RENAL VEIN THROMBOSIS WITH NEPHROTIC SYNDROME AND RENAL FAILURE

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Acute thrombosis of renal veins with renal infarction was first described by Rayer (1837-41). It may be either "primary" or, more commonly, a complication of dehydration, and is seen in infants. It presents as acute renal failure with anuria or oliguria, haematuria, and renal enlargement; it is usually rapidly fatal (Barenberg *et al.*, 1941).

A subacute or chronic thrombosis of the renal veins resulting clinically in nephrotic syndrome is a less common condition. Shattock (1913) described a case in which oedema of the legs and abdomen occurred in a 24-year-old medical student after he had run in a 120-yards race, during the whole of which he held his breath. Albuminuria persisted until death 25 years later. At necropsy the inferior vena cava was found to be converted into a flat impervious ribbon extending from the point of entry of the hepatic veins to below the renal veins. Both renal veins were occluded at their point of entry into the inferior vena cava. Derow *et al.* (1939) described a case of inferior vena caval, portal, and renal thrombosis in a 15-year-old boy who had the features of a nephrotic syndrome without renal failure and who died after six months' observation following an attack of acute gastro-enteritis. Fishberg (1939) described the case of a patient with migrating phlebitis who subsequently developed a nephrotic syndrome. At post-mortem examination canalization of thrombi of the inferior vena cava and renal veins was found. More recently Blainey *et al.* (1954) described three cases, in one of which thrombosis of the inferior vena cava and renal veins had resulted in typical nephrotic syndrome. This patient had a raised blood urea and died from pneumonia after one year's observation. Milne (1954) reports a case of intrarenal vein thrombosis in a patient with nephrotic syndrome who died following pneumococcal peritonitis.

A case is described below in which the nephrotic syndrome, with later progressive renal failure, was apparently due to a primary thrombosis of renal branch veins within the substance of the kidneys unaccompanied by thrombosis or occlusion of the main renal veins or the inferior vena cava.

Case History

The patient, a retired Army officer aged 57, leading an extremely active life, consulted his doctor on June 12, 1954, as he had noticed a sudden swelling of his legs and face. He had been playing tennis frequently, and the last game had been on the day before symptoms appeared. He had had no previous illnesses of note, but had had a bullet wound of his left loin in 1917. He was admitted to the Cambridge Military Hospital on June 20, and was found to have severe pitting oedema of the legs and oedema of the face, whilst his urine was loaded with protein. The blood pressure was 150/90 mm. Hg and there were no other abnormal signs.

Investigations.—Urine: protein, 20 g. per litre (albumin 62%, globulin 38%); the deposit showed a moderate num-

ber of granular casts and red cells with a few epithelial cells. Serum proteins: total 4.1 g. per 100 ml. (albumin 30.2%, globulin 69.8%—alpha one 3.1%, alpha two 31.2%, beta 11.3%, gamma 24.2%). Apart from a somewhat higher gamma globulin the electrophoretic pattern was similar to that quoted by Squire (1953) as being associated with nephrosis. Oedema fluid protein, total 0.6 g. per 100 ml. (albumin 33.6%, globulin 66.4%). Blood urea, 30 mg. per 100 ml. Blood cholesterol, 400 mg. per 100 ml. X-ray film of chest and E.C.G.: N.A.D.

For the first few days after admission he was given a low-protein diet with 30 oz. (852 ml.) of fluid intake daily. On this regime his urine output fell rapidly from over 50 oz. (1,420 ml.) to 10 oz. (284 ml.) a day, and his plasma albumin dropped to 0.7 g. per 100 ml. He was then given a high-protein diet with restriction of sodium to less than 0.5 g. daily, his fluid intake being maintained at 30 oz. (852 ml.) daily. This was followed by a continued diuresis reaching 90 oz. (2,556 ml.) a day one month later. It was necessary to raise the fluid intake to 40 oz. (1,136 ml.) and then to 50 oz. (1,420 ml.) daily, as he suffered from thirst. The plasma albumin climbed gradually to 1.8 g. per 100 ml. and he lost a considerable amount of his oedema. From July 29 his high urinary output began to drop slowly. On August 5 his output was 60 oz. (1,704 ml.) a day and his intake 50 oz. (1,420 ml.), but his blood urea, which had previously shown only a slight elevation, rose to 120 mg. per 100 ml. His blood cholesterol at this time was 550 mg. per 100 ml.; serum sodium, 140 mEq/l., and serum chloride 90 mEq/l. From then onwards his urinary output fell slowly but steadily and the blood urea rose progressively. Towards the end of August he became drowsy and developed intractable hiccups. He sank gradually into a uraemic state and died on September 5.

During all this time he had continued to pass large quantities of protein in his urine (20-45 g. per litre). Red cells and granular casts were continually present. Towards the end of his illness pus cells appeared in the urine in increasing numbers. No organisms were seen in the Gram films, and urine culture was sterile. Blood urea readings were: June 25, 30 mg. per 100 ml.; July 1, 46 mg.; July 11, 50 mg.; July 24, 59 mg.; August 7, 120 mg.; August 12, 160 mg.; August 19, 186 mg.; August 26, 200 mg.; August 31, 215 mg.

The blood pressure remained approximately the same throughout the illness.

Necropsy Findings.—The kidneys were pale and much enlarged (right 250 g., left 235 g.) (Fig. 1). Numerous stellate veins could be seen through the capsule. The capsules stripped with ease, leaving a smooth, pale surface with reddish mottling. The pelves, ureters, and bladder showed no lesions. The renal veins and inferior vena cava contained no thrombus and were of normal appearance. However, there was thrombosis of several of the major renal branch veins and multiple thromboses of the arcuate veins. Apart from the latter findings the macroscopical appearance of the kidney suggested subacute glomerulonephritis (Ellis Type II).

FIG. 1.—Hemisection of the right kidney.

Microscopical Examination of Kidneys.—The glomeruli were normal and the basement membrane showed no thickening or other lesions. Many of the convoluted tubules were dilated and the lumina contained large numbers of polymorphs, debris, and eosinophilic fluid. Gram's stain failed to demonstrate the presence of organisms. The dilated tubules were lined with atrophic epithelium. No regeneration of epithelium was present, and the appearances suggested a chronic tubular atrophy (Fig. 2). The collecting tubules were normal. The interstitial tissue was fibrotic and oedematous, there being a patchy infiltration by lymphocytes and polymorphs. Examination of the pelvis of the kidney revealed the presence of multiple intrarenal branch vein thrombi. Many of the thrombi showed organization and recanalization (Fig. 3).

FIG. 2.—Dilated convoluted tubules containing either large quantities of pus or eosinophilic fluid. Note increase of interstitial tissue. (Periodic acid Schiff.)

FIG. 3.—Branch of the renal vein within pelvis of kidney to show thrombus undergoing organization and recanalization. (H. and E.)

Discussion

This case differs from previously reported cases in that the nephrotic syndrome occurred in an adult, associated with renal vein thrombosis and occlusion which was wholly within the substance of the kidney. Furthermore, there is discrepancy between the findings of apparently typical "large white kidney" and the histological features. Chronic glomerulonephritis, amyloid disease, pyelonephritis, and eclampsia have been reported as having been complicated by multiple thrombi in the main and medium-sized branches of the renal veins resulting in acute terminal uraemia (Vilk, 1940). Bilateral renal vein thrombosis in a youth of 18 without involvement of the inferior vena cava was reported by Miller *et al.* (1954) and was associated with polyarteritis nodosa. However, in the case which we have described no associated disease was found. The case of thrombosis of main renal vein tributaries reported by Milne (1954) was in a boy of 7 who had a typical nephrotic syndrome. The thrombi were undergoing organization, and it was concluded that these could have dated from the onset of the disease. The histology of the kidney was not discussed.

In children renal vein thrombosis may be secondary to dehydration or it may be "primary" (Barenberg *et al.*, 1941; Sandblom, 1948; Zuelzer *et al.*, 1951). Thrombosis usually begins in the arcuate and interlobular veins, although even smaller veins may be involved (Morison, 1945). Moreover, in children, when the inferior vena cava is thrombosed there is evidence that the thrombus starts in the small veins of the kidney and extends from there into the renal vein and inferior vena cava (Kobernick *et al.*, 1951). It is common in these cases to find associated thrombosis in other vessels, suggesting that the thrombosis may be the expression of a systemic factor whether it be haemoconcentration, blood slowing, damage to the endothelial wall, or other cause (Zuelzer *et al.*, 1951; Becker, 1954). In our case thrombosis involving other organs was not found. In view of the organization and recanalization of many of the thrombi and the rapid course of illness it is likely that multiple renal branch vein thrombosis was present at the onset of the illness and did not constitute a terminal event. It is suggested that the high pressure in the tributaries of the renal vein produced by the presence of thrombi resulted in a heavy proteinuria and thus, ultimately, to a fully developed nephrotic syndrome. It has been shown experimentally in dogs that gradual progressive obstruction of the renal vein after unilateral nephrectomy results in persistent albuminuria with apparently normal renal function (Rowntree *et al.*, 1913).

Histological examination did not reveal glomerular lesions, and it must be assumed that protein escaped from the glomeruli in the absence of obvious structural changes. Corcoran (1952) draws attention to the fact that in a normal kidney up to 10 mg. of protein a minute may escape from the glomeruli: under normal circumstances this is all absorbed by the proximal tubules. In this case the presence of gross proteinuria is explained by the increased escape of protein from the glomeruli accompanied by considerable failure of tubular reabsorption due to the presence of chronic tubular atrophy (Fig. 2).

It is interesting that Shattock's case followed a period of acute exertion, as did this case. It is known that such exercise may cause proteinuria or even haematuria, and that the mechanism appears to be decreased renal blood flow accompanied by slowing of the renal circulation (Covian and Rehberg, 1937; Barclay *et al.*, 1947). It would seem possible that in the present case the thrombus occurred or extended during a period of severe exercise (not necessarily the last game of tennis), and that this was the precipitating cause.

Summary

A case of intrarenal branch vein thrombosis associated with nephrotic syndrome is described. The possibility that the nephrotic syndrome was secondary to the multiple thrombosis is discussed.

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