Unicentric Castleman’s disease complicated by systemic AA amyloidosis: a curable disease

H.J. LACHMANN, J.A. GILBERTSON, J.D. GILLMORE, P.N. HAWKINS and M.B. PEPYS

From the NHS National Amyloidosis Centre and the Centre for Amyloidosis and Acute Phase Proteins, Department of Medicine, Royal Free and University College Medical School, Royal Free Campus, London, UK

Received 16 November 2001 and in revised form 14 January 2002

Summary

Background: Castleman’s disease (angiofollicular lymph node hyperplasia) is a group of rare lymphoproliferative disorders sharing characteristic clinical and histological features, and usually accompanied by a marked systemic inflammatory response. All types may be complicated by acquired systemic amyloidosis, usually of AA type, but occasionally of AL type associated with monoclonal gammopathy.

Design: Descriptive study of five patients with unicentric Castleman’s disease complicated by systemic AA amyloidosis.

Methods: A diagnosis of amyloidosis was confirmed by microscopy and immunohistochemical staining. Serum concentrations of C-reactive protein (CRP) and serum amyloid A protein (SAA) were measured by immunoassays. Radiolabelled serum amyloid P component scintigraphy was used to monitor the progress of amyloid deposition.

Results: In four patients the primary diagnosis was made only after years of investigation of systemic symptoms. The tumours were resected in all cases, leading to remission of the systemic inflammatory state. Long-term follow-up in four patients, including scintigraphy, showed regression of amyloid deposits.

Discussion: This rare but usually fatal condition can be cured surgically even in advanced cases. Awareness of the diagnosis and its correct management are important in investigation of patients with unexplained systemic symptoms, especially associated with systemic amyloidosis.

Introduction

Castleman’s disease,1 or angiofollicular lymph node hyperplasia, is a rare B-cell lymphoproliferative disorder characterized by giant hyperplastic lymph node follicles, capillary proliferation and plasma cell infiltration, and often associated with marked constitutional symptoms. It is a disease spectrum, comprising anatomically unicentric and multicentric forms, and hyaline vascular and plasma cell histological variants.2 Multicentric disease, commonly of the plasma cell type, usually follows an aggressive and rapidly fatal course. Unicentric disease tends to occur in younger patients and is hyaline vascular type in more than 70% of cases, with plasma cell or mixed histology in the remainder.3,4 Most tumours occur within the mesenteries or mediastinum and are complex, consisting of a dominant mass surrounded by multiple enlarged lymph nodes, and may reach 15 cm or more in diameter. Constitutional symptoms including night sweats, fever and weight loss are common, and laboratory abnormalities, including anaemia, elevation of the erythrocyte

Address correspondence to Dr H.J. Lachmann, NHS National Amyloidosis Centre, Department of Medicine, Royal Free and University College Medical School, Royal Free Campus, Rowland Hill Street, London NW3 2PF. e-mail: h.lachmann@rfc.ucl.ac.uk

© Association of Physicians 2002
sedimentation rate (ESR) and polyclonal hyper-
gammaglobulinaemia, are almost universal. Acquired systemic amyloidosis is a recognized rare complication of all forms of angiofollicular lymph node hyperplasia, and is usually of reactive systemic (AA) type resulting from a persistent acute phase response. More rarely, immunoglobulin light chain (AL) type amyloidosis is associated with the presence of a monoclonal gammopathy. The treatment of localized Castleman’s disease is complete surgical excision. This is almost always curative, resulting in rapid resolution of systemic symptoms and laboratory abnormalities. In patients with multicentric disease or in whom complete resection is not possible, partial resection, radiotherapy, combination chemotherapy and anti-cytokine therapies have all been used, with variable responses.3,6

The aetiology of Castleman’s disease is poorly understood. It is possible that reactive lymphoid hyperplasia arises in response to chronic antigenic stimulation, although there may also be a contribution from primary developmental abnormalities.2 However, greatly increased production of the pleiotropic cytokine IL-6, which enhances B-cell proliferation and survival, possibly by interfering with normal apoptotic mechanisms,7 has been demonstrated in the germinal centres of plasma cell variants of Castleman’s disease,8 and is clearly responsible for the marked constitutional and systemic manifestations of disease. Exogenous administration of pharmacological doses of IL-6 mimics many of the disease features, including upregulation of the acute phase response proteins,2 and mice genetically modified to overexpress IL-6 are an excellent model of Castleman’s disease in man.9 A further association is suggested by evidence of human herpes virus 8 infection in aggressive multicentric tumours expressing a virus-derived IL-6 cytokine homologue.10,11 Treatment with monoclonal anti-IL-6 antibody has been reported to alleviate systemic manifestations,6,12 and after successful resection of unicentric disease, the resolution of systemic inflammation closely parallels the fall in circulating IL-6 values.

We report five cases of AA amyloidosis complicating occult Castleman’s disease, in whom the underlying primary diagnosis was made only after years of illness (Table 1). In each patient, surgical resection of the tumour was accompanied by complete resolution of systemic inflammatory activity and, importantly, we have definitively documented subsequent regression of amyloid deposits by 123I-labelled serum amyloid P com-

| Table 1 Details of five patients with biopsy-proven systemic AA amyloidosis complicating unicentric Castleman’s disease |
|---|---|---|---|---|---|---|---|
| Sex | Age at presentation (years) | Age at Castleman’s disease diagnosis (years) | Laboratory abnormalities at presentation | Variant of Castleman’s tumour | Change in amyloid load post resection | Site of tumour | Change in amyloid load post resection |
| F | 23 | 41 | Anaemia, polyclonal gammopathy, acute phase response | Plasma cell | Complete regression over 5 years | Mediastinum | Complete regression over 5 years |
| M | 30 | 45 | Anaemia, acute phase response | Plasma cell | Partial regression with improvement in renal and liver function over 2 years | Mesentery | Complete regression from liver, spleen and kidneys over 2 years |
| M | 37 | 43 | Anaemia, polyclonal gammopathy, acute phase response | Plasma cell | Complete regression over 6 years | Mediastinum | Complete regression from liver, spleen and kidneys over 6 years |
| M | 52 | 39 | Anaemia, acute phase response | Mixed | Symptomatic improvement in the 3 months since surgery | Retropertioneal | Symptomatic improvement in the 3 months since surgery |

Assessed by SAP scintigraphy, laboratory tests and clinical evaluation.
Methods

Amyloid histochemistry and immunohistochemistry

Amyloid was sought in 6 μm tissue sections stained with Congo red by demonstration of pathognomonic red-green birefringence when viewed under cross-polarized light. Immunochemical stains were performed as described previously using commercial antisera against κ and λ immunoglobulin light chains and serum amyloid A protein (Dako and Medix, respectively).

Serum protein assays

Serum concentrations of C-reactive protein (CRP) and serum amyloid A protein (SAA) were measured by commercial automated immunoassays with lower detection limits of 0.2 mg/l and 0.7 mg/l, respectively. IL-6 values were measured by commercial enzyme immunoassay (Biosource International) with a lower detection limit of 10 ng/l.

Radiolabelled serum amyloid P component scintigraphy

Whole-body scintigraphic imaging was performed after administration of 123I-labelled SAP, as previously described. Anterior and posterior whole-body scans and regional images were obtained with an IGE Starcam gamma camera 24 h after intravenous injection of 123I-SAP.

Results (case histories)

Patient 1

A 26-year-old woman with a 3-year history of severe iron resistant anaemia presented with right-sided supraclavicular lymphadenopathy and a right hilar mass on chest X-ray. She had a low serum albumin value of 34 g/l and ESR of 100 mm in the first hour. Biopsy of a supraclavicular lymph node was non-diagnostic, showing reactive changes only. Mediastinoscopy she was found to have a large group of lymph nodes lying anterior to the superior vena cava, excision biopsy of one of which revealed Castleman’s disease of the plasma cell type (Figure 1). Surgical resection of the whole mass was deemed too hazardous and she was managed conservatively. Despite a median haemoglobin of <8 g/dl, she remained relatively asymptomatic over the following 15 years until she presented, aged 41 years, with advanced renal failure. Renal biopsy demonstrated AA amyloid, and 123I-SAP scintigraphy revealed a moderate amount of amyloid in the spleen, kidneys and adrenal glands, a distribution typical of reactive systemic amyloidosis. The mediastinal mass had enlarged but was nonetheless completely resected at thoracotomy. Unfortunately, a septicaemic episode in the immediate postoperative period caused hypotension and precipitated end-stage renal failure. However, after resection of the Castleman’s lesion, the serum values of IL-6, CRP and SAA fell rapidly to within the normal range (Figure 2), and serial 123I-SAP scintigraphy demonstrated amyloid regression over the following year (Figure 3). Five years later, she remains dialysis-dependent but otherwise well.
Patient 2

A 30-year-old man presented with hepatomegaly, nephrotic syndrome and renal impairment. A renal biopsy demonstrated amyloidosis, which was presumed to be AL type secondary to an occult plasma cell dyscrasia. He received no treatment and remained well until end-stage renal failure supervened 10 years later. He had a successful renal transplant, but within 4 years his renal function had deteriorated and he was increasingly symptomatic from massive hepatomegaly. Scintigraphy with $^{123}$I-SAP demonstrated a large amount of amyloid in the liver, spleen and renal graft. He had a persistent...
acute phase response, with CRP 68 mg/l and SAA 79 mg/l, and direct sequencing of amyloid fibrils extracted from a transjugular liver biopsy identified AA protein. Further investigation revealed a mesenteric mass which was incompletely resected with the adjacent 25 cm of small bowel. The mass comprised a plasma cell variant of Castleman’s disease with widespread amyloid deposition in normal and tumour tissue. The acute phase response subsided after surgery, and over the ensuing three years his general condition, renal and liver function have consistently improved, with partial amyloid regression on serial SAP scans.

Patient 3
A 43-year-old man with a 6-year history of arthralgia, intermittent diarrhoea, and weight loss presented with hepatosplenomegaly and low-grade proteinuria. He had a normochromic normocytic anaemia, ESR persistently >150 mm in the first hour, and a polyclonal gammopathy. Rectal and liver biopsies contained extensive AA amyloid deposits, and SAP scintigraphy showed amyloid deposition in the grossly enlarged liver and spleen. A mediastinal shadow in the chest X-ray was found to be a circumscribed mass of lymph nodes with histology of the plasma cell variant of Castleman’s disease. The tumour was resected completely and his acute phase response rapidly subsided, all laboratory indices returned to normal, and the organomegaly gradually resolved. An SAP scan five years post-operatively showed complete regression of the amyloid deposits.

Patient 4
A 52-year-old woman with a 20-year history of intermittent fevers, normocytic anaemia and reactive thrombocytosis was found to have retroperitoneal and mesenteric lymphadenopathy with mildly deranged liver function, and biopsies were reported to show non-specific inflammatory changes. Over the following 8 years, no diagnosis was made despite extensive investigations, and his signs and symptoms were not affected by systemic anti-inflammatory and immunosuppressive treatment with methylprednisolone and cyclophosphamide. Duodenal biopsies taken at the age of 39 years and re-examination of the earlier liver and lymph node biopsies demonstrated AA amyloid deposition. Further investigation, specifically seeking Castleman’s disease, revealed an 8 cm mass of lymph nodes behind the head of the pancreas, and this was resected. Histology was consistent with Castleman’s of the mixed cell type with reactive changes in the surrounding lymph nodes and marked amyloid deposition. Post-operatively, his acute phase response, anaemia and diarrhoea resolved, and he gained weight.

Discussion
Reactive systemic (AA) amyloidosis is a potential complication of any disorder associated with a sustained inflammatory response. The amyloid fibrils are derived from a circulating acute phase reactant, serum amyloid A protein (SAA), and the fibril peptide subunits typically comprise a 76-amino-acid N-terminal cleavage fragment known as AA protein. SAA is an apolipoprotein of high-density lipoprotein (HDL), and is synthesized by hepatocytes under the transcriptional regulation of a number of cytokines, principally IL-1 and IL-6. In health, the circulating concentration of SAA is around 1 mg/l, but this can rise by more than a thousand-fold during the acute-phase response, and high values can be maintained indefinitely in the presence of inflammatory stimuli. A sustained high plasma concentration of SAA is an absolute prerequisite for the development of AA amyloidosis, but it is clearly not sufficient, as amyloid affects <10% of those with chronic inflammatory diseases.

Il-6 is a potent multi-functional cytokine, with effects on differentiation of B and T cells, haematopoiesis, and the neuroendocrine system, and it is also one of the major stimulants of acute phase protein synthesis by hepatocytes. The germinal centres of hyperplastic lymph nodes in the plasma cell variant of Castleman’s disease produce large amounts of IL-6, and the high circulating concentration of tumour derived IL-6 is evidently a major
contributor to the systemic manifestations of Castleman’s, including a sustained overproduction of SAA, leading in some patients to AA amyloidosis. Twenty-six cases of systemic amyloidosis associated with Castleman’s disease have been reported previously. Seventeen of these had confirmed reactive systemic (AA) amyloidosis (Table 2), two were confirmed as AL type derived from monoclonal immunoglobulins, and in the remaining seven the amyloid was not characterized. The characteristics of all these patient are broadly similar to those of our present series. The median age at tumour resection or medical treatment of the 17 cases with confirmed AA amyloid was 37 years, with a male to female ratio of 1:1.2. Eight of the 17 tumours were intra-abdominal (six mesenteric, one retroperitoneal and one perihepatic), two were located in the mediastinum, one in axillary lymph nodes and six were multicentric. Twelve tumours were of the plasma cell type, two were classified as hyaline vascular and three had mixed histological features. Three patients whose disease was multicentric and thus not amenable to surgery were treated with humanized anti-interleukin-6 receptor antibodies. This led to improvement in their constitutional symptoms, a fall in their acute phase response and, in one case, improvement in renal function suggesting amyloid regression. One patient with multicentric disease whose tumour was partly resected, and who then received corticosteroids, showed a fall in acute phase protein concentrations and partial remission of his nephrotic syndrome. Following complete resection of their Castleman’s tumours, one patient who was already in end-stage renal failure remained on dialysis and another became dialysis-dependent in the peri-operative period. The other 11 patients all showed clinical improvement, and this was sustained in those cases in whom follow-up was reported.

Regression of amyloid deposits with clinical improvement following tumour resection is not surprising. Although the natural history of untreated systemic amyloidosis is usually one of relentless progression, often leading to organ failure and death, amyloid deposition is not irreversible. Prospective studies in different types of systemic amyloidosis have confirmed that amyloid deposits are constantly turned over, and the disease course depends on the relative rates of deposition of new fibrils and clearance of existing deposits. As demonstrated by the five cases in the present

Table 2 Characteristics of 17 previously reported patients with Castleman’s disease complicated by AA amyloidosis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Site of Castleman’s tumour</th>
<th>Variant</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>49</td>
<td>M</td>
<td>Multicentric</td>
<td>Plasma cell</td>
<td>Improvement in anaemia and renal function with cyclophosphamide and prednisolone</td>
</tr>
<tr>
<td>31</td>
<td>46</td>
<td>F</td>
<td>Mesentery</td>
<td>Plasma cell</td>
<td>Resected, complete response, 1-year follow-up</td>
</tr>
<tr>
<td>31</td>
<td>23</td>
<td>F</td>
<td>Mesentery</td>
<td>Plasma cell</td>
<td>Resected, complete response, 19-year follow-up</td>
</tr>
<tr>
<td>39</td>
<td>37</td>
<td>M</td>
<td>Mesentery</td>
<td>Mixed</td>
<td>Resected, complete response, 14-month follow-up</td>
</tr>
<tr>
<td>32</td>
<td>44</td>
<td>M</td>
<td>Axilla</td>
<td>Plasma cell</td>
<td>Resected, complete response, 10/12-month follow-up</td>
</tr>
<tr>
<td>34</td>
<td>31</td>
<td>F</td>
<td>Mediastinum</td>
<td>Hyaline vascular</td>
<td>Resected, ESRF on dialysis, acute phase response and polyclonal gammopathy resolved</td>
</tr>
<tr>
<td>30</td>
<td>21</td>
<td>F</td>
<td>Perihepatic</td>
<td>Plasma cell</td>
<td>Resected, complete response, 9-month follow-up</td>
</tr>
<tr>
<td>36</td>
<td>53</td>
<td>F</td>
<td>Retroperitoneum</td>
<td>Plasma cell</td>
<td>Resected, progressed to ESRF but fall in acute phase response</td>
</tr>
<tr>
<td>35</td>
<td>28</td>
<td>F</td>
<td>Mesenteric</td>
<td>Mixed</td>
<td>Resected, complete response</td>
</tr>
<tr>
<td>33</td>
<td>48</td>
<td>F</td>
<td>Mesenteric</td>
<td>Plasma cell</td>
<td>Resected, complete response</td>
</tr>
<tr>
<td>29</td>
<td>29</td>
<td>F</td>
<td>Mediastinum</td>
<td>Plasma cell</td>
<td>Cyclophosphamide and prednisolone, died</td>
</tr>
<tr>
<td>49</td>
<td>36</td>
<td>M</td>
<td>Mesentery</td>
<td>Plasma cell</td>
<td>Resected, complete response, 18-month follow-up</td>
</tr>
<tr>
<td>40</td>
<td>39</td>
<td>M</td>
<td>Multicentric</td>
<td>Hyaline vascular</td>
<td>Partial resection, prednisolone, partial response, 3-month follow-up</td>
</tr>
<tr>
<td>28</td>
<td>39</td>
<td>M</td>
<td>Multicentric</td>
<td>Plasma cell</td>
<td>Not described</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>F</td>
<td>Multicentric</td>
<td>Plasma cell</td>
<td>Anti-IL-6 receptor antibody, improved symptoms, fall in acute phase response and improved renal function</td>
</tr>
<tr>
<td>6</td>
<td>51</td>
<td>M</td>
<td>Multicentric</td>
<td>Plasma cell</td>
<td>Anti-IL-6 receptor antibody, improved symptoms and fall in acute phase response</td>
</tr>
<tr>
<td>6</td>
<td>23</td>
<td>M</td>
<td>Multicentric</td>
<td>Mixed</td>
<td>Anti-IL-6 receptor antibody, improved symptoms and fall in acute phase response</td>
</tr>
</tbody>
</table>
series, amyloid deposits can regress quite rapidly when the supply of fibril precursors is reduced and, under favourable circumstances, this is accompanied by clinical improvement and stabilization or improvement in organ function.44–47 A prospective study48 of 80 patients with AA amyloidosis secondary to a variety of chronic inflammatory conditions demonstrated that patients in whom the underlying inflammatory disease is well-controlled (median SAA < 10 mg/l) have >90% 10-year survival, whereas in those with poorly-controlled disease, the 10-year survival is ~40%. This survival benefit reflects the natural history of the amyloid deposits with regression tending to occur in individuals with well-controlled disease and progression in those with uncontrolled chronic inflammation.48

Clearly the control of systemic inflammation is greatly facilitated when the nature of the underlying inflammatory condition is known, but in a significant proportion of patients diagnosis may be very difficult. Among 228 patients with confirmed systemic AA amyloidosis referred to our centre, the cause of the underlying chronic inflammation was not apparent in 21, and many of these individuals had received potent immunosuppressive treatment, often with considerable morbidity and limited clinical benefit. As we show here, almost 20% of this group were found to have a resectable Castleman’s tumour and have done well after surgery. Unicentric Castleman’s disease is a potentially fully remediable cause of AA amyloidosis, which often affects an unusually young age group, and the diagnosis should be actively sought in patients with unexplained chronic inflammation.

Acknowledgements

This work was supported in part by grants to MBP and PNH from the Medical Research Council (UK) and The Wellcome Trust, a Wellcome Trust Research Training Fellowship to JDG, and by NHS Research and Development Funds. We thank our many colleagues for referring the patients, and Beth Jones for expert preparation of the manuscript.

References
