PRIMARY AMYLOIDOSIS WITH RENAL AND MYOCARDIAL FAILURE

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In secondary amyloidosis the kidney is one of the commonest sites in the body for the deposition of amyloid, and renal failure is a common sequel. In primary amyloidosis renal involvement is less common and renal failure exceptional. Only four cases of renal failure due to primary amyloidosis have been described in the literature. The individual patients of Christian (1932), Gerber (1934), and Lindsay (1948) respectively were males whose average age at the time of death was 57 years. The average duration of their illness was three years. The case of Platt and Davson (1950) was in a 60-year-old woman whose illness lasted 18 months.

It has been stated (Dahlin, 1950) that death from myocardial involvement occurs in roughly half the cases of systemic primary amyloidosis.

The description that follows is concerned with the case of a middle-aged woman who developed progressive renal and myocardial failure due to primary amyloidosis.

Case History

The patient was an unmarried post-office worker. At the time of her death she was 49 years of age. Her health had always been good except for diphtheria at the age of 6 years and quinsy at the age of 35 years. Her illness began two years before death with attacks of precordial pain brought on by exercise. Her doctor treated her for anaemia and the pain completely disappeared. Three months later, however, the pain returned and the patient also noticed swelling of the ankles. At this time (July, 1949) she was admitted to hospital.

Clinical examination revealed gross oedema of the legs and lower trunk. The blood pressure varied between 118/92 and 140/100 mm. Hg. The heart appeared normal, but electrocardiograms showed a slightly increased P-R interval and low voltage waves.

Laboratory Investigations.—Haemoglobin was 5.5 g. per 100 ml. (40% Haldane), red cells 2.4 million per c.mm., white cells 6,000 per c.mm. Total serum cholesterol was 510 mg. per 100 ml. The serum albumin varied between 0.8 and 3.5 g. per 100 ml. and the serum globulin between 1.4 and 1.8 g. per 100 ml. The fibrinogen estimations averaged 850 mg. per 100 ml. The gamma globulin was less than 100 mg. per 100 ml. on the average. The erythrocyte sedimentation rate was 67 mm. in the first hour (Wintrobe). Using defibrinated blood, the reading was 29 mm. The Wassermann and Kahn reactions were negative. The blood urea was 60 mg. per 100 ml. The urine was sterile but contained much albumin, an occasional red cell, and fairly numerous granular and hyaline casts. The urea clearance was about 50% of normal. The basal metabolic rate was -6%.

A diagnosis of Ellis type 2 nephritis was made and the patient was treated with rest, high protein/low salt diet, and injections of mersalyl. After three months in hospital the

oedema subsided. For a time the patient was able to undertake part-time work, but she suffered increasing dyspnoea on exertion as well as pain in the chest. The oedema of the ankles returned.

She was readmitted in April, 1950, with extreme shortness of breath and continuous vomiting. It was evident that there was now severe renal failure. Oedema extended up to the mid-thoracic region posteriorly and up to the inguinal ligaments anteriorly. The patient also had large pleural effusions and papilloedema. The blood pressure was 130/75 mm. Hg. The pulse was 60 and regular. There was a systolic murmur at the left border of the sternum and a diastolic murmur at the pulmonary area. Electrocardiograms showed evidence of considerable myocardial damage with almost complete A-V block, and a marked lowering of the voltage in all leads. There was some enlargement of the thyroid. The haemoglobin was 6.9 g. per 100 ml. blood (50% Haldane), the blood urea 280 mg. per 100 ml., the total serum cholesterol 710 mg. per 100 ml., the serum albumin 2.1 g. per 100 ml., and the serum globulin 3.4 g. per 100 ml. The erythrocyte sedimentation rate was 146 mm. in the first hour (Wintrobe, uncorrected for fibrinogen).

On May 4, 1950, the patient was transfused with one pint of group O blood. On May 20, 1950, 2,400 ml. pale, serous fluid was aspirated from the pleural sacs. The fluid quickly re-accumulated. The high protein/low salt diet was continued, and Shohl's solution was administered to combat acidosis. In the last month before death the urine contained traces of glucose. The patient died on July 25, 1950. The necropsy was performed on the following day.

Post-mortem Findings

The body was that of a middle-aged female 1.6 m. in length and 80 kg. in weight. There was marked generalized oedema. The head and neck were cyanosed. Petechial haemorrhages were numerous over the front of the neck and a few were present on the face. The tongue appeared normal.

The heart weighed 440 g. Fibrinous pericarditis was present. All chambers were dilated. Both ventricles were thickened. The myocardium was of normal consistency but paler than usual. The left ventricle showed some fatty degeneration. At and below the line of closure of the mitral and aortic valve cusps were numerous rounded, grey-pink, semi-translucent deposits (Fig. 1). They were smooth or slightly roughened and measured 1–2 mm. in diameter. Some had apparently coalesced into masses measuring 4–6 mm. in diameter. They did not appear to be covered with fibrin and they could not be dislodged without tearing the cusps. Apart from these lesions, the mitral and aortic cusps showed some slight fibrous thickening. The coronary arteries were slightly thickened. There was severe atheroma in the abdominal aorta.

Massive pleural effusions had produced marked collapse of the lungs, which were very oedematous. Small, fibrous adhesions were present at the apices of both upper lobes.

About a litre of serous fluid occupied the peritoneal cavity. The liver was enlarged (1,772 g.) and showed nutmeg congestion. The intestines were congested and showed also small, scattered subperitoneal haemorrhages.

The spleen was enlarged (250 g.) and congested. The lymph nodes were normal except for calcification in two small ileo-caecal nodes.

With the exception of a unilocular cyst, containing watery fluid, in the upper pole of the right kidney, each kidney had the same features: reduction in volume

and weight (right kidney 96 g., left kidney 104 g.); the capsule stripped easily, revealing a finely granular surface; the cortex was pale and reduced in thickness (average thickness 3 mm.) but still well demarcated from the medulla; the interlobar and interlobular arteries were thickened, but there was no abnormality of pelvis, ureters, or bladder.

A few small fibromyomata

FIG. 1a

FIG. 1b

FIG. 1a.—Amyloid deposits in aortic cusps.

FIG. 1b.—Amyloid deposits in mitral cusps.

were present in the uterus. The whole of the vaginal aspect of the external os was reddened by an "erosion." Both ovaries had numerous superficial haemorrhages. The breasts were normal. The adrenals contained plentiful cortical lipoid. The left lobe of the thyroid was slightly enlarged. Both lobes were firmer than normal. On section the thyroid was greyish-pink and less glistening than normal. The brain (1,250 g.) was slightly oedematous. No abnormality was discovered in the joints or skeletal muscles.

Microscopic Findings

The subendocardial deposits consisted of masses of amyloid (Fig. 2a). The staining reactions are described later. The fibrinous pericarditis was confirmed. In the myocardium there was a variable degree of amyloid (Figs. 2b and 2c). A frequent finding was an amyloid investment of muscle fibres, which were often atrophied. Some fibres had been wholly replaced by amyloid, others had undergone hypertrophy. The walls of the larger myocardial blood vessels were thickened by amyloid. No amyloid was present in the largest arteries in the body, e.g. the carotids.

FIG. 2a

FIG. 2b

FIG. 2a.—Subendocardial amyloid deposits. The clefts are artefacts. Congo red $\times 40$.

FIG. 2b.—Amyloid deposits in the myocardium. Note the involvement of the arteriole. Haematoxylin and eosin $\times 70$.

FIG. 2c.—Amyloid deposits in the myocardium. There is replacement of muscle fibres by amyloid. Congo red $\times 200$.

FIG. 2c

The lungs were markedly oedematous. Pulmonary arterioles, venules, and capillaries frequently showed amyloid thickening. Small patches of amyloid were also scattered irregularly in the alveolar walls.

The arteries and veins in the portal tracts of the liver were markedly thickened by amyloid (Fig. 4). No amyloid was present in the lobules themselves. There was pronounced centrilobular congestion. In the spleen the sinuses were dilated from chronic venous congestion. Some of the Malpighian corpuscles were largely replaced by amyloid (Fig. 5). There was also slight amyloid thickening of the blood vessels, mostly arterioles, and patchy amyloid deposits were present in the trabeculae.

In the kidneys there was amyloid infiltration, more or less severe, of all glomeruli (Fig. 3). Those that were most affected were much larger than normal. In

FIG. 3

FIG. 3.—Considerable amyloid deposit in the glomeruli of the kidney, also in the blood vessels. Congo red $\times 70$.

FIG. 4

FIG. 4.—There is considerable amyloid thickening of the blood vessels in the portal tracts of the liver. No amyloid is present in the lobules. Haematoxylin and eosin $\times 70$.

FIG. 5.—Amyloid deposit in Malpighian corpuscle of the spleen. Haematoxylin and eosin $\times 70$.

FIG. 5

addition, there was marked amyloid thickening of arterioles, some arteries and, to a lesser degree, of some venules and capillaries. As in the liver, all the coats of the larger vessels were affected. Many tubules had disappeared entirely. Those that remained were often dilated and frequently were lined by atrophic epithelium. Small amounts of fat were present in the tubules, especially the convoluted parts, and in the glomeruli. Hyaline casts were frequent in the tubules, and moderate numbers of polymorphonuclear leucocytes were present in some tubules, though they were not seen in the interstitial tissues of the kidney. A small amount of fibrosis had occurred in many glomeruli and a larger amount in the interstitial tissue, but there was no special fibrous thickening around Bowman's capsule.

Arteries in the pericapsular connective tissue of the adrenals, as well as in the adrenal medulla, were thickened by amyloid. The ovaries showed marked amyloid thickening of arteries, also of some of the smaller blood vessels. They also showed small recent haemorrhages.

In the stomach and intestines there was amyloid thickening of submucosal arteries.

Sections of the thyroid showed scanty acini separated by broad bands of interstitial tissue containing abundant amyloid (Fig. 6). The acinar lining was often atrophic and colloid was very scanty. Some amyloid thickening of vessels, mainly veins, was present.

Most lymph nodes were normal. In a few of them there was some amyloid thickening of the arteries.

There was slight patchy amyloidosis of the fibrous connective tissue in the tongue. The arteries of many skeletal muscles were slightly thickened by amyloid.

In the salivary glands there was amyloid thickening of the arteries and of the basement membranes of ducts and some acini.

Sections of the brain revealed no abnormality.

Positive staining reactions for amyloid were given by iodine, iodine green, P.A.S. (McManus, Hotchkiss, modified by Pearse), silver (modified Hortege, after King), and Congo red. The amyloid material also stained metachromatically with methyl violet and crystal violet.

The preparations stained by Congo red deserve special mention because it was observed that the combination of amyloid and Congo red was doubly refractile, as described by Ladewig in 1945. Only patches of the amyloid material were doubly

FIG. 6.—Considerable amyloid deposit in the connective tissue of the thyroid. Haematoxylin and eosin $\times 70$.

refractile, however, and there was no correlation between the density of Congo red staining and the emergence of double refraction.

Discussion

Wild (1886) reported the first case of primary amyloidosis, but it received little attention until the classical papers of Königstein (1925) and Lubarsch (1929). It differs from secondary amyloidosis by the absence of demonstrable pre-existing disease, by a special tendency toward the involvement of the heart, lungs, muscles, skin, and other structures not often or seriously affected in secondary amyloidosis, and by its staining reactions, which are sometimes atypical. It is of interest that it occurs in animals, particularly in horses and dogs.

Approximately 70 cases of primary systemic amyloidosis have appeared in the literature. The vast majority were not diagnosed until necropsy. In a recent review of 55 cases Dahlin (1950) reported death from cardiac involvement in at least 14 examples. Lesions of the skin and skeletal muscles were present in more than a fourth of the cases. Several patients had purpura. The liver, spleen, kidneys, and adrenals contained amyloid in more than a third. In three patients, all males, severe renal failure occurred. Christian's patient (case reported in 1932) was a man of 53 who died of bronchopneumonia after an illness lasting nearly three years. He had generalized oedema with marked albuminuria and a reduced total plasma protein with reversal of the normal albumin-globulin ratio. The blood pressure and blood urea were normal. The basal metabolic rate was subnormal. Occasional hyaline and granular casts were present in the urine. At necropsy amyloid was present in the kidneys, spleen, liver, and adrenals. The right kidney weighed 295 g. and the left 300 g. Both kidneys were oedematous. The capsule stripped easily. There was marked deposition of amyloid in the glomeruli. Marked tubular degeneration, with fatty change, was present. The blood vessels are reported as showing "hyaline" change. There was patchy interstitial fibrosis, and occasional casts were present in the tubules.

The case reported by Lindsay (1948) resembles Christian's closely except for the addition of amyloidosis of the heart. The patient was a man of 66 who was ill for two years. He had generalized oedema and severe albuminuria. Occasional hyaline and granular casts were seen in the urine, as well as a few white cells. The plasma albumin was markedly reduced. The blood cholesterol was raised. The blood pressure and basal metabolic rate were normal. Electrocardiograms showed low voltage curves. The patient died of pulmonary oedema and pulmonary infarction. At necropsy extensive amyloid deposits were present in the heart, in the sub-epicardial fat, throughout the myocardium, and beneath the endocardium of the atria and tricuspid valve. Deposits were also found in the pulmonary vessels and in many other visceral blood vessels, e.g. in the liver, gall-bladder, gastro-intestinal tract, kidneys, pancreas, ovaries, pituitary, thyroid. Arteries, arterioles, veins, venules, and capillaries were all affected. Amyloid deposits were especially noted under the endothelium of arteries. A slight deposition of amyloid was noted in the dermis.

The right kidney weighed 240 g. and the left kidney 250 g. The outer surface was slightly granular and pale yellow. The capsule was slightly adherent. The

cortico-medullary junction was ill-defined. There was much deposition of amyloid in the glomeruli, but only a few of the latter were completely replaced by amyloid. Subendothelial amyloid was seen in afferent arterioles and in some smaller vessels in the medulla and pelvis. There was severe tubular damage and lipid droplets were frequent in the degenerate epithelium. Small deposits of amyloid were present in the interstitium of the cortex as well as collections of lymphocytes.

The report of Gerber (1934) concerned a 51-year-old Russian Jew who was ill for three years. The patient had complained of pruritus of the thighs and vague pains and weakness in the back and thighs. He was found to have marked albuminuria and an enlarged liver. Doubly refractile crystals and a few white and red cells were found in the urine, and slight glycosuria was also reported. The blood pressure and plasma proteins were normal; the blood cholesterol was raised; the basal metabolic rate was subnormal. The patient died in uraemia with pulmonary oedema. At necropsy there was extensive amyloid deposit in the vertebrae, with partial collapse of the bodies of the ninth thoracic and first lumbar vertebral bodies, and in the iliac bones, femur, and ribs. The liver showed diffuse amyloid deposits, with involvement of blood vessels. Similar deposits were found in the pancreas, spleen, kidneys, suprarenals, thyroid, and stomach mucosa. The right kidney weighed 120 g., the left 110 g. Both kidneys showed the same features: finely-granular outer surface, waxy cut surface, normal-looking cortico-medullary junction; the glomeruli were largely replaced by amyloid, and amyloid was present in the media of the small and medium-sized vessels as well as in the basement membranes of the tubules; the larger vessels were free of amyloid; there was considerable tubular atrophy and degeneration with dilatation of many surviving tubules and fibrosis of the interstitial tissue.

Platt and Davson in their study of renal disease (1950) refer briefly to a case of primary amyloidosis with renal failure in a woman of 60. She had been ill for 18 months with weakness, tiredness, loss of weight and appetite, shortness of breath on exertion, and swelling of the legs. Examination showed evidence of myxoedema as well as generalized oedema, enlargement of the liver and spleen, hypertension (150/100), albuminuria, and a mild hypochromic, normocytic anaemia. The serum albumin was 3.1 g. per 100 ml. and the serum globulin 2.8 g. per 100 ml. The blood urea was 180 mg. per 100 ml., rising to 232 mg. per 100 ml. before she died "apparently in uraemia." At necropsy the ventricles of the heart were seen to be hypertrophied, the spleen was enlarged (750 g.), and the kidneys (150 g. and 85 g.) were finely granular and showed loss of cortical pattern and yellow lipid deposition in the boundary zone. Histologically, amyloid was present in the liver, spleen, lung, thyroid, adrenals, kidneys, pancreas, myocardium, and aorta, but no details are given. This case differs from those already mentioned in that the kidneys were so different in weight. In the absence of histological details in this case the inequality of the kidneys raises doubt as to the "primary" nature of the amyloidosis, since it seems possible that one kidney might have been the seat of old-standing pyelonephritis.

The case reported in this paper affected a woman aged 49. Clinically, her condition resembled that of Lindsay's patient and Platt and Davson's patient. On histopathological grounds, the widespread amyloidosis of the heart and blood vessels was an additional point of similarity to Lindsay's patient; but, whereas the kidneys

in Lindsay's and Christian's cases were enlarged, the kidneys of the case here reported resembled those of Gerber's patient in being reduced in size.

Christian made no comment on the distribution of amyloid in the walls of blood vessels. Platt and Davson, apart from referring to the presence of amyloid in the aorta of their patient, gave no details concerning the distribution of the amyloid within the wall of that vessel. Lindsay referred to deposits of amyloid in the subendothelial part of arteries. Gerber mentioned special involvement of the media of the renal arteries. In my own case most arteries affected by amyloid showed deposits throughout their walls, but in some arteries the amyloid was confined almost entirely to the media.

Summary

A case of primary systemic amyloidosis in a woman of 49 is described. The illness lasted two years and was accompanied by progressive renal and myocardial failure. The amyloid was mainly of cardiovascular distribution.

Reference is made to the four other cases of primary systemic amyloidosis with renal failure reported in the medical literature.

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