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Synthesis of abnormal heavy and light chains in multiple myeloma with visceral deposition of monoclonal immunoglobulin

J. L. PREUD'HOMME, LILIANE MOREL-MAROGER, J. C. BROUET, EDITH MIHAESCO, J. P. MERY* & M. SELIGMANN *Laboratory of Immunochemistry and Immunopathology (INSERM U 108, Research Institute on Blood Diseases and Laboratory of Oncology and Immunohaematology of CNRS), Hospital Saint Louis and Research Group on Normal and Pathologic Nephrology (INSERM U 64), Hospital Tenon, Paris, France*

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SUMMARY

In a patient treated for IgA κ myeloma, bone marrow relapse and a sharp drop in the serum IgA level paralleled tissue deposition of a non-amyloid material reactive with anti-κ and anti-α sera in immunofluorescence studies of kidney and liver biopsies. Clinical manifestations were progressive renal failure with nephrotic syndrome, with both tubular and glomerular lesions (including nodular glomerulosclerosis), hepatomegaly, cardiac and neurological symptoms. Biosynthesis experiments showed the production of α chains diminished in length by about one domain which were rapidly degraded predominantly after secretion and of two species of light chains; normal-sized light chains which assembled with α chains and abnormally short ones which were secreted as free light chains. The apparent molecular weight of the light chains was larger in secretions than in cytoplasmic extracts, suggesting their glycosylation. These results suggest a causal relationship between tissue deposition and production of abnormal immunoglobulins by a variant clone, the emergence of which was possibly induced by Melphalan therapy.

INTRODUCTION

Randall *et al.* (1976) reported two cases of a new syndrome which they called 'systemic light chain deposition'. This syndrome was characterized by a widespread tissue deposition of a material which lacked the characteristics of amyloid and was reactive with anti-light chain sera. In a recent study of three patients with similar tissue deposits, we found that monoclonal bone marrow plasma cells secreted abnormal κ chains which were not detected in appreciable amounts in serum and urine. These light chains had an aberrant size (abnormally short or large), their apparent molecular weight was larger in secretions than in cytoplasmic extracts (suggesting their glycosylation) and they were secreted as polymers (Preud'homme *et al.*, 1980). We report here the study of a myeloma patient in whom the occurrence of similar tissue deposits paralleled a relapse under chemotherapy. Deposits contained material reactive with anti-κ and anti-α sera and the bone marrow cells produced abnormally short α and κ chains which were not detectable in the patient's serum and urine.

* Present address: AURA, Centre Pasteur-Vallery-Radot, Paris

Correspondence: Dr J. L. Preud'homme, INSERM U 108, Hôpital Saint Louis, 75475 Paris Cedex 10, France.

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PATIENT AND METHODS

Case report. The patient, a 52-year-old man, was affected with a typical multiple myeloma with a monoclonal serum IgA1κ. At first examination, his renal function was normal and there was no proteinuria. He was treated with prednisone and Alkeran for 8 months when a nephrotic syndrome developed (urinary protein 8 g/day) with a diffuse electrophoretic pattern and no monoclonal light chains detectable after concentration, microscopic haematuria (2×10^6 red cells/ml) and hypercreatininaemia (35 mg/l). Clinical examination disclosed hepatomegaly, congestive heart failure and high blood pressure (200/120 mm Hg) with a left bundle branch block and a lengthening of the PR interval (20 msec) at the EKG, and a polyneuropathy. At the same time, the course of the myelomatous disease had become obviously aggressive with massive invasion of the bone marrow by 95–100% malignant plasma cells. In contrast, the IgA spike on electrophoresis had dropped from 4·5 g/100 ml at the onset of the disease to 2·5 g/100ml. Renal and hepatic biopsies were obtained and chemotherapy was modified to a regimen which incorporated prednisone, cyclophosphamide and nitrosourea. However, the general condition of the patient deteriorated and he died with end-stage renal failure. Post mortem was not allowed.

Immunofluorescence study of bone marrow cells. Bone marrow samples obtained by sternal puncture were sedimented in Plasmagel (Roger Bellon, Paris, France) to remove red cells. Aliquots were processed for immunofluorescence study. Surface and cytoplasmic immunoglobulins (SIg and cIg) were studied using rhodamine-conjugated $F(ab')_2$ fragments of rabbit IgG monospecific for μ, δ, γ, α, κ and λ chains. The preparation, characteristics and specificity controls of these reagents and the procedures used to detect SIg on living cells and cIg in fixed cells have been described in detail before (Preud'homme & Seligmann, 1972; Preud'homme & Labaume, 1976).

Biosynthesis experiments. Ig biosynthesis by bone marrow cells was studied with the same sample as used in immunofluorescence studies as previously described (Birshtein, Preud'homme & Scharff, 1974; Preud'homme *et al.*, 1977, 1980). Briefly, the cells were washed in spinner Eagle's minimal essential medium depleted in valine, threonine and leucine and containing 10% foetal calf serum (GIBCO BIOCULT, Paisley, Scotland). The cells were labelled continuously with ^{14}C-valine, threonine and leucine for 1, 2 and 3 hr. Supernatants (secretions) were separated by centrifugation and the cell pellets were lysed by Nonided-P40 (Shell). Cell lysates and secretions were incubated at 4°C with a rabbit antiserum specific for human Ig, then with a sheep anti-rabbit IgG antiserum in double-antibody excess. The resulting immunoprecipitates were washed, dissolved in 2% sodium dodecyl sulphate (SDS) and placed in a boiling water bath for 1 min. Reduction of disulphide bridges was carried out with 0·15 M 2-mercaptoethanol and followed by alkylation with iodoacetamide at a final concentration of 0·18 M. The samples were applied on 19-cm 5% acrylamide gels containing 0·1 M sodium phosphate, pH 7, and 0·1% SDS. The internal markers in each gel were ^{3}H-labelled Ig produced by the mouse plasmacytoma MPC 11 and by a variant clone from MPC 11 producing IgG with short heavy chains (Birshtein *et al.*, 1974). SDS gels were fractionated in a Maizel's gel grinder (Savant Instruments, Hicksville, New York) and the radioactivity of individual fractions was determined. Apparent molecular weights were calculated from the relative migration of the ^{14}C-labelled proteins and of the ^{3}H-labelled marker proteins.

Study of the kidney and liver biopsies. Percutaneous renal and liver biopsies were studied by light and immunofluorescence microscopy. The samples for light microscopy were fixed in Duboscq–Brazil fixative and processed as described before (Morel-Maroger *et al.*, 1970). The other samples were snap-frozen in liquid nitrogen and stored at −80°C. Cryostat sections were studied by immunofluorescence using fluoresceinated rabbit antisera to C3, C1q, C4, fibrinogen and albumin) Behringwerke, Marburg, W. Germany), to α_2-macroglobulin (Hyland, Los Angeles, California) and to Ig chains. Conjugates specific for α and μ chains were obtained from CTS, Bois-Guillaume, France whereas the conjugated $F(ab')_2$ fragments specific for γ, κ and λ chains were the same as in the study of bone marrow cells.

Study of the serum monoclonal IgA. The IgA1κ myeloma protein was isolated from the

patient's serum by block electrophoresis followed by gel filtration on Sephadex G-200 (Pharmacia). The purified protein was partially reduced with 0·01 M dithiothreitol and alkylated by addition of iodoacetic acid at 10% equivalent excess. Heavy and light chains were separated by chromatography on a calibrated Sephadex G-100 column in 1 M acetic acid. Their molecular weight was determined from their elution position from the Sephadex column and from their migration in SDS-acrylamide gradient slab gels by comparison with various proteins of known molecular weight. In addition, the patient's IgA was reduced and alkylated with ^{14}C-iodoacetic acid whereas a normal-sized IgA protein was reduced and alkylated with ^{3}H-iodoacetic acid. Small aliquots were co-electrophoresed in 7·5% SDS–acrylamide cylindrical gels. The gels were crushed and counted as described above.

For carbohydrate determination, the heavy and light chains were separated by chromatography on Biogel P200 (Biorad, Richmond, California) since traces of carbohydrate may leak from the dextran matrix of Sephadex. The methods used for carbohydrate determinations are described fully in Gottschalk (1972); specifically, they were as follows: total hexoses were determined by the anthrone reaction according to Mokrash (using D-mannose and D-galactose in equimolar amounts as standards) and by the orcinol reaction according to Weimer & Moshin. Fucose was assayed following the method of Dishe & Shettles and sialic acid was determined with thiobarbituric acid reagent following Warren. Total hexosamines were determined using the Elson Morgan reaction as described by Boas. Amino sugars were qualitatively recognized on the short column of an amino acid analyser.

RESULTS

Light microscopy and immunofluorescence study of tissue biopsies

Kidney biopsies from the patient showed both tubular and glomerular lesions, the latter being characterized by a picture of nodular glomerulosclerosis (Fig. 1). The nuclei were displaced to the periphery of the nodules which were both strongly positive for periodic acid Schiff (PAS) and intensely eosinophilic. The stains for amyloid were negative. At the periphery of the nodules the capillary walls appeared somewhat thickened, although no deposits could be detected after silver impregnation. An irregular cellular proliferation was found in the most severely damaged glomeruli. There were no tubular casts with macrophagic cell reaction. Many tubular basement membranes were markedly thickened, with a membrane-like material strongly stained by PAS. This thickening was apparently more conspicuous along the distal tubules, although the distinction between proximal and distal tubules was not always easily made because of extensive epithelial atrophy. The interstitial tissue was sclerotic. No infiltration by plasma cells was noted.

The immunofluorescence study of kidney sections showed a very strong staining of most tubular basement membranes with the anti-κ conjugate (Fig. 2) and a weak one with the anti-α conjugate. The mesangial nodules were weakly positive with both reagents. No staining could be found with the antisera to the other Ig chains, to complement components, fibrinogen, albumin and α_2-macroglobulin. Studies of liver biopsy material showed diffuse amorphous deposits in the perisinusoidal areas. These deposits were brightly stained with the anti-κ serum (Fig. 3) and faintly with the anti-α conjugate.

Study of bone marrow cells

Ninety to 95% of bone marrow-nucleated cells from the patient were plasma cells which all contained determinants reactive with anti-α and anti-κ conjugates in their cytoplasm and on their plasma membrane. After radioactive amino acid incorporation, SDS–gel electrophoresis of unreduced immunoprecipitates from the cell cytoplasm showed a very similar pattern after 1, 2 and 3 hr of labelling (Fig. 4a, b and c). Four main peaks were found on these gels: one peak which consistently ran two fractions after the normal light chain marker (apparent molecular weight 20–21,000) and three larger molecules with apparent molecular weights of 35–36,000, 60,000 and 110–120,000 respectively. Reduction and alkylation yielded two major peaks of 42–43,000 daltons and 23,000 daltons (Fig. 4d, e and f). An additional peak of 20,000 daltons was found as a

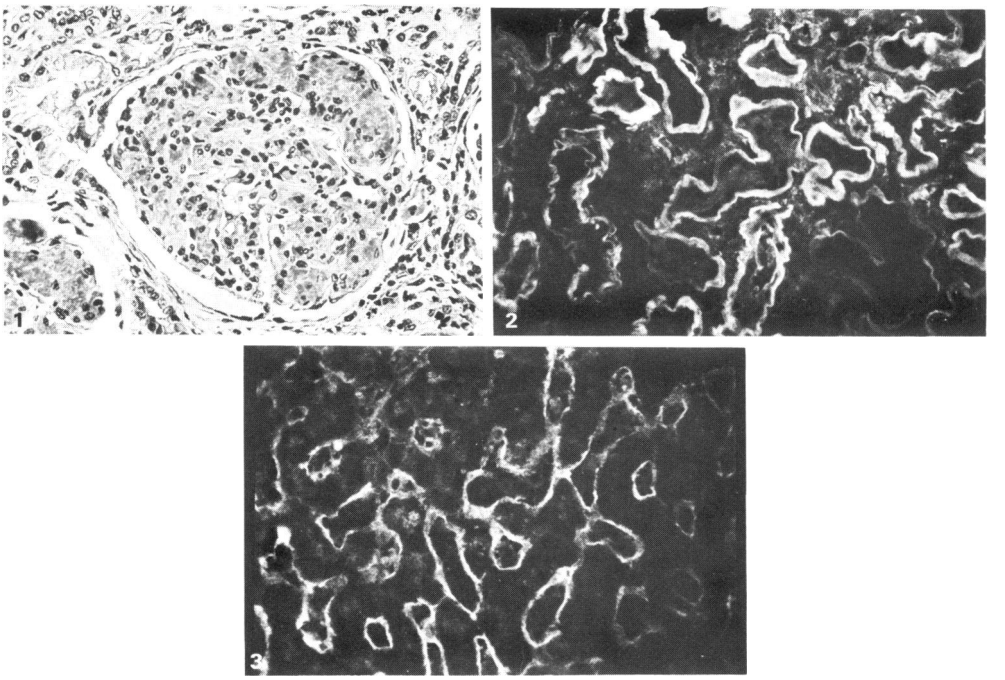

Fig. 1. Nodular glomerulosclerosis. Note the marked accentuation of the glomerular lobulation with a segmental intracapillary cellular proliferation. (Haematoxylin–eosin stain. Original magnification × 250.)

Fig. 2. Immunofluorescence study of kidney biopsy. Strong staining of deposits along most tubular basement membranes with anti-κ conjugate. (Original magnification × 250.)

Fig. 3. Liver biopsy. Conspicuous deposits of anti-κ reactive material along the sinusoids. Immunofluorescence with anti-κ serum. (Original magnification × 250.)

shoulder and most probably corresponded to the 20,000-dalton peak seen in the unreduced samples.

Since immunofluorescence studies showed that the plasma cells contained α and κ chains, one may conclude that the cells synthesized short α heavy chains (42,000 daltons) which lacked about one domain and which assembled with normal-sized κ-type light chains (23,000 daltons) (since these light chains were detected only after reduction–alkylation). The 110–120,000-dalton peak in unreduced samples was therefore probably an H2L2 molecule and the 60,000-dalton peak an HL half molecule. Since the latter intermediate was the major component even after 3 hr of labelling, there was probably a partial block in Ig assembly by the cells. The 20,000-dalton peak best seen in the unreduced precipitates most likely represented an abnormally short light chain which did not assemble with heavy chains and was secreted as free light chains (see below).

Electrophoretic analysis of unreduced immunoprecipitates from secretions (Fig. 5a, b) showed a peak which co-migrated with the marker light chain (23,000 daltons), one peak of about 35,000 daltons and various peaks with apparent molecular weights of 47,000, 66,000, 74,000 and 85,000 daltons. Due to technical reasons, we could not analyse molecules of larger molecular weight in these experiments. After reduction and alkylation (Fig. 5c, and d), the major peak in secreted material had a mobility corresponding to about 24–25,000 daltons. Thus, as in the cytoplasmic samples, light chains of two different sizes were detected in unreduced material and after reduction and alkylation. Strikingly, the apparent molecular weights of these two species of light chains were larger in secreted material than in cytoplasmic material (23,000 and 25,000 *vs* 20,000 and 23,000 daltons). We did not find any peak with the mobility of the cytoplasmic heavy

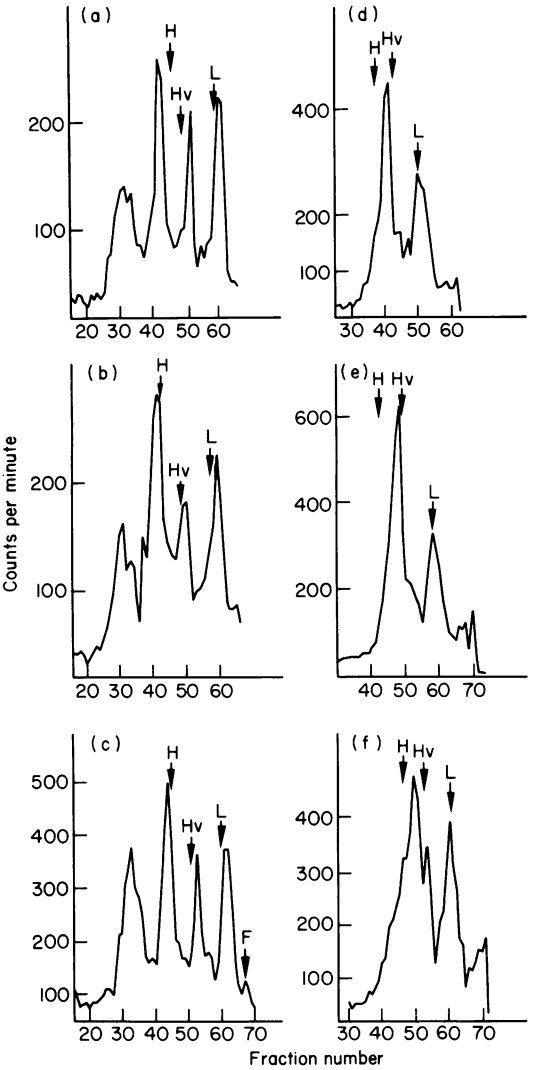

Fig. 4. SDS–gel electrophoresis of immune precipitates from cell lysates obtained after 1 hr (a & d), 2 hr (b & e) and 3 hr (c & f) of labelling of patient's bone marrow cells. (a), (b) and (c) Unreduced samples; (d), (e) and (f) reduced and alkylated precipitates. Arrows indicate the position of the internal markers in the gels. H=MPC 11 heavy chains (55,000 daltons), Hv=variant heavy chain (40,000), L=MPC 11 light chain (23,000).

chain (43,000) but two peaks which migrated faster (with apparent molecular weights of 32–35,000 and 39–40,000). The presence in unreduced samples from secretions of various peaks with molecular weights ranging from 35,000 to 85,000 daltons and the finding on reduced gels from cytoplasmic samples after 3 hr of labelling of one peak with a migration intermediate between that of heavy and light chains suggests that the Ig molecules were degraded predominantly after secretion.

Study of the serum IgA κ

The heavy and light chains of the serum IgA1 κ appeared to have a molecular weight similar to that of normal α and κ chains on the calibrated Sephadex G-100 column. SDS–polyacrylamide

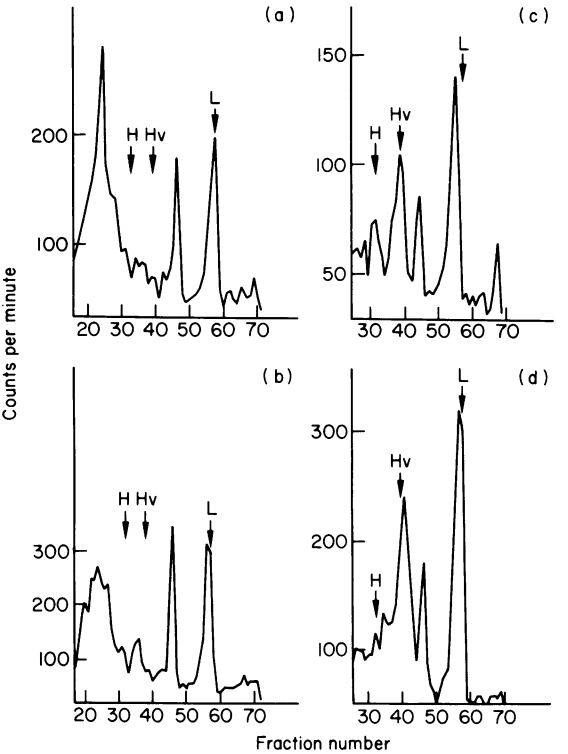

Fig. 5. SDS–gel electrophoresis of immune precipitates from secreted material obtained after 2 hr (a & c) and 3 hr (b & d) of labelling. (a) and (b) Unreduced gels; (c) and (d) reduced and alkylated. Arrows indicate the position of the markers. (See legend to Fig. 4.)

gradient gel electrophoresis confirmed this finding. Moreover, when ^{14}C-labelled chains from the patient's protein were run on cylindrical SDS–gels together with ^{3}H-labelled normal-sized α and κ chains (see Patient and Methods), both heavy and light chains co-electrophoresed perfectly. By these criteria, the size of the polypeptide chains of the serum IgA were clearly normal and different from that of the IgA produced by the bone marrow plasma cells *in vitro*.

The carbohydrate content of the light chains from the serum IgA was as follows (expressed as moles of sugar residue per mole of light chain): fucose 0·13, neutral sugars 0·59, *N*-acetyl glucosamine 0·30, *N*-acetyl galactosamine present, *N*-acetyl neuraminic acid 0·1. These light chains therefore clearly contained small amounts of carbohydrate but there was obviously not an oligosaccharide unit for each molecule of light chain. This probably reflects some heterogeneity of the light chains with respect to glycosylation since it is known that myeloma cells may secrete both glycosylated and non-glycosylated Ig chains (Weitzmann, Nathenson & Scharff, 1977).

DISCUSSION

The patient reported here was affected with a syndrome closely resembling that described by Randall *et al.* (1976) as 'light chain deposition disease'. He had tissue deposition of an amorphous material which was clearly different from amyloid protein and stained strongly with anti-κ and weakly with anti-α sera by immunofluorescence. Similarly, in one of the patients reported by Randall *et al.* (1976) tissue deposits stained strongly with anti-κ and weakly with anti-γ reagents. Our previous study strongly suggested that tissue deposition was directly related to the synthesis of structurally abnormal Ig chains (Preud'homme *et al.*, 1980). The present study further supports

this view since deposition probably corresponded to the emergence of a variant clone producing abnormal Ig chains. Indeed, the patient first presented with a common IgA myeloma and the manifestations of tissue deposition developed after 8 months of Melphalan therapy at a time when the bone marrow plasmacytosis had increased but the serum monoclonal IgA level had sharply decreased. The IgA molecules still present in serum were different from those found in biosynthesis experiments (since they had normal-sized heavy and light chains) and were therefore presumably produced by plasma cells either predominant in other locations or accounting for a small percentage of the cells studied. The biosynthesis studies indicated the production of abnormal molecules in which the α chains lacked about one domain and were assembled with light chains with a partial assembly block at the level of HL half molecules. These IgA molecules were degraded shortly after being secreted and participated in the tissue deposition as shown by immunofluorescence.

The dim staining with the anti-α conjugate does not mean that the heavy chains were present in small amounts in the deposits since they could have lost many antigenic determinants. Light chains of two different sizes were also synthesized: short light chains secreted as free light chains and normal-sized chains found after reduction and presumably coming from assembled molecules. All plasma cells stained for both α and κ chains and we do not know if the two light chains were produced by the same or by different cells. As in our other patients (Preud'homme *et al.*, 1980), striking differences in apparent molecular weights were observed between cytoplasmic and secreted light chains. Similar differences have been related to the addition of carbohydrate which takes place mainly close to secretion and modifies the mobility of proteins in acrylamide gels (Weitzmann *et al.*, 1977). Lack of material precluded biosynthesis experiments with radiolabelled carbohydrates. However, the hypothesis that the abnormal light chains from our patient are glycosylated is supported by the strong PAS-positivity of the tissue deposits. The finding of glycosylated light chains in all cases would be unusual since glycosylated human myeloma light chains account for only 15% of cases or less (Sox & Hood, 1970; Spiegelberg *et al.*, 1970; Garver & Hilschmann, 1972). In a murine myeloma variant producing short heavy chains, an abnormal glycosylation of Ig chains (and of unrelated molecules) appeared to be a consequence of the structural abnormality of the heavy chain (Weitzmann *et al.*, 1977). The light chains of our patient's serum IgA contained small amounts of carbohydrate which could not possibly account for the apparent size difference between cytoplasmic and secreted light chains. The light chains found in the biosynthesis experiments were therefore different from those of the serum protein by this criterion also and the situation in our patient is possibly similar to that documented in mouse myeloma.

The mechanism leading to the production of short Ig chains is most likely a genetic mutation since stable murine myeloma variant clones producing such short chains have been obtained as a result of chemical mutagenesis (Birshtein *et al.*, 1974). An alternative possibility is that the short size may be due to proteolysis of normal-sized chains. Since our study could not include very short labelling experiments, we cannot rule out this possibility although we believe it to be unlikely since normal-sized Ig chains have been found in all the numerous cases of common human and mouse myeloma and other B cell proliferations studied in our laboratory in routinely performed biosynthesis experiments with the same methods and reagents. The finding of light chains of a normal size and the fact that the short chains appeared to undergo degradation after only 3 hr of labelling and in the secretions in our patient also argues against this hypothesis.

The emergence of a variant clone in our patient may be due to the mutagenic action of Melphalan which has previously been suggested in human myeloma (Hobbs, 1971) and proven for mouse myeloma cells (Preud'homme, Buxbaum & Scharff, 1973). One murine mutant clone induced by Melphalan (M3.11) showed properties quite similar to those found in our patient: lack of one domain of the heavy chain, similar assembly block and abnormal glycosylation (Preud'homme *et al.*, 1973; Birshtein *et al.*, 1974; Weitzmann *et al.*, 1977). One subclone of M3.11 also produced an abnormally short light chain (Preud'homme *et al.*, 1973) and the defect was located in the constant region by peptide mapping (Preud'homme, Kuehl & Scharff, unpublished). The monoclonal IgG secreted by M3.11 was not found in the serum of tumour-bearing mice (Birshtein *et al.*, 1974) and this may be related to its high sensitivity to proteolytic

enzymes and very rapid serum decay (Weitzmann, Palmer & Grennon, 1979). In view of this observation, it is not surprising that the abnormal IgA found in the study of our patient's bone marrow cells was not detectable in serum and urine. Similarly, we found no monoclonal Ig or only trace amounts of free light chains in serum and urine from the other patients with light chain deposition studied by us (Preud'homme *et al.*, 1980). This situation is reminiscent of the so-called 'non-secretory myeloma' where the cells often appear to synthesize and secrete abnormal Ig which is then rapidly degraded (Preud'homme *et al.*, 1976). Biosynthesis experiments are therefore critical to demonstrate the major feature of the syndrome, i.e. the production of structurally abnormal Ig chains.

Our patient suffered from renal, hepatic, cardiac and neurological symptoms and Ig deposition was documented in kidney and liver. The major clinical manifestations have been due to kidney involvement in all patients with light chain deposition reported so far, except for one of our patients who died from hepatic failure due to peliosis hepatis secondary to liver deposition (Preud'homme *et al.*, 1980). The four patients studied by us had a nephrotic syndrome and the renal lesions involved both glomeruli and tubules and differed slightly from patient to patient. However, three main features were apparent: (1) a thickening of tubular (and sometimes glomerular) basement membranes with light chain determinants detectable by immunofluorescence; (2) an increase in mesangial matrix with or without mesangial cell proliferation; (3) in two cases a nodular glomerulosclerosis similar to that found in diabetic nephropathy (Olsen, 1972).

Although light chain deposition has at present been documented by immunofluorescence in only 10 patients (including our cases) (Randall *et al.*, 1976; Ganeval *et al.*, 1977; Herf *et al.*, 1979; Solling *et al.*, 1980; Preud'homme *et al.*, 1980) the syndrome is probably not exceptional since more than 20 cases of myeloma with similar renal lesions have been reported (Beaufils & Morel-Maroger, 1978) without any immunohistochemical investigations. Although usually omitted in routine kidney immunofluorescence we believe that such studies should include anti-light chain reagents.

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