access to their patients, all the medical and nursing staff concerned for their co-operation, and Mr M C K Tweedie, of the department of biostatistics, University of Liverpool.

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(*Accepted 11 December 1980*)

Systemic lambda light-chain deposition in a patient with myeloma

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Abstract

Systemic lambda light-chain deposition occurred in a 73-year-old man with myeloma. An initial renal biopsy specimen showed the features of myeloma kidney. When he died 22 months later lambda light chains were detected by immunofluorescence in kidneys, liver, spleen, and heart. They were probably responsible for cardiac dysfunction and the fatal arrhythmia.

It is suggested that in this patient deposition was due to a structural alteration of the light chains, possibly induced by cyclophosphamide.

Introduction

Renal tubular casts due to precipitation of M component are the classical lesions of multiple myeloma. Recently unusual histological features have been described attributable to deposition of light chains, which react with specific antisera by immunofluorescence and are sometimes associated with nodular glomerulosclerosis.[1-5] In some patients light-chain deposits have been found in other organs,[3 6] so-called "systemic light-chain deposition disease."[3] Until now all patients have shown deposits of kappa light chains. We describe a patient with a typical myeloma kidney who subsequently developed systemic, lambda light-chain deposition.

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Case report

A 73-year-old man was admitted in May 1976 with rapidly progressive renal failure after an episode of diarrhoea. A diagnosis of multiple myeloma was established by finding 20% abnormal plasma cells in the bone marrow aspirate and monoclonal free lambda light chain by serum immunoelectrophoresis. Urine output ranged from 1 to 2 l/day, with 1·5 g protein, mainly lambda light chains. Serum creatinine concentration varied between 980 and 1100 μmol/l (11·1 and 12·4 mg/100 ml), with a calculated clearance of about 3 ml/min. Renal biopsy was performed on the third day, and haemodialysis was started on the fifth day and continued until death. Cyclophosphamide (150 mg/day) and prednisone (30 mg/day) were given for 15 days.

The patient remained well until December 1977, when he had two episodes of supraventricular tachycardia. Over the next two months intracardiac conduction defects recurred, with bouts of tachycardia, one of which resulted in transient cardiovascular collapse. He died in March 1978 after cardiac arrest. Two weeks before death the myeloma had shown no progression; there were no visible osteolytic lesions, and bone marrow plasma cells (23%) had not increased. Free lambda light chains were still detectable in serum, and light chains in the urine represented half of the 2·8 g protein excreted daily.

PATHOLOGICAL INVESTIGATIONS

Biopsy specimens were frozen in isopentane, cooled by liquid nitrogen, and cut at 2 μm. Sections were incubated with fluorescein-labelled antisera against human immunoglobulins G, A, and M (heavy-chain specific; Behringwercke Lab) and kappa and lambda light chains (light-chain specific; Atlantic Antibodies).

Initial renal biopsy specimen—Microscopical examination showed typical myeloma kidney, characterised by numerous polychromatophilic casts surrounded by giant cells. There was extensive interstitial fibrosis without plasma cell infiltration. Glomeruli showed segmental ischaemic changes related to non-specific vascular lesions (fig 1). Stains for amyloid were negative. Immunofluorescence showed a weak reaction with antilambda light-chain antiserum of tubular casts but no staining of tubular basement membrane or glomeruli. Electron microscopy disclosed thickening of glomerular and tubular basement membranes but no abnormal deposits.

Necropsy specimens—Light microscopy of the kidneys showed ischaemic glomeruli, interstitial fibrosis, and tubular atrophy, with only a few tubular casts. In contrast with the renal biopsy specimen, most of the tubular basement membranes were irregularly thickened, chromophilic, and refringent with light green trichrome stain. Refringent material was also present within the walls of blood vessels.

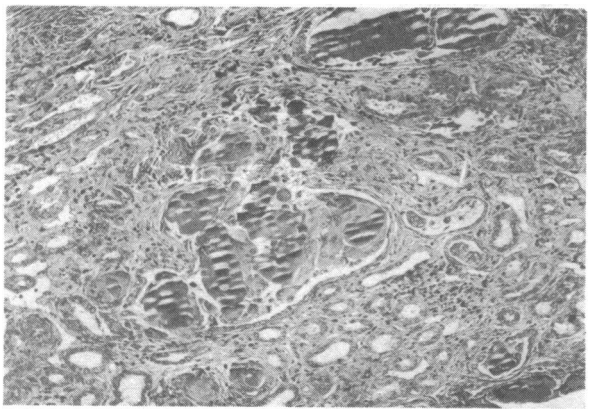

FIG 1—Biopsy specimen at presentation. Typical myeloma kidney with numerous casts surrounded by giant cells. Light green trichrome × 300 (original magnification).

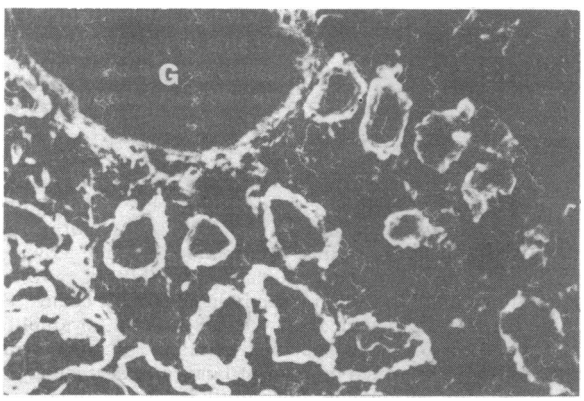

FIG 2—Necropsy specimen of kidney. Strong fluorescence with antilambda antiserum along tubular basement membranes. G = Glomerulus. × 400 (original magnification).

Samples from liver, spleen, and large blood vessels showed similar material, which was located along sinusoids in the liver and spleen, between myocardial fibres, and in the outer part of vessel walls. Specimens were examined for metachromasia with crystal violet, by polarised light with congo red, and for fluorescence with thioflavine T, but no amyloid was detected. Immunofluorescence showed a strong, bright fixation of antilambda antiserum on renal tubular basement membranes (fig 2) but not on the glomeruli, on hepatic and splenic capillaries, and in myocardium. No fixation was observed with IgG, IgA, IgM, or kappa antisera. In contrast with the kidney biopsy specimen, electron microscopy showed granular and strongly electron-dense deposits on the outer side of tubular basement membranes and along peritubular capillaries (fig 3). No fibrillar structures were detected at high magnification.

Discussion

Myelomatosis was diagnosed on the findings of abnormal cells in bone marrow and free lambda chain in serum and urine. At that time the renal biopsy specimen showed lesions of myeloma kidney, but 22 months later at necropsy deposits which were strongly fluorescent with antilambda antiserum were found in kidneys, heart, liver, and spleen.

Systemic light-chain deposition has been reported in only a few patients,[3 6] though frequency may have been underestimated because immunofluorescence studies with specific antisera have not always been carried out. So far the light chain concerned has always been of kappa type, and our patient is the first recorded with lambda light chains.

Renal failure appears to be the consequence of deposition of light chains,[1-9] though in our patient it was present before they were detected. The cardiac disturbances which occurred later and probably contributed to death could, however, have been caused by light-chain deposits in the myocardium.

The mechanisms leading to deposition of light chains remain speculative. Such proteins are cleared from plasma through glomerular filtration, tubular catabolism, and urine excretion.[10]

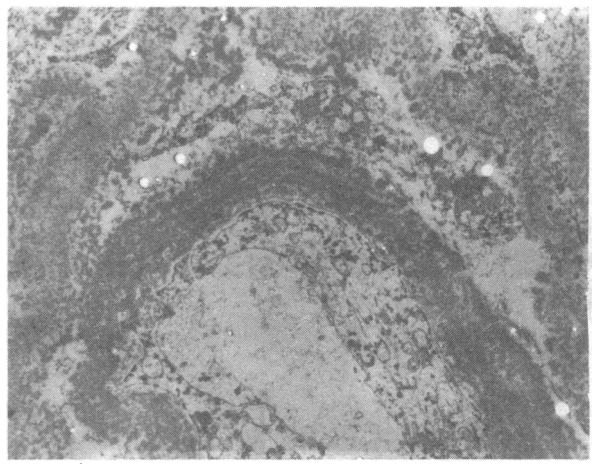

FIG 3—Necropsy specimen of kidney. Granular, electron-dense deposits on outer side of tubular basement membranes. × 9000 (original magnification).

When there is profound shutdown in renal clearance plasma light chain values rise,[11] and haemodialysis, even with highly permeable membranes, extracts only small amounts.[2 12] Prolonged uraemia might therefore result in accumulation of free light chains in plasma and consequently in tissues. Alternatively the light chains may become structurally abnormal, resulting in their deposition. We found such structural abnormalities of the light chains in two patients with the same disease,[7] and similar findings have also been reported in two other patients.[5 6] In the present case the change in the structure of the light chains might have been provoked by the initial course of cyclophosphamide, since treatment of myeloma with alkylating agents may induce mutant clones and secretion by plasma cells of abnormal products, both in mice[13] and in man.[14]

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(*Accepted 3 December 1980*)

New assessment of the effects of birth order and socioeconomic status on birth weight

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Abstract

A survey of the 20 698 singleton births occurring in one year to women resident in the Greater Dublin area provided information on birth weight, birth order, and social class. Low (⩽2500 g), suboptimal (⩽3000 g), and optimal (3001-4499 g) birth weights all showed a linear relation with social class. The incidence of low and suboptimal birth weight was highest in first, fifth, and subsequent births, and conversely optimal weight was commonest in second, third, and fourth births. Analysis indicated that a major part of the birth-order effect was attributable to social class.

Birthweight categories give information which may be distorted when using mean weight alone. The use of suboptimal and optimal weight offers the possibility of more accurate assessment of trends in performance, particularly in small samples, than does the conventional sole use of low birth weight. Low and suboptimal birth weights are uncommon in Dublin.

Introduction

Birth weight is generally acknowledged as the single most potent indicator of the risk of both mortality and handicap in the neonate. It is therefore important to understand as far as possible the factors which influence birth weight. Two such factors are birth order and social class.

Bakketeig and Hoffman[1] reopened the whole question of the effect of birth order on the outcome of pregnancy, particularly its effect on perinatal mortality. They found that in Norway mortality was higher in all birth orders among babies born to mothers who had three or four, as opposed to one or two, births during the seven-year study period. They noted that socioeconomic differences probably existed between the two groups of mothers. A WHO report[2] showed a consistent trend towards higher parities in the lower socioeconomic groups in all countries from which data were available. Hence it seemed important to make a new assessment of the effects of birth order and socioeconomic factors on the outcome of pregnancy, using a reference population with sufficient high parity to enable the birth-order effect to be fully investigated. Birth weight is used as the indicator of outcome in this study.

The Republic of Ireland offers a special opportunity to examine the influence of birth order. High parity is common, and as a result many high-order births may be studied over a short period during which there is unlikely to have been any dramatic change in obstetric practice or socioeconomic conditions. Secondly, the standard of antenatal and obstetric care is high, and most births in Dublin take place in large, well-staffed maternity hospitals.

This study is the first based on the whole population of women in Greater Dublin (that is, Dublin City and County and Dun Laoghaire Borough). It is therefore not subject, as individual hospital studies may be, to distortion of proportions of socioeconomic groups and of cases coming from outside the area, some as high-risk referrals.

Methods and data sources

The study covers singleton births, both live and dead, after gestation of at least 28 weeks, which occurred during 1 April 1978 to 31 March 1979. All such births to mothers normally resident in the Greater Dublin area are included. The population of this area was assessed as 983 683 in the national census on 1 April 1979.[3]

All births to unmarried mothers which took place in the area are included. It was not possible to ascertain the home address in these cases. An unknown number of unmarried mothers come from other parts of the country to have their babies in Dublin; however, a further, also unknown number of unmarried mothers normally resident in Dublin leave the area to have their babies or to obtain a termination.

By law hospitals and midwives must notify the health board of all births to mothers normally resident in its area. Information for the study was obtained from files of notification forms at the Eastern Health Board, which covers the Dublin area. Almost 4% of cases were without birth weights. The birth weights for these cases were obtained by searching patients' charts and delivery ward records in the various hospitals. All cases with weight still missing were excluded from analysis.

The father's occupation was classified according to the British Registrar General's social classes I, II, IIIN, IIIM, IV, and V, referred to here as social groups 1 to 6. The unemployed were classified separately (group 7), as were the never married and unsupported mothers (group 8). This group consisted almost entirely of never-married mothers. Military personnel and unclassified occupations are listed separately.

"Birth order" includes the present pregnancy and all other pregnancies lasting 28 weeks or more. The large number of cases facilitated detailed comparison of the birth weights by social group and by birth order. This was done by using mean weights and classifying birth weights into four categories: low birth weight (⩽2500 g), suboptimal birth weight (⩽3000 g), optimal birth weight (3001-4499 g), and

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