Primary 'acquired' hypogammaglobulinaemia and amyloidosis

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SYNOPSIS The clinical details and post-mortem findings are given of a patient who had primary 'acquired' hypogammaglobulinaemia and was found at necropsy to have amyloidosis. The relationship of gamma globulin deficiency to amyloidosis is discussed, and the possible relevance of the hypogammaglobulinaemia to the formation and nature of amyloid is noted. It is suggested that a disordered immune response may be an essential prerequisite for the development of amyloidosis.

Over the past 10 years a great deal of interest has been taken in idiopathic or primary hypogammaglobulinaemia because of the possibilities that the antibody deficiency syndrome offers an 'experiment of nature' in the investigation of immune mechanisms and the functions of gamma globulin. For some time it was postulated that gamma globulin was an important constituent of amyloid but recent work has contradicted this view (Paul and Cohen, 1963; Cathcart, Comerford and Cohen, 1965; Cathcart and Cohen, 1966). In this context the development of amyloidosis in a patient with primary 'acquired' hypogammaglobulinaemia is of relevance. Only five other fully documented reports of this association have been found in the literature (Gras, Latorre, and Gamissans, 1954; Teilum, 1964a; Clinicopathological Conference, 1965; Forssman and Herner, 1964; Conn and Quintiliani, 1966). The present case was reported previously before the diagnosis of amyloidosis was made (Cook and Melrose, 1958).

CASE REPORT

This patient was born in 1914 and, apart from scarlet fever and chickenpox in childhood, remained well until 1947 when she developed a chronic cough, worse in winter than summer, with copious purulent sputum and occasional haemoptysis. She had pneumonia in 1949 and right otitis media in 1953. In 1954 a hysterectomy was carried out for uterine fibroids and postoperatively she developed cystitis, vaginitis, and recurrent Bartholin gland infection.

She was admitted to hospital in January 1957 for investigation and treatment of the cough and purulent sputum which was associated with tiredness and loss of

weight. On examination she was thin and pale, she had early finger clubbing, and there was dullness on percussion with bronchial breath sounds and coarse crepitations over the right lower lobe. The spleen was enlarged 7 cm. beyond the left costal margin but there was no hepatomegaly or lymphadenopathy. The E.S.R. was 5 mm in one hour, the haemoglobin 10.2 g%, the P.C.V. 38%, and the W.B.C. 3,000 per mm.³ with a normal differential count. There was no proteinuria. A bronchogram showed bronchiectasis involving the basal segments of the right lower lobe. Because of the association of bronchiectasis and splenomegaly a diagnosis of amyloidosis was considered but a Congo red test was normal (78% of the dye excreted one hour after injection of 100 mg. Congo red). It was then found that the total serum protein was 6.80 g. per 100 ml. and that a serum protein electrophoretic pattern showed almost complete absence of gamma globulin. The serum gamma globulin estimated by the gel diffusion precipitin technique was 80 mg. per 100 ml. There was no agglutination of standard suspensions of *S typhi* and *paratyphi* before and after T.A.B. inoculations. Sternal marrow examination showed normoblastic erythropoiesis but no plasma cells were seen.

During a course of treatment with tetracycline the patient developed severe diarrhoea. Despite treatment with intramuscular gamma globulin in a dose of 0.025 g. per kg. weekly, the diarrhoea was still present three weeks later with up to 12 stools daily containing blood and mucus. Sigmoidoscopy showed that the rectal mucosa was hyperaemic, friable, granular, and covered with mucopurulent exudate, and in the sigmoid colon, where these changes were less marked, several discrete ulcers were seen. A diagnosis of ulcerative colitis was made and treatment with oral cortisone 100 mg. daily and rectal cortisone acetate 100 mg. daily was started. Within a week there was a striking improvement in the symptoms which did not recur when cortisone was slowly withdrawn. A further sigmoidoscopy before discharge from hospital showed that the mucosa of the lower colon was virtually normal.

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Treatment with weekly injections of gamma globulin was continued and in spite of occasional respiratory and urinary infections she made satisfactory progress, gaining about one and a half stones in weight over the next 18 months. In November 1959 she was readmitted to hospital because of a severe urinary infection. A coliform bacillus was grown on culture and the infection cleared with a course of chloramphenicol.

Over the next year she remained reasonably well although her weight fell gradually. In December 1960 she had a recurrence of the diarrhoea with blood in the stools and was again treated with corticosteroids in the form of oral prednisolone and rectal hydrocortisone hemisuccinate. This produced some symptomatic improvement but in spite of continuing regular treatment with rectal hydrocortisone a further exacerbation of bowel symptoms developed in January 1961. A barium enema at this time showed redundant looping of the colon with complete loss of haustration. Energetic treatment with corticosteroids and an increase in the dose of gamma globulin produced some benefit but her general condition slowly deteriorated with further weight loss. She also continued to have recurrent respiratory infections which showed a poor response to antibiotic therapy.

In June 1961 she was, for the first time, found to have proteinuria regularly present in moderate amounts, although this was attributed to urinary infection. In July 1961 she had another exacerbation of the ulcerative colitis and her general condition deteriorated progressively until her death in August 1961.

POST-MORTEM FINDINGS

The body was that of an emaciated middle-aged woman of average stature.

THORAX On the right side the layers of the lower pleura were adherent and on both sides the pleura was adherent to the pericardium and also to the diaphragm. There were encysted collections of pus on the left side between the pleura and pericardium and also above the diaphragm. There was severe bronchiectasis affecting the basal segments of the right lower lobe.

The myocardium was rather pale and soft but the valves were within normal limits and the coronary vessels showed only patchy atheroma without narrowing.

ABDOMEN The wall of the stomach was rather thin but the mucosa showed a normal pattern with no ulceration or erosion. The duodenum showed no gross abnormality. The small bowel only showed some mucosal congestion. The large bowel was thin-walled with a smooth mucosa and with numerous superficial ulcers affecting the whole of the large bowel apart from the caecum and the first six inches of the ascending colon. Histological examination of the colon showed non-specific ulceration and congestion with a considerable number of plasma cells in the mucosa and with some small blood vessels, mainly in the mucosa, involved by amyloid.

The liver surface was smooth and on section the substance was pale and rather shiny. Histological examination showed severe amyloidosis.

The spleen was smooth and the substance extremely firm and rubbery. On section the Malpighian bodies were large and prominent. Histological examination showed extensive amyloid deposits, and although occasional reticulum cells were seen there were no definite mature plasma cells.

The kidneys were of normal consistency. The capsules stripped easily revealing a smooth, pale surface. On section the appearance was normal apart from pallor of the cortex and congestion of the medulla. Histological examination showed some involvement of the glomeruli by amyloidosis.

DISCUSSION

It is impossible to be certain that the amyloidosis did not precede the hypogammaglobulinaemia, but there are several reasons for considering this unlikely. The absence of proteinuria and the negative Congo red test when hypogammaglobulinaemia was diagnosed do not exclude amyloidosis, but they make it unlikely that, at that time, the patient had extensive amyloidosis. Although the serum gamma globulin level may be raised in amyloidosis it sometimes falls as the disease progresses but rarely, if ever, to a level of 80 mg. per 100 ml. Seventeen of the 27 cases of amyloidosis reported by Osserman, Takatsuki, and Talal (1964) were said to have low gamma globulin levels on serum protein electrophoresis but the lowest serum gamma globulin level given was 300 mg. per 100 ml., and from the electrophoretic patterns it would appear that this case had a lower serum gamma globulin level than any of the others. It is, therefore, virtually unknown for hypogammaglobulinaemia secondary to amyloidosis to fall within the range accepted by the M.R.C. Working Party for a diagnosis of primary hypogammaglobulinaemia, *i.e.*, 200 mg. per 100 ml. or less (Soothill, 1962). Finally, the absence of plasma cells from the sternal marrow makes the diagnosis of primary hypogammaglobulinaemia virtually certain, as in almost all cases of amyloidosis there is an excess of plasma cells. In the series of 27 cases described by Osserman and his co-workers all but one of the patients had an excess of plasma cells in the marrow. There is little doubt, therefore, that the present case had primary 'acquired' hypogammaglobulinaemia and that she developed amyloidosis because of the resulting infections.

Although this case shows that amyloidosis can develop when plasma cells are absent or extremely scanty, this does not exclude the possibility that in most instances amyloid may be a product of plasma cells. It seems probable, however, that amyloid can also be produced by other protein-forming cells. Teilum (1964b) believes that amyloid is formed *in situ* by fixed reticuloendothelial cells producing a local secretion of polysaccharide-containing globulins, and

his view of the development of amyloid as a biphasic process seems to be in accordance with the association of hypogammaglobulinaemia and amyloidosis. In hypogammaglobulinaemia the reticuloendothelial pyroninophilic cells are stimulated to proliferate by the recurrent infections, but this proliferation is suppressed by the acquired, but probably genetically determined, defect underlying the hypogammaglobulinaemia, and it is this process which results in amyloid formation.

There seems to be little doubt that amyloid is a protein-polysaccharide complex but there is considerable controversy as to its nature. It was generally believed that gamma globulin was the essential component of amyloid (Osserman, 1961), but the majority of recent studies oppose this view as does the development of amyloidosis in the presence of hypogammaglobulinaemia. Two recent articles (Cathcart and Cohen, 1966; Schultz, Calkins, Milgrom, and Witebsky, 1966) present conflicting views as to whether or not amyloid fibrils contain gamma globulin, but even Schultz and his co-workers, who demonstrated gamma globulin in amyloid, concluded that gamma globulin is not the only, and perhaps not even the major, component. It has now been suggested from antibody studies that the main constituent of amyloid is an alpha globulin (Cathcart *et al.*, 1965).

The association of diarrhoea and hypogammaglobulinaemia has recently been fully reviewed by Conn and Quintiliani (1966) who collected 38 cases from the literature. They reported that usually the large bowel was radiographically normal. Although, at necropsy, the present case showed histological evidence of involvement of the colon by amyloidosis this was not extensive, and it is improbable that the bowel symptoms, which started four years before her death, were due to amyloidosis. It seems likely, therefore, that this patient had true ulcerative colitis in view of the appearances of her barium enema, the findings at sigmoidoscopy, and the response of bowel symptoms to corticosteroids. The post-mortem finding of a considerable number of plasma cells in the colonic mucosa (although none was seen in the spleen) is surprising. It is known, however, that some cases of dysgammaglobulinaemia have normal numbers of plasma cells in bone marrow and lymph nodes (Gleich, Condemni, and Vaughan, 1965), and

a patient with hypogammaglobulinaemia, pure red cell aplasia, and thymoma previously reported by one of the authors (Murray and Webb, 1966) had a normal number of plasma cells in the sternal marrow on two occasions, although no plasma cells could be found in the lymph nodes at necropsy.

Lastly, it is of interest that amyloidosis has been found in a number of different experimental animals with immunological deficiencies (Gabrielsen and Good, 1966). Rabbits subjected to removal of the central lymphoid tissue sometimes develop amyloidosis, and in these animals the incidence of amyloidosis is increased by irradiation (Sutherland, Archer, Peterson, Eckert, and Good, 1965). Bradbury and Micklem (1965) have shown that amyloidosis develops in mice which have lymphoid aplasia produced by a lethal dose of irradiation, but which have been kept alive by a bone marrow transplant insufficient to repopulate the lymphoid tissues. There can be no doubt, therefore, that amyloidosis is frequently associated with defective or disordered immunological mechanisms, and it may be that some such abnormality is the primary aetiological factor in all forms of amyloidosis.

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