Review

Amyloidosis in the rheumatic diseases

Amyloidosis is a heterogeneous group of diseases with different clinical manifestations but characterised by the histological finding of amyloid deposits. Amyloid is a dense insoluble waxy substance found extracellularly, disrupting the structure and function of vital organs. This review focuses on the amyloidosis that complicates rheumatic diseases (and other chronic inflammatory diseases)—reactive systemic amyloidosis. The protein subunit of reactive amyloid is termed amyloid A (AA).

Reactive amyloidosis reduces the prognosis of patients, with death often occurring from renal failure. It is thus important to be aware of which rheumatic diseases are likely to be complicated by amyloidosis and of newer methods of diagnosis.

Structure of amyloid deposits

Amyloid deposits consist of fibrils thought to be composed of polypeptide chains arranged in β pleated sheets. This proposed antiparallel β pleated sheet structure is like silk fibroin and so might explain the insolubility of the fibrils in vivo. The x-ray diffraction studies on which this model was based were, however, performed on dried preparations of fibrils and may not therefore reflect the in vivo situation.

Turnell et al proposed a model from x-ray diffraction studies of wet preparations of amyloid A fibrils. Their results showed that although β structure is present, it is not exclusively so, and they proposed that fibrils are composed of stacks of globular subunits, with α helices and random coils as well as β sheets. This implies that the persistence of amyloid A in vivo may be the result of a much more complex dynamic mechanism than the formation of indestructible β pleated sheets.

The protein subunit of AA fibrils is derived from the first 76 amino acid residues from the amino terminal of serum amyloid A (SAA). SAA is an apolipoprotein found mainly in the high density lipoprotein fraction of plasma. It is synthesised in the liver and is an acute phase protein, though its function is as yet unknown. Amyloid deposits contain two further constituents: sulphated glycosaminoglycans, which are mainly heparin or heparan sulphate, and amyloid P component (AP). Both AP and glycosaminoglycans are present in all types of amyloid deposits, irrespective of the protein constituents of the fibrils.

AP is identical with serum AP (SAP)—a normal serum protein of the pentraxin family. SAP is homologous with the acute phase protein C reactive protein (51% amino acid identity), but is not an acute phase protein in man. SAP is also a normal constituent of glomerular basement membrane and elastic fibre microfibrils throughout the body.

Glycosaminoglycans have been shown to appear at the time of amyloid formation in experimental amyloidosis in mice. The material seems to be synthesised by cells locally, at or near the site of amyloid deposition. Although its significance in amyloidogenesis is not yet known, it may be involved in binding of amyloid P component.

Problems with diagnosis

A clinical diagnosis of reactive amyloidosis is usually suspected with the onset of any of the following features: proteinuria, abdominal pain and diarrhoea, frank nephrotic syndrome, or hypertension. It is necessary to keep the possibility of amyloidosis in mind as it can currently only be diagnosed histologically.

Proteinuria is often discovered on routine urine analysis. It may be difficult to establish the cause of proteinuria in a patient attending the clinic infrequently for review, in whom the possibility of urinary tract infection and drug related renal damage may exist. Even if a biopsy is performed in each patient with proteinuria this test is subject to sampling error. Therefore studies of the prevalence of amyloidosis in rheumatic diseases so far are likely to be only approximate.

Tissue diagnosis

Diagnosis is usually confirmed by rectal biopsy. Tribe and Mackenzie analysed biopsy material from 110 patients from 1971 onwards and found sufficient material in 65 cases for a proper correlation between rectal and renal amyloidosis (44 with AA and 21 with amyloid AL (whose protein subunit is derived from monoclonal immunoglobulin light chains); otherwise known as primary amyloid). Their
accuracy rate for predicting renal amyloidosis with rectal biopsy was 98.5% with no false positives. Only one of these patients had an odd form of AL amyloidosis with membranous type of glomerular amyloid deposition in her renal biopsy specimen, but no amyloid in the rectal biopsy specimen. To attain these high levels of accuracy the rectal biopsy specimen must contain submucosal blood vessels.

Renal biopsy is an alternative but potentially hazardous method of confirming the diagnosis, especially as abnormal haemostasis can be a serious problem in systemic amyloidosis involving liver as well. Yood et al found bleeding diatheses in 7 of 17 (41%) patients with AA amyloid. They studied 100 patients, and five of the six who had bleeding sufficient to warrant blood transfusion had AL amyloid. Abnormal coagulation tests (prolonged partial thromboplastin time and thrombin time) were common but did not predict those who would bleed as a result of biopsy. Clotting factor deficiency is essentially confined to AL amyloid. Bleeding diatheses were probably a combination of abnormal haemostasis and amyloid infiltration of blood vessels, leading to poor clot formation.

Fine needle biopsy of subcutaneous abdominal fat has been proposed as an easier and well tolerated test by Westermark and Stenhurst. Pettersson and Tornroth compared this method with the results of rectal and renal biopsy in 20 patients suspected of having amyloidosis. They found an excellent correlation with both techniques; there were no false positives or false negatives. In contrast, Tribe and Mackenzie did not recommend the use of subcutaneous fat aspiration because they reported that fat is rarely involved. Libbey et al reported a 20% false negative result rate. It thus appears that abdominal fat aspiration is a less sensitive method for detecting AA in the rheumatic diseases than rectal biopsy, provided the biopsy specimen includes submucosa.

Tissue sections with amyloid are stained positive with Congo red, which has a characteristic apple green birefringence under polarised light. Treatment of the sections with potassium permanganate under specific conditions causes the AA fibrils to lose their capacity to bind Congo red, unlike AL or prealbumin amyloid. The potassium permanganate test is unreliable, however, and specific immunohistochemical stains with specific antibody to amyloid A protein should be used in every case.

**DIAGNOSIS BY IMAGING**

An important advance in the diagnosis of AA amyloid and a potential method of monitoring treatment has been developed by Pepys. He showed in experimental murine AA amyloidosis that it is possible to demonstrate by gamma camera imaging the localisation and retention of radiolabelled serum AP in organs containing amyloid. This technique has recently been applied to humans, with very encouraging results.

**Pathogenesis**

Current views on the pathogenesis of AA amyloidosis are described in detail elsewhere.

In AA amyloidosis a persistently increased production of the protein precursor SAA is a prerequisite. The magnitude of the rise in serum concentration of SAA seems to reflect disease activity in chronic inflammation. Grundulis et al reported that SAA is a more sensitive marker of disease activity than C reactive protein or erythrocyte sedimentation rate. Schnitzer and Ansell found that at diagnosis all their amyloid patients had active disease. Sustained high concentrations of SAA are found in diseases which predispose to amyloidosis—for example, systemic onset juvenile chronic arthritis. Neither the concentration nor the pattern of raised SAA can be used, however, to predict which patients would develop amyloidosis. This contrasts with systemic lupus erythematosus (SLE) where C reactive protein is normal or slightly raised during active disease uncomplicated by infection, and where there is a very low incidence of amyloidosis (see below). It is interesting that in the two more convincing case reports of amyloidosis associated with SLE both patients had high SAA concentrations.

Despite persistently active disease and high SAA concentrations, only a small proportion of patients develop amyloidosis—for example, 10% in juvenile chronic arthritis (see below). Thus interactive factors that are genetically determined are important. Pepys has suggested that AP may bind to the amyloid fibrils, thus shielding them from degradation. Woo et al reported a significant association between patients with juvenile chronic arthritis with amyloidosis and a DNA polymorphic site 5-6 kb upstream of the SAP gene, which may be in linkage disequilibrium with DNA sequence variations in either the promoter or coding regions of the SAP gene.

**Prevalence (Table 1)**

**DISEASES OFTEN COMPLICATED BY AMYLOIDOSIS**

**Rheumatoid arthritis**

Husby quoted the prevalence in living patients with rheumatoid arthritis as ranging from 5 to 11%, and Mladenovic et al showed a prevalence of 5-3% in 75...
patients. Several postmortem studies have confirmed the findings of Missen and Taylor in 1956. They found amyloidosis at necropsy in 14% of 181 patients with rheumatoid arthritis.

A recent 10 year retrospective study by Mutru et al showed that renal amyloidosis is still a major cause of death in patients with rheumatoid arthritis.

**Juvenile chronic arthritis**

Patients with juvenile chronic arthritis with systemic involvement at onset have a higher prevalence of amyloidosis than those with non-systemic disease. Amyloidosis is responsible for 43-47% of deaths in European patients with juvenile chronic arthritis. It is an important cause of death even when the disease has burnt out some years before.

**Ankylosing spondylitis**

All four patients (4%) with amyloidosis in a series of 90 reported by Mladenovic et al had proteinuria, three of these had nephrotic syndrome, and one of the four had a negative rectal biopsy specimen.

A similar figure for amyloidosis in ankylosing spondylitis was obtained by Christoph et al in a population of 113. Three out of five patients had no renal involvement.

**Psoriatic arthritis**

All the patients with amyloidosis from the series of 131 patients reported by Maldykowa and Krasnowska (prevalence 10%) had 'very severe' arthritis.

**Diseases seldom complicated by amyloidosis**

**Reiter's disease**

The only patient with amyloidosis in the series of 70 patients described by Miller et al did not have the amyloid type characterised, though AL type was felt to be unlikely by the exclusion of monoclonal gammopathy. Forty seven patients with ankylosing spondylitis and 41 with HLA-B27 associated arthropathies were also studied, none of whom was shown to have amyloidosis.

**Dermatomyositis**

There is only one reported case of amyloidosis complicating dermatomyositis to our knowledge. Galdenman et al reported a 42 year old man who had very aggressive dermatomyositis diagnosed clinically, by electromyography and by muscle biopsy. Although his serology and erythrocyte sedimentation rate were normal, his disease remained clinically very active despite treatment with steroids and antimalarial drugs. After four years he presented with hepatomegaly, peripheral oedema, and albuminuria. Biopsy specimens taken in life were reported negative, but postmortem review of these specimens showed extensive amyloidosis affecting almost every organ. The amyloid type was not characterised.

### Table 1: Prevalence (%) of amyloid AA in the rheumatic diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence (%)</th>
<th>Comments</th>
<th>References</th>
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<tbody>
<tr>
<td>Rheumatoid arthritis</td>
<td>5-20</td>
<td>Variable figures according to whether studies were at necropsy or during life, and the duration of disease at time of study</td>
<td>11, 24-27</td>
</tr>
<tr>
<td>Juvenile chronic arthritis</td>
<td>10</td>
<td>This figure is generally agreed in European studies, but much reduced in Australian and US studies</td>
<td>19, 28-34</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>4-5</td>
<td>Generally confined to patients with severe disease and peripheral arthritis</td>
<td>25, 35, 36</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>10</td>
<td>This figure requires confirmation</td>
<td>37, 38</td>
</tr>
<tr>
<td>Reiter's disease</td>
<td>1-2</td>
<td>Series of 70 patients</td>
<td>39</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td></td>
<td></td>
<td>40</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
<td></td>
<td>21, 22, 41, 42</td>
</tr>
<tr>
<td>Progressive systemic sclerosis</td>
<td></td>
<td></td>
<td>43-47</td>
</tr>
<tr>
<td>Sjögren's syndrome</td>
<td></td>
<td></td>
<td>48, 49</td>
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- Dhillon, Woo, Isenberg
Systemic lupus erythematosus
There are two case reports in which the criteria for the diagnosis of SLE were clearly met. Unlike most patients with SLE, both had high SAA concentrations during the course of the disease.

Huston et al reported a 43 year old Egyptian man with SLE present for 20 years diagnosed on American Rheumatism Association criteria and treated with several immunosuppressive drugs, but who always had active disease. He then presented with clinical signs indicating possible amyloidosis: proteinuria and deteriorating renal function. Renal biopsy showed AA amyloid with no evidence of lupus nephritis.

Pettersson et al reported a 36 year old woman with an 18 year history of SLE diagnosed clinically (photosensitivity, rash, arthralgia, acrocyanosis, pleuritis, pericarditis, and fever) and serologically (haemolytic anaemia, leucopenia, positive antinuclear antibody test, DNA, SMA, and RNP antibodies, and LE cells). Thirteen years after diagnosis she developed WHO classification SLE class IIIB nephritis indicated by renal biopsy, but no amyloid stain was done. She then developed clinical features more suggestive of scleroderma, and biopsy indicated myositis; she was treated with a variety of immunosuppressive drugs. Five years later she developed nephrotic syndrome and a pericardial effusion. Rectal and abdominal wall subcutaneous fat aspiration showed amyloid of type AA, confirmed by immunohistochemistry. The patient died and at necropsy amyloid was found in heart, spleen, and kidneys.

Progressive systemic sclerosis
In none of the six cases reported was the amyloid type determined. Brandwein et al measured SAA protein concentrations in 62 patients with progressive systemic sclerosis. Forty seven patients (76%) had normal or slightly raised SAA concentrations (<1000 μg/l). Fifteen patients (24%) had moderately to markedly raised SAA concentrations, similar to those observed in active rheumatoid arthritis (>1000 μg/l). Five patients with progressive systemic sclerosis had SAA concentrations corresponding to those observed in amyloidosis secondary to rheumatoid arthritis. High SAA concentrations were associated with more severe skin thickening and diminished cumulative survival at five years. The authors commented that the rarity of amyloidosis in progressive systemic sclerosis was unlikely to be related to an intrinsic defect in SAA production.

Sjögren's syndrome
A recent review of this illness alluded to only one case complicated by amyloidosis proved by biopsy. In this case the nodular nature and unusual site of the amyloid (lung and salivary gland) led the authors to conclude that it was primary amyloid, usually associated with a plasma cell dyscrasia.

Treatment
Cytotoxic drug treatment has been used in an attempt to control the underlying rheumatic disease. Schnitzer and Ansell began treatment with chlorambucil in selected patients with juvenile chronic arthritis in 1967. This controlled the activity of the disease within one to two years after the start of treatment. All patients had proteinuria at onset of treatment and after three or more years 64% had no proteinuria. At the time of reporting, continuous treatment with chlorambucil had produced a significant improvement in patient survival.

Berglund et al reported a significant improvement in survival in 14 patients with rheumatic disease and renal amyloidosis treated with alkylating agents, chlorambucil being their drug of choice. Ahlen et al found an improvement in five year survival from 27% (untreated controls) to 89% in 22 patients who took part in a randomised prospective trial of treatment with a variety of cytotoxic drugs. The improved survival in these studies was paralleled by a deceleration of decline in renal function.

The benefit from treatment with cytotoxic drugs, which presumably reduce circulating concentrations of the fibril precursor protein SAA, must be weighed against the adverse effects of these drugs. The cited studies did not show an actual reduction in the amount of amyloid present. No treatment has yet been described which removes amyloid deposits. Monitoring with radiolabelled SAP may provide a useful method for assessing treatment in the future.

Conclusion
It is evident that studies of the prevalence of amyloidosis in the rheumatic diseases have been incomplete because of the method of making the diagnosis. Nevertheless, between five and 15% of patients with rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis have been shown to develop amyloidosis. In contrast, SLE, progressive systemic sclerosis, and Reiter's disease are very rarely complicated by amyloidosis. The recent development of a new method of diagnosis by imaging should provide the tools to reassess the prevalence of amyloidosis in these diseases.

There is an underlying trend indicating that patients with unusually active disease are more at risk of developing amyloidosis. Persistently-raised...
concentrations of the precursor SAA are a prerequisite, but other interactive factors appear to be important for amyloidogenesis. Diseases with low or moderately raised acute phase proteins—for example, SLE and progressive systemic sclerosis, are less likely to be complicated by reactive amyloidosis.

The elucidation of the factors which determine amyloidogenesis are crucial for future prevention and treatment of this life threatening complication of chronic arthritis.

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References


