Multifocal fibrosclerosis and renal amyloidosis

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Summary

A 34-year-old female with a 14-year history of multifocal fibrosclerosis developed the nephrotic syndrome due to renal amyloidosis. Although the association between chronic inflammatory processes and amyloidosis is well known, this is the first report of amyloidosis occurring in a patient with multifocal fibrosclerosis. Other interesting features of this case are the involvement of subcutaneous adipose tissue in the inflammatory-fibrotic process and the presence of features of multifocal fibrosclerosis in the patient's twin sister.

KEY WORDS: multifocal fibrosclerosis, renal amyloidosis, necrobiosis lipoidica.

Introduction

Multifocal fibrosclerosis is a rare condition which is characterized by a low grade inflammatory process in certain anatomical regions, resulting in pleural, retro-peritoneal and mediastinal fibrosis. In addition, it may be complicated by Riedel's thyroiditis, sclerosing cholangitis or pseudotumour of the orbit. The aetiology is unknown, although an immune process has been postulated, and occasionally steroids may result in some improvement (Jones *et al.*, 1970). There has been one report of an association with alpha-1-antitrypsin deficiency (Palmer, Wolfe and Kostas, 1978).

We wish to report the occurrence of nephrotic syndrome secondary to amyloidosis in a 34-year-old woman with multifocal fibrosclerosis.

Case report

A 34-year-old woman was admitted for investigation of ankle swelling of 6 months duration together with puffiness of her face in the morning.

In 1956 at the age of 9 years and at the time of tonsillectomy, a chest X-ray showed mild pleural

thickening and this was noted again in 1966 in a mass chest X-ray. She gave a history of recurrent bilateral pleurisy and was found to have a mild anaemia and raised erythrocyte sedimentation rate (ESR) of 41-73 mm/hr.

She presented again in 1970 with abdominal pain and was found to have a large mass in the right upper quadrant. At laparotomy, inflammatory adhesions were found involving the hepatic flexure of the colon, the second part of the duodenum, and the lower surface of the right lobe of the liver. Biopsy of the mesentery showed perivascular lymphocytic infiltration. She experienced loin pain. An intravenous urogram revealed medial displacement of the ureters, and a renogram showed delayed excretion from both kidneys. Chest X-rays were compatible with pleural fibrosis and lung function tests showed a restrictive defect with no evidence of a reduction in gas transfer. A diagnosis of multifocal fibrosclerosis were made and she was treated with prednisolone and azathioprine for 33 months with a fall in the ESR and some subjective improvement. In 1977, a renogram was normal and chest X-ray did not show progression of the pleural fibrosis.

On examination in July 1980, she had marked oedema and ascites. Investigations confirmed nephrotic syndrome, creatinine clearance 80 ml/min serum albumin 23 g/litre and urinary protein excretion 3 g/24 hr. Haemoglobin was 13.9 g/dl and ESR 98 mm/hr. Obstructive uropathy was excluded by ultrasound examination and renography. Chest X-ray showed pleural fibrosis. HLA typing was A1, A2, B17-1, B18, BW4, DR1, DR2 and α -1-anti-trypsin was normal. Renal biopsy showed on light microscopy evidence of amyloid deposition in at least 50% of the glomeruli both in the glomerular basement membranes and within the mesangium. There was also prominent deposition in arterioles, peritubular capillaries, tubular basement membranes and medullary interstitium. Crystal violet stain demonstrated the characteristic metachromatic staining of amyloid and the congo red stain showed green birefringence under polarized light. The effect of permanganate on the

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congoophilia of the amyloid deposits (Wright, Calkins and Humphrey, 1977) revealed the fibrils to be off AA protein. Electron microscopy confirmed the light microscopic findings (Fig. 1). Immunofluorescence examination showed focal, granular fluorescence for IgM along the glomerular basement membrane and in the peritubular region of interstitium.

FIG. 1. Electronmicrograph of renal biopsy showing amyloid fibrils in mesangial matrix ($\times 21000$).

Three months treatment with dimethylsulphoxide, which may improve renal function in patients with secondary amyloidosis (Donker, Ruinen and Marink, 1976), failed to halt the development of progressive renal failure.

In January 1981, she presented with a diffuse papular eruption over the anterior left shin; histology of the skin biopsy showed irregular thickening of the epidermis with mild hyperkeratosis. The dermis contained a moderate perivascular mononuclear inflammatory cell infiltrate, predominantly lymphocytes and histiocytes, present around superficial and deep vessels and extending into subcutaneous fat. In the upper dermis there were also scattered small foci of fibrinoid degeneration of collagen surrounded by chronic inflammatory cells and reactive fibroblasts. The abnormalities, though not diagnostic, were

suggestive of the early stage of necrobiosis lipoidica. There was no evidence of amyloid deposition.

The patient's twin sister was found, at another hospital, to have anaemia, elevated ESR and pleural shadowing in both bases on chest X-ray in 1972. There was a grossly reduced vital capacity and an intravenous urogram showed medially displaced ureters with minor early obstructive changes in both pelvicalyceal systems. In 1969 at appendicectomy dense adhesions were found around the pelvis although there was no evidence of overt peritonitis. She was treated with steroids and azathioprine for a period of one year. A recent urine specimen showed no proteinuria.

Discussion

Multifocal fibrosclerosis is an inflammatory fibrotic process occurring in connective tissues and may involve the retroperitoneum, root of the mesentery, mediastinum and pleura. In addition, it may be associated with sclerosing cholangitis, pseudotumour of the orbit and Riedel's thyroiditis. The pathology of these disorders is fairly similar with a non-specific vascular, fibrous process infiltrated by lymphocytes and plasma cells. Although these entities are considered diseases of undetermined aetiology, various theories of pathogenesis have been put forward (Schully, Galdabini and McNeeley, 1976), especially in the case of retroperitoneal fibrosis, and include abdominal and retroperitoneal surgery, infections, urine extravasation, aneurysmal leakage, radiation and an association with ergot alkaloids. Also, the widespread systemic changes which can occur in multifocal fibrosclerosis have invariably raised the possibility of a collagen-vascular disease due to an immune or autoimmune process, although the antigen concerned has not been defined.

The pathogenesis of amyloidosis is not known, but again immune mechanisms have been implicated (Glennner, 1980), and it is well established that it can complicate long-standing inflammatory and infective conditions. As multifocal fibrosclerosis is characterized by a chronic inflammatory response, it is perhaps not coincidental that this patient has developed amyloidosis. However, this is the first reported case of these 2 disorders occurring together and until more information is available, an open mind should be kept about this association. There has been a previous report of renal amyloidosis associated with retro-peritoneal fibrosis in which a 61-year-old female with a 9-year history of retroperitoneal fibrosis developed nephrotic syndrome (Littman, 1971).

Although the usual spectrum of multifocal fibrosclerosis does not include skin and subcutaneous involvement, subcutaneous involvement has been

reported in a 30-year-old female with progressive inferior and superior vena caval obstruction caused by retroperitoneal and mediastinal fibrosis (Coopersmith and Appelman, 1971). The extent of skin involved was much greater than our case, but the histologic abnormalities reported appear to be quite similar. It would be of interest to see if our patient develops progressive lesions thus adding another facet to the spectrum of multifocal fibrosclerosis. Some family studies (Comings *et al.*, 1967; Phills *et al.*, 1973) have suggested a genetic predisposition to the development of retroperitoneal fibrosis and multifocal fibrosclerosis and the possible familial involvement is another interesting aspect of our case.

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(Accepted 27 October 1982)