Renal involvement in Gaucher’s disease

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Summary
A patient with chronic Gaucher’s disease is described who developed glomerulopathy 24 years after splenectomy terminating in renal failure. The pathological changes of this very rare complication of Gaucher’s disease are described. The few similar cases reported in the literature are reviewed and the possible pathogenetic pathways discussed.

Introduction
A case of extensive visceral involvement by Gaucher’s cells (GCs) in an adult with an unusual renal disease is presented.

Case report
A 51-year-old Ashkenazi woman with a 12-year history of hypertension was admitted to the Meir Hospital in March 1975 because of paroxysmal atrial fibrillation. At the age of 29 years splenectomy had been performed at the Hadassah Hospital in Jerusalem because of Gaucher’s disease.

Chest X-rays showed an enlarged heart. Following appropriate treatment, atrial fibrillation reverted to sinus rhythm. Laboratory findings were: Hb 12-2 g/dl, platelets 82 \times 10^9/l, total serum protein, albumin, urea, serum creatinine, cholesterol and urinalysis were normal. In December 1977 an electrocardiogram showed slow atrial fibrillation with signs of left ventricular hypertrophy. For the first time proteinuria of 1-3 g/l was found.

In October 1979 she entered the hospital because of pitting oedema of the lower limbs and vulva with erysipelas of the right leg. She also complained of severe general pruritus. A non-tender liver was palpable 7 cm below the costal margin. Abnormal laboratory values included: Hb 10-7 g/dl, MCV 118 fl, reticulocytes 13-2%, normoblasts 20-40/100

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WBC, platelets 40 \times 10^9/l, haptoglobin below 0-25 g/l, folic acid above 16 μg/l, vitamin B_{12} above 2 mg/l, total bilirubin 0-05 mmol/l (25 direct and 25 indirect), alkaline phosphatase 580 i.u./l, serum total protein 55 g/l, albumin, 25 g/l, serum electro-phoresis was normal. Blood urea was 733 mmol/l, serum creatinine 66 μmol/l and urinalysis showed 4-5 g/l proteinuria without sediment. The erysipelas responded to ampicillin.

A month later, she was readmitted for the last time, with progressive dyspnoea, marked peripheral oedema, ascites and severe pruritus. She gradually deteriorated, developing renal failure with serum urea up to 2282 mmol/l, serum creatinine 204 μmol/l, serum phosphorus 2-5 mmol/l and creatinine clearance 12 ml/min. Total protein was 55 g/l with 18 g/l albumin. Hb was 8-7 g/dl, reticulocytes 14% and haptoglobin below 0-25 g/l. There was marked macrocytosis (MCV 125 fl) with many sideroblasts and Gaucher’s cells in a bone marrow smear. The latex test was negative and C3 normal. L.E. cells and ANF were not found. Bilirubin was 171 μmol/l mostly direct, alkaline phosphatase 660 i.u./l. SGOT and SGPT were within normal limits. X-rays showed a right upper lobe infiltrate of the lungs, fracture of the neck of the left humerus and the Erlenmeyer flask appearance of the lower femora.

On the tenth day tachypnoea, acidosis and marked hypertension developed. She died of a cardio-respiratory arrest.

Post-mortem findings
The heart (Fig. 1) weighed 450 g and showed massive and diffuse infiltration by GCs mainly in the left ventricle, accompanied by severe interstitial fibrosis.

The kidneys (Fig. 2) weighed 180 g each. GCs were seen in many glomeruli, inside the capillary lumen or in a centrolobular position. Many foci of
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GCs were present in the interstitium of the cortex. Glomeruli without evidence of GCs showed hyalinization and fibrosis in a lobular fashion. There was diffuse interstitial fibrosis with atrophy of tubules.

Electron microscopy of a glomerulus (Fig. 3) showed tubular ‘Gaucher bodies’ in the cytoplasm of mesangial and endothelial cells. Mesangial cells were proliferated. Small electron-dense deposits were seen in endothelial position and in mesangial matrix. The basement membrane was convoluted and the visceral epithelial cells showed focal fused foot-processes.

Infiltration by GCs was seen in the liver, bone marrow, alveolar walls of the lungs, in the pancreas, in the lamina propria of the stomach and the cortex of adrenals, always accompanied by interstitial fibrosis. No GCs were seen in the many lymph nodes examined.

Discussion

Pathological changes in Gaucher’s disease are the result of abnormal accumulation, due to enzyme deficiency, of glucocerebroside (ceramide-glucose) which is a normal intermediate in the degradation of membrane compounds (Peters, Lee and Glew, 1977). Glucocerebroside from leucocytes, considered the most important source of accumulation in Gaucher’s patients, involves the reticulo-endothelial system and not the parenchymal cells. Gaucher’s cells are transformed macrophages and monocytes with phagocytic activity (Djaldetti, Fishman and Bessler, 1979). Certain organs (spleen, liver, bone marrow) are always involved and others, such as heart and kidney, very rarely (Smith et al., 1978).

Even more unusual are clinical manifestations of organ dysfunction directly related to massive GC infiltration such as appeared in the present case. Cardiomegaly and chronic heart failure could be explained not only by hypertension but also by GCs present throughout the cardiac muscle.

This case is also remarkable in its renal manifestations. Twenty-four years after the diagnosis of Gaucher’s disease and splenectomy, proteinuria appeared, followed 2 years later by nephrotic syndrome which progressed rapidly to chronic renal failure.

Only 8 cases of renal involvement in Gaucher’s disease have been reported in the English literature.
and have been reviewed by Chandler, Nurse and Pirani (1979). All patients except one had a splenectomy performed a few years previously. Only 3 had clinical renal disease (Smith et al., 1978; Ross, 1969; de Brito et al., 1973), while the others were incidental findings at post-mortem (Horsley, Baker and Apperly, 1935; Reich, Siete and Kessler, 1951; Chang-Lo, Yam and Rubenstone, 1967; Eulderink and Cleton, 1970). Only the patient of Chandler et al. (1979) had massive GC involvement of heart and lungs with organ dysfunction, in addition to the usual bone marrow and liver infiltration. Whenever clinical renal disease was present, there were glomerular lesions. They consisted of lobular enlargement of the tufts by GC infiltration occluding the capillaries, mesangial cell or matrix proliferation with interposition (de Brito et al., 1973; Chandler et al., 1979). Basement membranes appeared focally thickened and reduplicated. Many of the glomeruli were partly or completely sclerosed. Similar findings were observed in this present case. Immunofluorescent studies were reported in only 2 cases. They were negative in the de Brito et al. case (1973). The presence of IgM and IgA within capillary loops without IgG were noted by Smith et al. (1978). No immunofluorescent study was performed in the present case. On electron microscopy mesangial and endothelial cells were enlarged by typical Gaucher's bodies forming what appeared as Gaucher's cells (Pennelli, Scaravilli and Zacchelo, 1969). Similar structures were seen extracellularly within mesangial matrix but none in the epithelial cells. In addition, as in the present case, small mesangial, subendothelial or intramembranous electron-dense deposits were seen (de Brito et al., 1973; Chandler et al., 1979). The authors suggested that the Gaucher's cells in the kidney are not circulating GC (very uncommonly found in peripheral blood), but locally transformed mesangial and perhaps endothelial cells in glomeruli and interstitial capillaries. All these cells have phagocytic properties (Peters et al., 1977). A continuous load of cerebrosides and lack of cerebrosidase enzyme would transform all cells of reticulo-endothelial origin into typical Gaucher's cells. It was found that splenectomy induces an abrupt rise in plasma glucocerebrosides with increased load on the reticulo-endothelial system (Matoth et al., 1974).

However, renal involvement was not found in a higher percentage of Gaucher cases after splenectomy than it was in non-splenectomized patients, in contrast to increased hepatic and bone involvement (Matoth and Fried, 1965). This is perhaps due to a different genotype or to a more severe type of Gaucher's disease necessitating early splenectomy (Chandler et al., 1979).

A history of previous episodes of acute post-infection glomerulonephritis, causing mesangial abnormalities, could have facilitated accumulation of glucocerebrosides in the glomeruli.
Association of Gaucher's disease with immunoglobulin abnormalities has been well documented, but the underlying cause is unclear (Pratt, Eschen and Kochwas, 1968).

Gaucher's disease in some rare instances and particularly several years after splenectomy can be the cause of a glomerulopathy. Its aetiology could be local deposit of glucocerebroside and/or an immunological reaction.

References

CHANDLER, P.N., NURSE, H.M. & PIRANI, C.L. (1979) Renal involvement in adult Gaucher's disease after splenectomy. Archives of Pathology and Laboratory Medicine, 103, 440.


REICH, C., SIEDE, M. & KESSLER, B.J. (1951) Gaucher's disease: a review and discussion of 20 cases. Medicine, 30, 1.


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doi: 10.1136/pgmj.57.668.398

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