Systemic amyloidosis AL with temporal artery involvement revealing lymphoplasmacytic malignancy in a man presenting as polymyalgia rheumatica

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Abstract

A 68 year old man presented with a clinical and biological picture that suggested polymyalgia rheumatica. Temporal artery biopsy disclosed no inflammatory change but massive light chain amyloid deposits in the media. Further exploration showed a malignant lymphoplasmacytic haemopathy with a triclonal gammopathy and a muscular, rectal, and probable cardiac amyloidosis. Cryoglobulinaemia and high concentrations of soluble interleukin 2 receptor (sIL-2R) were also found. This is the fifth case with confirmed involvement of the temporal artery. The especially high sIL-2R concentration was thought to reflect the tumour mass rather than lymphocyte activation.

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Numerous musculoskeletal and rheumatological manifestations are induced by amyloid deposition into periarticular soft tissues (mainly causing carpal tunnel syndrome), synovial tissue, bone or bone marrow, or muscles. Such manifestations are more specifically seen in amyloidosis related to light chain immunoglobulins (including 'primary' and multiple myeloma amyloidosis, that is, so called amyloidosis AL),^{1 2} and in β_2 microglobulin related amyloidosis in patients undergoing long term dialysis. Amyloid deposits may develop in interstitial tissues, in small vessels, or in both. Involvement of medium sized or large vessels seems rare, however.

We report a case with symptoms that suggested polymyalgia or inflammatory myopathy associated with temporal artery amyloidosis. This led to disclosure of an AL systemic amyloidosis and a complex lymphoplasmacytic dyscrasia.

Case report

A 68 year old man complained of nightly and daily scapular girdle and neck pain with morning stiffness worsening over three months. His medical history showed a chronic respiratory failure with right cardiac insufficiency. On examination pain and amyotrophy of shoulders and arms, dyspnoea with productive cough, and moderate liver enlargement were found. There was no fever, headache, or peripheral arthritis. Temporal arteries seemed clinically normal.

Erythrocyte sedimentation rate (Westergren) was 90/110 mm/h with fibrinogen at 5.45 g/l. Blood cell count, creatine kinase, and transaminase activity, creatinine concentration, and coagulation tests were normal. Moderate γ and β peaks and raised β_2 globulin concentrations were seen on serum electrophoresis. Waaler-Rose reaction was positive to a 1:128 dilution, but antinuclear antibodies were absent. Serum concentration of soluble interleukin 2 receptor (sIL-2R), assessed by sandwich enzyme immunoassay (Immunotech, Marseilles), was as high as 2500 pmol/ml (normal values 70 (SD 45)). Complement fractions C3 and C4 were normal, as were plain x ray films and a radionuclide bone scan.

Provisional diagnoses were late onset rheumatoid arthritis, polymyalgia rheumatica, or polymyositis. Biopsy of the temporal artery disclosed narrowing of the lumen secondary to thickening of the artery wall and massive amyloid deposits in the media with apple green birefringence after Congo red staining and fluorescence after thioflavine staining, but no inflammatory change was seen (fig 1). Immunofluorescence was strongly positive with anti- λ light chain monoclonal antibody (fig 2), and poor with anti- κ , A, and β_2 microglobulin antibodies.

Thus diagnosis of amyloidosis AL was made and further tests were performed. Serum protein immunofixation showed a triclonal gammopathy IgA λ (main component, 10 g/l), IgG λ and IgM κ ; immunofixation also showed a Bence-Jones λ protein in urine (1 g/24 hours). Bone marrow aspiration and biopsy showed a malignant lymphoplasmacytic infiltration (18%) of λ

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Figure 1 Large amyloid deposit in media and adventitia of temporal artery (Congo red.)

phenotype on immunohistochemistry. Serum β_2 microglobulin concentration was raised at 7.2 mg/l (normal value 2.5 mg/l). Type I cryoglobulin IgG λ /IgA λ was present. Interstitial and vascular amyloid deposits positive with anti- λ chain immunofluorescence were found in deltoid muscle and rectal biopsy specimens but not in bone marrow and skin biopsy specimens. Echocardiography showed thickening of mitral and tricuspid valves, and of atrioventricular and interventricular septa, suggesting heart amyloidosis. Several clusters of mononucleated cells were found on muscle biopsy. Immunohistochemistry showed that these cells were mainly B lymphocytes (CD19; fig 3); they expressed class I MHC molecules and about 30% of them also expressed the IL-2 receptor (CD25). In addition, these lymphocytes were strongly immunostained with the λ chain antibody and some of them were immunoreactive with the κ chain antibody. The lymphocytes did not express the CD3, CD4, CD7, and CD8

antigens. A bone marrow sample was not available for the same study.

Despite daily prednisolone (20 mg) chlorambucil (10 mg), and colchicine (1 mg) the patient's condition worsened and death occurred by sudden respiratory and circulatory failure three months later. Necropsy could not be performed.

Discussion

This case has several unusual features, including the location of amyloid deposits, the causative lymphoplasmacytic proliferation, and some biological abnormalities.

Involvement of medium sized and large arteries has mainly been described in coronary arteries.³ Few cases of widespread and prominent vascular disease have been reported.⁴⁻⁵ Our case is the fifth one with involvement of the temporal artery confirmed by biopsy. The two cases described by Gertz *et al* both had claudication of shoulders, arms, and jaws with evidence of amyloidosis without inflammation in temporal arteries, secondary to Bence-Jones proteinaemia.⁴ The patient of Taillan *et al* experienced painful stiffness in the shoulders and headache with hard and painful temporal arteries. He was found to have obstructive temporal artery vasculopathy caused by AL amyloid deposits and a multiple myeloma.⁶ Lastly, Hamidou *et al* reported a case with jaw claudication, scalp hyperpathia, and hardness of the temporal artery with temporal artery AL amyloidosis related to a light chain myeloma.⁷ It is difficult to state whether arterial involvement by amyloidosis is truly rare or underestimated. Indeed, vascular biopsy is rarely performed in this disease, and amyloidosis may be overlooked when a temporal artery is biopsied for suspected giant cell arteritis if specific staining is not performed. Senile amyloidosis has been reported as a common finding in temporal artery specimens from elderly patients,⁸ but has no clinical implication. We are not aware of any case of temporal artery involvement by secondary (AA) amyloidosis. Gertz *et al* found a 9% prevalence of jaw claudication in their 237 patient series of amyloidosis AL.⁴ They also discussed the published cases whose features were compatible with a specific amyloid vasculopathy. The role of vascular amyloidosis in most of these cases remained hypothetical, however, as pathological proof was lacking.

The relation between the symptoms of our patient and the involvement of the temporal artery is questionable and the role of the muscular amyloidosis or an association with polymyalgia rheumatica must also be considered. Polymyalgia-like syndromes have been reported in multiple myeloma and related diseases.⁹⁻¹⁰ In most cases no muscle or temporal artery biopsy was done and the origin of the symptoms is unclear. A coincidental association is theoretically possible because of the age of these types of patient. Patients with evidence for giant cell inflammation in pathological specimens or who are dramatically improved by corticosteroid treatment might be considered as having 'true' giant cell arteritis or polymyalgia rheumatica.

Figure 2 Strong positivity of immunofluorescence of amyloid deposits in adventitia and vasa vasorum of temporal artery with anti- λ light chain serum.

Figure 3 Perivascular inflammatory exudate in deltoid muscle. B-lymphocytes appear dark delineated with CD19 antibody.

On the other hand, some authors have stated that ischaemic manifestations, such as coronary disease or limb claudication, were directly related to narrowing of the vascular lumen secondary to wall enlargement by amyloidosis.³⁻⁵ The findings of Zelis *et al* have led to the concept of an ischaemic type of muscular amyloid disease.¹¹ The lack of corticosteroid efficacy in our patient suggests ischaemic symptoms as a result of vascular amyloidosis rather than the coexistence of two distinct diseases.

Amyloidosis AL may occur in multiple myeloma, and to a lesser extent in Waldenström's macroglobulinaemia, lymphocytic chronic leukaemia, and lymphoma. More often, the so called primary amyloidosis is related to the secretion of monoclonal light chain immunoglobulins without evidence of lymphoplasma-cytic malignancy.¹⁻² Triclonal gammopathy is rare,¹² but is likely to have the same amyloidogenic potential. The malignant lymphoplasma-cytic proliferation with secretion of a triclonal gammopathy in our patient could not be adequately classified in a definite subset of lymphoproliferative disorders. This supports the concept of amyloidosis AL as a unique entity, which can occur in the wide range of monoclonal gammopathies.¹

Lastly, the very high concentration of sIL-2R in the serum of this patient was unusual. The sIL-2R is principally found on T lymphocytes, and in a general manner an increase in sIL-2R is induced by T cell activation in many immunological disorders.¹² However, B cells in vitro have been shown to produce IL-2R at their surface under some conditions. Several reports have recently emphasised that sIL-2R concentrations in plasma are increased in B lymphoproliferative disorders such as hairy cell leukaemia, chronic lymphocytic leukaemia, lymphoblastic leukaemia, lymphoma and Hodgkin's disease.¹³ More recently, high concentrations of sIL-2R, a decrease in IL-2 serum concentrations and the presence of IL-2R on some circulating B lymphocytes and marrow plasma cells have been shown in multiple myeloma.¹⁴ The neoplastic cells are thought

to be an important source of production of this molecule in these lymphoproliferative diseases, and this must be considered as an alternative cause of enhanced sIL-2R concentrations. In our opinion, the sIL-2R in our patient came directly from the tumour cells rather than from a secondary immunological activation.

In summary, polymyalgia rheumatica is a clinically defined syndrome for which clinical presentation is not specific. Other diseases, such as muscular disorders or amyloidosis, have to be kept in mind. Furthermore, the pathological changes of amyloidosis found in biopsy specimens and the causative gammopathy are often not prominent and require specific investigations.

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