AN 84-YEAR-OLD WOMAN WITH POLYARTHRITIS

Dr. Man-Ching Leung, MBBS(HK) MRCP(UK)
Medical Officer

Dr. Sik-Ling Choi, MBBS(Lon) MRCP(UK)
Senior Medical Officer

Dr. Wai-Po Mak, MBBS(HK) FRCP(Edin)
Chief of service

Department of Geriatrics
Caritas Medical Center
Shamshuipo, Kowloon, Hong Kong

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Address correspondence to: Dr. M. C. Leung

Summary

We report an 84-year-old woman who presented with symmetrical polyarthritis involving large joints and periarticular nodular deposits for 2 years. She was eventually found to have AL amyloidosis, multiple myeloma (IgG/Kappa). She also demonstrated the classical ‘shoulder pad sign’. Trucut biopsy of the right shoulder mass revealed congophilic material with apple green birefringence under polarized light. Other clinical features included anaemia, nephrotic range proteinuria, osteolytic bone lesions, but there was no hypercalcaemia, hyperglobulinaemia or elevated erythrocyte sedimentation rate (ESR). Echocardiogram showed sparkling myocardial appearance. Review of a gastric biopsy done 2 years ago also showed congophilic angiopathy in the muscularis mucosae. Patient succumbed unexpectedly before the initiation of treatment.

Introduction

Amyloidosis is both an old and new disease. The term was first introduced by Virchow more than 100 years ago. It was not until the last 2-3 decades did we know about the chemical compositions of amyloid fibrils. So far, 17 different amyloidogenic proteins have been identified. It is a heterogeneous group of diseases with variable clinical presentations. We discuss the latest WHO classification, pathogenesis, epidemiology, various clinical syndromes, diagnosis, treatment and prognosis of amyloidosis.

Case Report

An 84-year-old woman was first admitted to the Geriatrics Department of Caritas Medical Center (CMC) in April, 1997 for cerebellar infarction when she presented with slurred speech and limb weakness. She had a two-year history of joint pain involving both shoulders, elbows, wrists and knees and was treated as rheumatoid arthritis (RA) by a rheumatologist with non-steroidal anti-inflammatory drug (NSAID) and oral levamisole 150 mg once a week for 2 years. She was admitted to CMC in 1995 for NSAID-induced upper gastrointestinal bleeding requiring blood transfusion. She lived with her son and was home bound. Due to her joint problems, she could only walk a few steps with frame and assistance. She never smoked or drank excessive alcohol. She had an exacerbation of polyarthritis during hospitalisation but tested negative for rheumatoid factor. The ESR was not elevated and she was thought to have crystal-induced arthritis based on X-ray finding of non-erosive joint disease and chondrocalcinosis. In addition, she had normochromic, normocytic anaemia and proteinuria in nephrotic range. Renal biopsy was not performed at that time. She returned home after a month of rehabilitation but she remained bed bound. Her Barthel Index was 18/100 on discharge.

Two weeks later, she was admitted again for sacral sore. Examination revealed symmetrical swelling of both shoulders, elbows and knees. There were firm, immobile, non-fluctuant, non-pulsate and non-tender periarticular nodules around shoul-

Fig. 1. Solid firm masses over bilateral shoulders and solid nodules near the lateral ends of both clavicles.
ders, wrists, elbows and knees. Both shoulder joints were subluxed with prominent enlargement, and the periarticular tissue had a rubbery firm consistency (Figure 1). There were also subcutaneous nodules on the back and sacrum with ulceration. The patient was pale, cachetic and had bruises on both forearms. Blood tests and urine studies from the last admission were reviewed (Table 1).

Table 1. Laboratory findings

<table>
<thead>
<tr>
<th>Haematological</th>
<th>Liver function test</th>
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<tbody>
<tr>
<td>Haemoglobin 8.1 g/dL</td>
<td>Bilirubin 16 µmol/L</td>
</tr>
<tr>
<td>White cell count 6.1x10^9/L</td>
<td>Alkaline phosphatase 60 IU/L</td>
</tr>
<tr>
<td>Platelet 247x10^9/L</td>
<td>Aspartate transaminase 45 IU/L</td>
</tr>
<tr>
<td>ESR 24 mm/hour</td>
<td>Alanine transaminase 10 IU/L</td>
</tr>
<tr>
<td>Albumin 31 g/L</td>
<td>Total protein 58 g/L</td>
</tr>
</tbody>
</table>

Blood chemistry Immune Markers

| Sodium 138 mmol/L | Rheumatoid factor non-reactive |
| Potassium 4.2 mmol/L | Anti-nuclear factor negative |
| Urea 5.3 mmol/L | Anti-DNA negative |
| Creatinine 148 µmol/L | C3 (mg/dL) 97.6 (68-135) |
| Chloride 105 mmol/L | C-reactive protein reactive |
| Bicarbonate 26.2 mmol/L | Anaemia workup |
| Calcium 2.2 mmol/L | Iron 22.3 µmol/L |
| Phosphorus 1.22 mmol/L | Total iron binding capacity 61.2 µmol/L |
| Urine protein 7.24 g/day | Creatinine clearance 53 ml/minute |

Arthrocentesis of the right knee joint in the previous admission during exacerbation of arthritis revealed low white blood cell (WBC) count in the synovial fluid. (Table 2). Besides, synovial fluid analysis for crystal substances was negative, rendering the diagnosis of crystal-induced arthritis questionable. Ultrasonogram of the abdomen showed that the kidneys were normal in size but had increase in echogenicity. Liver and spleen were normal.

Table 2. Synovial fluid cell counts

| red cells | numerous |
| white cells | 216/mm³ |
| lymphocytes | 50% |
| polymorphs | 50% |

Review of the history and investigation results showed evidences incompatible with RA or crystal-induced arthropathy. Fine needle aspirate of right shoulder mass was performed, showing no crys-

...tals or calcified material but amorphous eosinophilic substance suspected to be amyloid (Figure 2). A trucut biopsy of the same lesion showed congophilic material with apple green birefringence under polarized light, confirming the presence of

![Fig. 2. Fine needle aspirate of right shoulder mass.](image)

![Fig. 3. Serum protein electrophoresis and immunofixation.](image)
amyloid. Investigating for the causes of amyloidosis, urine analysis turned out positive for Bence-Jones protein and serum protein electrophoresis showed the presence of monoclonal IgG/Kappa (Figure 3). β₂-microglobulin was also elevated (3.8 mg/L). Bone marrow biopsy demonstrated 85% plasmacytosis (Figure 4). Review of X-rays showed lytic changes in bilateral humeral heads, both medial femoral condyles with soft tissue swelling and calcification (Figure 5). Skull X-ray was normal. Electrocardiogram showed non-specific ST- and T-wave abnormalities over V₂ to V₄. Echocardiogram showed sparkling texture of the myocardium (Figure 6), consistent with amyloidosis. In addition, there was a small increase in left ventricular wall thickness (interventricular septal wall thickness 1.33 cm, left ventricular posterior wall thickness 1.14 cm). Doppler echocardiography revealed evidence of diastolic dysfunction (early-diastolic filling (E) to atrial filling (A) ratio = 0.64/1.13). Deceleration time was 171 msec and isovolumic relaxation time was 120 msec. Review of gastric biopsy done in 1995 also detected the presence of amyloid (Figure 7).
The diagnosis was multiple myeloma associated amyloidosis, with IgG/Kappa serum monoclonal component. Unfortunately, the patient succumbed unexpectedly before definitive treatment. Her relatives did not give permission for a post-mortem.

**Discussion**

**Physical and chemical nature of amyloid**

Amyloid deposit is always extracellular and presents a fibrillar conformation. The fibril is non-branching, of indefinite length, 7.5-10 nm in diameter and in a β-pleated anti-parallel configuration that can be demonstrated by X-ray diffraction. Eighty-five percent of the amyloid protein is constituted of a specific protein (fibrillar protein) of each variety of amyloidosis. The rest 15% (extrafibrillar proteins) consists of other proteins, such as serum amyloid P (SAP) and the glycosaminoglycans (GAG) that are common to all types of amyloidosis. Amyloid is resistant to proteolytic degradation, thus always persists and accumulates.

**Table 3. Nomenclature and classification of human amyloid and amyloidosis**

<table>
<thead>
<tr>
<th>Amyloid</th>
<th>Protein</th>
<th>Protein Type</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>SAA</td>
<td>Reactive(secondary);FMP; familial amyloid nephropathy with urticaria and deafness</td>
<td>Muckle-Wells’syn-syndrome</td>
</tr>
<tr>
<td>AL</td>
<td>κ, λ, eg, κIII</td>
<td>Aκ, Aλ, eg, AκIII</td>
<td>Idiopathic (primary), myeloma- or macroglobulinemia-associated</td>
</tr>
<tr>
<td>AH</td>
<td>IgG(γ/δ)</td>
<td>Aγl</td>
<td>Familial amyloid polyneuropathy, Portugal</td>
</tr>
<tr>
<td>ATTR</td>
<td>Transthyretin</td>
<td>eg, Met30</td>
<td>Familial amyloid polyneuropathy, Denmark</td>
</tr>
<tr>
<td></td>
<td></td>
<td>eg, Met111</td>
<td>Familial amyloid polyneuropathy, Denmark</td>
</tr>
<tr>
<td>AAprAl</td>
<td>apoAl</td>
<td>Arg26</td>
<td>Systemic senile amyloidosis</td>
</tr>
<tr>
<td>AGel</td>
<td>Gelsolin</td>
<td>Asn187</td>
<td>Familial amyloid polyneuropathy, Iowa</td>
</tr>
<tr>
<td>ACys</td>
<td>Cystatin C</td>
<td>Gin68</td>
<td>Hereditary cerebral hemorrhage with amyloidosis, loeland</td>
</tr>
<tr>
<td>Aβ</td>
<td>β-protein precursors, eg, ßPP 695</td>
<td>Gin618</td>
<td>Hereditary cerebral hemorrhage with amyloidosis, the Netherlands</td>
</tr>
<tr>
<td>Aβ, M</td>
<td>β-microglobulin</td>
<td>Glu187</td>
<td>Alzheimer’s disease, Down’s syndrome</td>
</tr>
<tr>
<td>AScr</td>
<td>Scapie protein precursor 33-35, cellular form</td>
<td>eg, Leu 102</td>
<td>Gerstmann-Staussler-Scheinker syndrome</td>
</tr>
<tr>
<td>ACal</td>
<td>(Pro)calcitonin</td>
<td>(Pro)calcitonin</td>
<td>In medullary carcinoma of the thyroid</td>
</tr>
<tr>
<td>AANF</td>
<td>Atrial natriuretic factor</td>
<td>Isolated atrial amyloid</td>
<td></td>
</tr>
<tr>
<td>AIAPP</td>
<td>Islet amyloid Polypeptide</td>
<td>In islets of Langerhans, diabetes typeII; insulinoma</td>
<td></td>
</tr>
</tbody>
</table>

**The WHO classification system**

The most recent attempt to standardise the classification of amyloidosis was that of Husby 1, which was later expanded by the WHO-IUIS Nomenclature Subcommitee (1993). The essential feature of this approach is that ‘the basis for nomenclature and classification should be the fibril making up the amyloid deposits’ 2 (Table 3).

**Pathogenesis**

The mechanisms by which the various soluble precursor proteins are converted to insoluble aggregates are not clear. Furthermore, the predilection of certain amyloid fibrils for particular tissues or organs, often distant from the cells producing them, also remains a mystery. It is generally agreed that the following pathogenic factors are important in amyloidosis.

1. **Availability of precursor protein**

It is conceivable that amyloid is converted from excessive precursor protein, as a consequence of increased production or decreased catabolism. Elevation of serum amyloid A (SAA) in chronic inflammatory diseases, monoclonal immunoglobulin in lymphoproliferative disorders and β₂-microglobulin in chronic hemodialysis are examples.

2. **Structural properties of amyloid precursor protein**

Normal transthyretin (TTR) is associated with benign systemic senile amyloidosis occurring in old age 3. Point mutations of the TTR gene lead to mutant TTR proteins that are associated with the more severe and early onset inherited amyloid polyneuropathies or cardiomyopathies 4. AA amyloidosis affects only a minority of patients with chronic inflammatory disorders such as RA, although the majority of patients have chronically increased SAA levels 5. Additional pathogenic factors are thus required for amyloidosis to develop. SAA is polymorphic, meaning that more than one gene code for the protein 6. In the mouse model, SAA2, one of the two defined SAA protein variants in the circulation, forms amyloid whereas SAA1 does not 7. A structural subgroup of immunoglobulin light chains, namely λ VI, is associated with amyloidosis far more often than statistically expected 8.

3. **Defective degradation of precursor**

Chemical analyses of different purified amyloid proteins have shown that in most instances they comprise a smaller or larger fragment of their precursors, pointing to incomplete degradation 9. This suggests that fragmentation of precursor protein promotes fibril formation. In-vitro studies in which
limited proteolysis of both SAA and Bence Jones protein resulting in the formation of Congo red-positive fibrils support this theory\(^9\). However, some amyloid fibril proteins (e.g. TTR, \(\beta_2\)-microglobulin) are identical in size to their precursors, indicating that fragmentation is not an absolute pre-requisite for fibrillogenesis\(^5\).

4. Amyloid-enhancing factor and glycosaminoglycans

Amyloid-enhancing factor (AEF) is a poorly defined substance that probably consists of both protein and carbohydrates. It is induced in the spleen, liver, and kidney during persistent inflammation, and is probably synthesised and secreted by reticuloendothelial cells in these organs. In mouse and hamster, AEF consistently precedes the occurrence of amyloid in these organs\(^11,12\). Intravenously injected AEF can also shorten the induction time from weeks down to 24-48 hours in experimental amyloidosis. There is probably an alteration in the degradation and processing of SAA to fibrils due to AEF\(^13\). AEF extracted from human organs laden with AA, AL and TTR-related amyloid enhances experimental murine AA amyloidosis\(^14\). Glycosaminoglycans and possibly proteoglycans that are persistently present in amyloid deposits may account for the carbohydrate moiety in AEF. The large negative charge of GAG may have an effect on precursor protein folding and incorporation into the fibrils\(^15\).

5. Protein AP - the amyloid P component

Protein AP is an \(\alpha\)-glycoprotein that is invariably present in amyloid deposits\(^16\). A normal plasma pentraxin protein, SAP, identical to protein AP in structure and binding properties, is its precursor\(^17\). Although the serum concentration of SAP is not increased in the acute phase or in patients with amyloidosis, the synthesis of the protein is increased in amyloidotic patients, indicating a specific role in amyloidogenesis. Purified human AP inhibits proteolytic activity of elastase in vitro\(^18\). This may have implications in amyloidogenesis because AP could inhibit the enzymatic breakdown of amyloid precursor protein at the site of fibril deposition\(^19\).

**Epidemiology**

In the Netherlands, a minimal estimate for the incidence of AL and AA (approximate ratio, 1:2) amyloidosis based on official death registrations could be 1 in 75,000 persons (13.3 per million person-years). In a Dutch series of 91 AA amyloidosis, the most common underlying disease was RA (56%), followed by recurrent pulmonary infections (11%), Crohn’s disease (5%), tuberculosis (3%), osteomyelitis (2%), familial Mediterranean fever (2%) and Hodgkin’s disease (2%). In RA, amyloidosis occurs as a complication in approximately 10-15% of patients\(^20\). In a recent Japanese study, gastrointestinal fibrosities and biopsies performed on 789 RA patients detected amyloidosis in 77 cases (10.5%)\(^21\). The mean duration of RA in patients with amyloidosis was 15.4 years\(^22\).

**Clinical Amyloidosis Syndromes**

A description of AA amyloidosis and AL (idiopathic and myeloma-associated) amyloidosis syndromes in relation to their fibril protein follows.

1. Reactive AA amyloidosis

Reactive (secondary) amyloidosis is associated mainly with long-standing inflammation, and less frequently with cancer, mainly renal cell carcinoma or Hodgkin’s disease\(^23\). Interestingly, AA amyloidosis is extremely rare in systemic connective tissue diseases such as systemic lupus erythematosus, dermatomyositis, systemic sclerosis and Sjogren syndrome\(^24\). The last three conditions are associated with lower serum concentrations of SAA than RA. Furthermore, amyloidosis is quite prevalent in Crohn’s disease, which stimulates acute-phase proteins, and is infrequent in ulcerative colitis, which does not stimulate such proteins\(^5\). Arthritic patients with prominent systemic disease activity are more prone to develop amyloidosis than those with milder disease, but the development of amyloidosis in individual cases cannot be predicted\(^23\). HLA studies have failed to disclose markers for reactive amyloidosis. AA amyloid has a tendency to localise in small vessels and parenchymal organs (Table 4). Renal disease, often with the nephrotic syndrome and/or renal failure, is the chief manifestation and the major cause of death. Hematuria occurs less frequently\(^19\). Hypertension is uncommon in adult-onset RA with amyloidosis but is found in about half of the patients with juvenile RA associated amyloidosis\(^25\). Arthropathy and carpal tunnel syndrome are not features of AA amyloidosis but are characteristic of both AL and \(\beta_2\)-microglobulin-associated amyloidosis\(^19\).

**Table 4. Clinical features common to AL and AA amyloidosis**

- Weakness, fatigue and weight loss (most prominent in AL amyloidosis)
- Kidneys: Cause of death in the majority of AA amyloidosis and in 1/3 of AL amyloidosis. Nephrosis and/or renal failure
- Gastrointestinal tract: Malabsorption, malnutrition, obstruction, diarrhea (disturbed motility), bleeding
- Liver: Mainly enlargement, rarely functional disturbance
- Spleen, endocrine glands: Severe symptoms infrequent
Table 5. Clinical characteristics of AL amyloidosis

- Heart
  - Cause of death in - 50% of AL amyloidosis
  - Restrictive cardiomyopathy
  - Conduction disturbances
  - Angina pectoris-myocardial infarction
  - Low voltage on electrocardiogram
  - Digitalis hypersensitivity
- Lung(90%)
  - Cough
  - Dyspnea
- Skin(40%)
  - Purpura
  - Papules
  - Tumors
- Peripheral neuropathy(10%)
- Carpal tunnel syndrome(20%)
- Autonomic disturbances
  - orthostatic hypotension, etc
- Macroglossia(20%)
- Bleeding due to vasulopathy and coagulation factor X deficiency
- Amyloid arthropathy
  - Mainly large joints (e.g., ‘shoulder pad sign’)

2. Idiopathic and myeloma-associated AL amyloidosis

The mean age at diagnosis of AL amyloidosis is approximately 60 years; idiopathic and myeloma-associated amyloidosis have similar organ distribution. The most severe clinical consequences of AL amyloidosis are caused by accumulation of amyloid in the heart and kidneys (Table 5). Glomerular and vascular amyloidosis of the kidneys with consequent nephrosis and/or renal failure causes one third of the deaths. Increased numbers of plasma cells in the bone marrow, M components in serum, and Bence Jones proteinuria are frequent findings in idiopathic AL amyloidosis. This indicates that such disorder belongs to the immunocyte dyscrasias resulting from the same basic pathogenic mechanisms as myelomatosis. The major difference between them is the osteolytic lesions of myelomatosis, which are absent in idiopathic AL amyloidosis. Another difference is that the Kappa to Lambda ratio, approximately 2:1 in myelomatosis, is reversed (1:2) in AL amyloidosis, reflecting the more amyloidogenic nature of the lambda light chain.

Amyloid arthropathy occurs most frequently in association with multiple myeloma (up to 5% of cases), but has also been reported in patients with primary amyloidosis. It is typically symmetrical and involves the shoulders, wrists, hands and knees. The shoulder-pad sign is pathognomonic. It describes prominent enlargement of the shoulders with a rubbery hard consistency of the periarticular tissue caused by amyloid infiltration. Glenner made this analogy to football players’ shoulder pads. Amyloid arthropathy may mimic RA in its presentation but is non-erosive. Radiographic findings include preserved joint spaces, well-defined cystic lesions with or without surrounding sclerosis. Synovial fluid contains fewer leukocytes (200-4,500/mm³), predominantly mononuclear cells.

Table 6. Diagnosis of AA amyloidosis by biopsy

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Sensitivity</th>
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<tbody>
<tr>
<td>subcutaneous fat aspirate</td>
<td>60%</td>
</tr>
<tr>
<td>rectal biopsy</td>
<td>80%</td>
</tr>
<tr>
<td>stomach-duodenum biopsy</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>labial salivary gland</td>
<td>86%</td>
</tr>
<tr>
<td>kidney</td>
<td>90%</td>
</tr>
</tbody>
</table>

Diagnosis

The diagnosis of amyloidosis must be confirmed by biopsy. For routine identification of amyloid, the Congo red stain remains the method of choice. Examination of Congo red-stained tissue sections under polarising light microscope shows the apple-green birefringence. Potential biopsy sites and their corresponding sensitivities are listed in Table 6. Amyloid β₂-microglobulin is rarely found by rectal biopsy and abdominal fat aspiration. Biopsy of a bone cyst or synovial biopsy gives better yield. Immunohistochemical techniques using specific antisera to classify the various amyloid fibril proteins are increasingly used but are not routinely available. Electron microscopy may also confirm the diagnosis. Drawbacks of the biopsy procedures are that they are invasive, prone to sampling error, and provide limited information on the distribution and extent of amyloid deposits. Scintigraphic and turnover studies with radioiodinated SAP are new methods for the detection of amyloid deposits. They are based on the affinity of SAP for all types of amyloid fibril. Turnover studies of labelled SAP yield information on the whole-body amyloid burden. Serial studies show promise in evaluating the progression or regression of systemic amyloidosis. However, SAP scintigraphy is not available in Hong Kong. It is also not useful in evaluation of β₂-microglobulin amyloidosis because SAP clearance is disturbed in hemodialysis patients. Echocardiography, radiology, nerve conduction study, bone marrow examination, detection of monoclonal immunoglobulins in serum and urine and gene studies are all useful in diagnosing various amyloidosis syndromes.
Management and prognosis

The principles of treating amyloidosis are early diagnosis, reduction of precursor proteins and supportive therapies. In AA amyloidosis, suppression of the underlying disease process by alkylating agents in RA and colchicine in Familial Mediterranean fever have been shown to preserve renal function and improve survival\(^3\). In AL amyloidosis, cytotoxic drug regimes are identical to those used for the treatment of multiple myeloma\(^31\). Intensive chemotherapy combined with bone marrow transplantation or autologous stem cell infusion is encouraged in patients with myeloma related AL amyloidosis. Local application of dimethyl sulfoxide, an amyloid fibril denaturing agent, has been effective in the treatment of cutaneous and urologic amyloid lesions. Successful renal transplantation is the only mode of therapy that can arrest the progression of a \(\beta_2\)-microglobulin amyloidosis. A switch to high-flux dialyzers may result in amelioration of subjective symptoms, but no concurring effect on objective signs\(^32\). Supportive therapy includes active treatment of cardiac and renal failure. Digitalis and calcium channel-blocking agents may aggravate heart failure in patients with cardiac amyloid. Amyloid appears to bind such agents in vitro and possibly in vivo, and they should be used with caution\(^32\).

Systemic amyloidosis is a serious condition with a high mortality. Data extrapolated from three studies on patients with AA amyloidosis shows a 50% survival ranging from 2 to 4 years. Elevation of serum creatinine is a strong adverse prognostic indicator in AA amyloidosis\(^30\). The prognosis of AL amyloidosis is even worse. Average survival is less than 2 years for idiopathic AL amyloidosis and 7 months for myeloma associated AL amyloidosis\(^33\). Cardiac amyloidosis is the most common cause of death and the major determinant of prognosis among AL patients\(^34\). Peripheral neuropathy as the sole manifestation in AL amyloidosis has the best outcome (median survival: 40 months)\(^35\).

Case discussion

Our patient presented with amyloid arthropathy for two years, and was misdiagnosed as RA and then crystal arthritis. The low WBC count in the synovial fluid actually suggested a non-inflammatory joint disease. A traditional rule of thumb is that synovial fluid with a total WBC count less than 2,000/mm\(^3\) indicates a non-inflammatory disease. These include conditions like osteoarthritis, sickle cell disease, hypertrophic pulmonary osteoarthropathy, hypothyroidism and amyloidosis\(^36\). The shoulder pad sign in this case is pathognomonic of AL amyloidosis.

The diagnosis of multiple myeloma was definitive. She had 85% bone marrow plasmacytosis, Bence Jones proteinuria, serum monoclonal protein (>3g/dL) as well as osteolytic bone lesions. \(\beta_2\)-microglobulin level was also elevated. The patient did not have elevated ESR, hypercalcemia or hyperglobulinemia. The monoclonal protein in this case was the commonest type seen in multiple myeloma (i.e. IgG/Kappa). The total IgG was not elevated (863 mg/dL), which may explain the normal ESR and globulin levels. There was suppression of both IgA and IgM levels. Her renal function was normal for her age despite heavy proteinuria.

Amyloidosis is one of the most likely causes of nephrotic syndrome in older adults\(^37\). In the United States, over 75% of amyloid related nephrotic syndrome is due to AL amyloid, and \(\lambda\) light chain deposition occurs in over 75% of such cases. Our patient most likely had the less common \(k\) light chain AL amyloidosis, although this was not confirmed by immunohistochemical studies. She had nodular amyloidosis during her terminal illness. Despite the absence of cardiac symptoms, the granular and sparkling appearance on echocardiography is characteristic of cardiac amyloidosis. Her sudden death could be due to cardiac cause. Cardiac amyloidosis is the most common cause of death in AL amyloidosis\(^38\).

Concerning her admission for NSAID induced gastrointestinal bleeding in 1995, upper endoscopy at that time showed a 1.0 cm gastric ulcer at 45 cm on the lesser curve, unassociated with Helicobacter pylori. Her haemoglobin on admission was 4.7 g/dL. Post-transfusion haemoglobin was 11.4 g/dL. No more NSAID was prescribed to her. She was given a course of ranitidine and rescued after 8 weeks. The second endoscopy showed healed ulcer. However, her haemoglobin dropped to 7.4 g/dL and stool for occult blood was positive. Patient declined colonoscopy. She was given iron supplement on discharge. Review of her gastric biopsy from 1995 showed the presence of amyloid deposition. Her persistant anaemia and occult gastrointestinal bleeding in 1995 may be in fact related to gastrointestinal amyloidosis.

Amyloidosis may not have accounted for the cerebellar infarction in our patient. This is because the brain and intracerebral blood vessels are rarely affected in the systemic amyloidosis but are common sites for the local deposition of amyloid in the absence of amyloid elsewhere in the body (e.g. age-related amyloid angiopathy, hereditary amyloid...
angiothiopathy, Alzheimer’s disease, cerebral amyloid associated with prion disease, and Icelandic or Dutch type hereditary amyloid angiothiopathy of meningeal and cortical vessels associated with cerebral haemorrhage [39]. Besides, in AL amyloidosis, central nervous system involvement was absent, but autonomic and sensory neuropathy are relatively common features [40].

References