroid may also be effective for patients with organ failure. Matsuda et al pointed out that administration of intermediate-dose prednisolone might suppress the deterioration of vital organ function due to the decreased production of SAA without harmful effects on vital organs (6).

See also p 403.

In the near future, with more studies, it is hoped that the pathogenesis of various amyloidoses will be clarified and a treatment for the elimination of the pre- and post precipitated amyloid fibrils will be established.
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References


