SHORT REPORT

AL κ amyloid in a solitary extradural lymphoma

D M Vigushin, P N Hawkins, J J Hsuan, N F Totty, M B Pepys

Abstract

A 68 year old man with a 10 year history of apparently benign IgM κ paraproteinaemia presented with dysarthria, left hemiparesis, and a sensory peripheral neuropathy. A calcified right temporoparietal extradural mass was shown by scintigraphy with ^{123}I -serum amyloid P component to contain amyloid. There were no extracranial amyloid deposits. Clinical improvement followed craniotomy and partial resection of tissue which consisted of amyloid and a mixed mononuclear cell infiltrate. The amyloid fibrils consisted of the framework 1 region of the variable domain of monoclonal κ_{IV} immunoglobulin light chains. There was a prominent B-cell clonal immunoglobulin gene rearrangement in the tumour tissue, supporting a diagnosis of lymphoplasmacytic lymphoma, but no sign of systemic lymphoma. Neurological state, tumour volume, and quantity of amyloid have remained static for two years after treatment with chlorambucil.

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Intracranial amyloidoma is uncommon and cases have rarely been well characterised either clinically or biochemically. We report here the clinical course in a patient with a localised mass of AL κ -type amyloid¹ in the skull vault, associated with an IgM κ -secreting lymphoplasmacytic lymphoma. Scintigraphy with ^{123}I -serum amyloid P component (SAP) confirmed the predominant amyloid composition of the intracranial tumour, demonstrated that no systemic amyloid deposits were present, and was used prospectively to monitor tumour volume.

Case report

A 68 year old right handed man, with apparently benign macroglobulinaemia for 10 years, presented in 1988 with a slowly progressive left hemiparesis. Biopsy of a calcified extradural lesion adjacent to the right parietal bone contained amyloid, a moderately dense mixed mononuclear infiltrate, and necrotic bone fragments. A circulating monoclonal IgM κ paraprotein (8.7 g/l) was present but

bone marrow aspirate was normal. No treatment was given.

Disability progressed and two years later there was a dense left hemiparesis, dysarthria, left visual and sensory inattention, and also severe proprioceptive loss, limb ataxia, and distal areflexia due to predominantly sensory symmetrical peripheral polyneuropathy affecting upper and lower limbs. Monoclonal κ chains were detected by immunofixation in concentrated urine but the serum IgM κ paraprotein concentration was unchanged and full blood count, erythrocyte sedimentation rate, serum biochemistry, polyclonal immunoglobulin concentrations, and skeletal radiographic survey were normal.

Causes of peripheral neuropathy other than macroglobulinaemia were excluded. Sensory action potentials were absent at both median nerves, the right ulnar, radial, and sural nerves; motor action potentials and sampling were consistent with severe demyelinating neuropathy and associated axonal loss. There was severe depletion of myelinated fibres in a sural nerve biopsy, but no amyloid, inflammatory infiltrate or connective tissue abnormality. Remaining fibres were all small diameter with thin myelin sheaths suggesting remyelination or regeneration; occasional regeneration clusters and some onion bulbs were present. There was no evidence of active fibre degeneration or demyelination, and no abnormal Schwann cells or axonal inclusions were seen. These results were all consistent with a macroglobulinaemia associated peripheral neuropathy.

A large extradural mass in relation to the right lateral convexity contained foci of calcification, and compressed the frontal and parietal lobes with inward displacement of the intact dura and distortion of the lateral ventricles (fig 1). Scintigraphy 24 hours after intravenous injection of ^{123}I -SAP (200 MBq/100 μg)^{2,3} showed intense tracer uptake in the right frontoparietal region consistent with the extent of the tumour. Sagittal single photon computed tomography (SPECT) showed amyloid deposits extending anteriorly to the right temporal fossa and orbital plate. Whole body scans showed no evidence of systemic amyloid deposits (fig 2(A) and (B)).

A large extradural mass of friable yellow-grey tissue that extended deep to the inner skull plate was partly resected at craniotomy.

Immunological
Medicine Unit, Royal
Postgraduate Medical
School, Hammersmith
Hospital, London, UK
D M Vigushin
P N Hawkins
M B Pepys

Ludwig Institute for
Cancer Research,
University College and
Middlesex Hospital
School of Medicine,
London
J J Hsuan
N F Totty

Correspondence to:
Professor M B Pepys,
Immunological Medicine
Unit, Royal Postgraduate
Medical School,
Hammersmith Hospital,
Du Cane Road, London
W12 0NN, UK.

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Figure 1 T1 weighted coronal MRI showing a large extradural lesion displacing the intact dura inwards and causing distortion of the underlying brain and ventricles. Previous burr holes are seen.

It consisted of amyloid with an infiltrate of small T and B lymphocytes, plasma cells without detectable immunoglobulin light chain restriction, and occasional mast cells. Immunoglobulin gene analysis by the Southern blot technique with a probe to the joining region of the heavy chain gene,⁴ identified a prominent B-cell clonal rearrangement, supporting a diagnosis of lymphoplasmacytic lymphoma. There was, however, no clinical or radiological evidence of systemic lymphadenopathy, organomegaly, or soft tissue masses; and bone marrow aspirate, trephine biopsy, and immunoglobulin heavy chain gene analysis on DNA from peripheral blood and bone marrow were normal.

The hemiparesis substantially resolved within one week of surgery but proprioceptive

loss and impaired vibration sense persisted in the lower limbs. By one month there was an improvement in verbal and performance IQ from 120 to 133 and 79 to 87 respectively, although a superficial crescent of residual tumour was seen in cranial CT. The paraprotein concentration fell from 5 g/l perioperatively to 3 g/l after three months. Planar ¹²³I-SAP scintigraphy showed only a thin border of tracer uptake in the right frontoparietal region but in sagittal SPECT the anterior tumour extension was unchanged and he was therefore treated with low dose oral chlorambucil. Neurological state, paraprotein level, serial CT estimates of tumour volume, and quantitative ¹²³I-SAP scintigraphic measurements of amyloid deposition remained unchanged over the next two years.

Characterisation of the amyloid fibril protein

HISTOLOGY

Amyloid was identified by Congo red staining⁵; there was also specific immunohistochemical staining⁶ with antisera to SAP and κ light chains (Dakopatts a/s, Glostrup, Denmark) but not λ light chains (Dako) or a panel of other known amyloid fibril proteins.¹

ISOLATION OF AMYLOID FIBRILS

Amyloid fibrils isolated⁷ from tumour tissue were composed of subunit peptides forming a set of major bands of apparent M_r ~ 14 000 in reduced sodium dodecyl sulphate (SDS) gradient polyacrylamide gel electrophoresis (PAGE).

IMMUNOBLOTTING

Reduced fibril subunit proteins separated by SDS-PAGE and semi dry electroblotted (Novablot, Pharmacia Biosystems, Milton Keynes, Bucks, UK) on to nitrocellulose membrane (Schleicher and Schull AG, Anderman and Co Ltd, Kingston-upon-Thames, Surrey, UK) were immunostained with rabbit antihuman κ light chain antibodies (Dako), horseradish peroxidase labelled affinity purified goat antirabbit IgG (Dako), and 3,3'-diaminobenzidine (Sigma Chemical Co Ltd, Poole, Dorset, UK), according to the Bio-Rad immunoblot protocol (Bio-Rad Labs Ltd, Hemel Hempstead, Herts, UK). All the ~ 14 kD bands stained immunospecifically.

Figure 2(A) Anterior (left) and posterior whole body ¹²³I-SAP scintigraphs showing a discrete area of intense tracer uptake into amyloid within the cranial vault concordant with the apparent anatomical extent of the tumour. Extracranial distribution of tracer activity is confined to the blood pool, trace free iodide uptake in the thyroid, and breakdown products in the urine, as seen in normal controls; there is no other tissue or organ localisation. (B) ¹²³I-SAP sagittal single photon emission computed tomography shows the extension of amyloid deposition anteriorly in the region of the right orbit and inferiorly into the temporal fossa.

Figure 3 N-terminal amino acid sequence of the framework 1 region of κ_{IV} immunoglobulin light chain. Sequence of the first 24 residues obtained from the N-terminus of the amyloid fibril subunit peptide is emboldened.

**AspIleValMetThrGlnSerProAspSerLeuAla
ValSerLeuGlyGluArgAlaThrIleAsnCysLys
Ser Ser Gln Ser Val Leu**

AMYLOID FIBRIL SUBUNIT PEPTIDE SEQUENCE ANALYSIS

The major band at 14 kD after reduced fibril subunit proteins had been separated by SDS-PAGE, electroblotted on to Problott membrane (Applied Biosystems), and stained with Coomassie blue R250, was excised and sequenced on a modified Applied Biosystems 477A sequencer.⁸ The N-terminal sequence of the fibril subunits up to 24 cycles was identical to the framework 1 region of the κ_{IV} immunoglobulin light chain (fig 3).⁹

Discussion

Primary extranodal lymphoma accounts for only 1% of intracranial tumours. Most are monoclonal in origin, of B-cell lineage, and express surface or cytoplasmic immunoglobulins that can usually be demonstrated immunohistochemically.¹⁰ The demonstration of clonality is important in differentiating between a benign and malignant process. When malignant B-cells are abundant, a clonal B-cell population is often identified by restricted surface expression of immunoglobulin light chains. In cases where the number of malignant B-cells is small or in the presence of numerous reactive B or T lymphocytes, however, identification of the clone may not be possible by this method, as in our case.¹¹ We therefore used immunoglobulin gene rearrangement studies to identify a clonal B-cell population in the resected tumour tissue. The absence of a detectable clonal rearrangement in peripheral blood and bone marrow supported the clinical and radiological impression of an apparently localised lymphoma.

Systemic AL amyloidosis occurs in 5%–15% of patients with myeloma, and probably fewer patients with monoclonal gammopathy of undetermined significance (MGUS), especially those with IgM paraproteinaemia.¹² The molecular mechanism by which certain monoclonal immunoglobulin light chains form amyloid fibrils, and the factors determining the anatomical site, extent, and clinical effects of amyloid deposition, are poorly understood.¹ We are aware of only one previous reported case of primary intracranial lymphoma with massive focal amyloid deposition.¹³ Five cases of solitary intracranial plasmacytomas with localised amyloid deposits have been described¹⁴ and there are numerous reports of intracranial tumour-like focal amyloid deposits or amyloidomas; most were intracerebral and the histological features in all were similar: abundant amyloid deposition, a scanty mononuclear cell infiltrate and occasional giant cells.^{13 15–28} Complete excision of resectable lesions was associated with a good prognosis, and recurrence did not occur within several years of follow up.^{17 20 28}

The present case was unique in that the nature and extent of the intracranial lesion were confirmed by SAP scintigraphy, and the identity of the amyloid fibril protein determined immunochemically was confirmed by amino acid sequencing. Whole body SAP imaging studies excluded systemic amyloidosis, and no amyloid was found in the sural nerve biopsy, the histology of which was compatible with macroglobulin associated damage.

Scintigraphy after injection of radiolabelled SAP is a sensitive, specific, and quantitative diagnostic procedure in amyloidosis.²³ Its anatomical precision is enhanced by SPECT, which was notably more sensitive and informative than MRI in the present case. Serial SAP scintigraphy has shown no change in the residual amyloid mass during the two years after initiation of systemic chemotherapy.

Patients with monoclonal gammopathy in whom there is less than 30 g/l of circulating M-protein, trace Bence Jones proteinuria, fewer than 5% plasma cells in the bone marrow, normal serum albumin, and no anaemia, hypercalcaemia, renal insufficiency, or bone lesions are currently regarded as having MGUS,²⁹ a more appropriate term than benign monoclonal gammopathy. In 430 patients at the Mayo Clinic with IgM monoclonal gammopathies, 56% were classified at presentation as MGUS, 7% lymphoma, 5% chronic lymphocytic leukaemia, 6% AL amyloidosis, and 14% as unclassified lymphoproliferative disease.³⁰ Seventeen per cent of the MGUS group developed malignant lymphoid disease within five months to 22 years.²⁸ Our patient falls into this category: he had an apparently benign IgM κ paraprotein for 10 years before he presented with disease caused directly by the primary intracranial lymphoma, exacerbated by local AL amyloid deposition and by macroglobulinaemia associated, non-infiltrative, peripheral neuropathy.

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