Renal Papillary Necrosis in Sickle-cell Haemoglobinopathy

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Abel and Brown (1948) first drew attention to profuse haematuria in sickle-cell anaemia. Subsequent reports have confirmed that this association is more than fortuitous (Harrison and Harrison, 1952 ; Chapman *et al.*, 1955 ; Sharpe *et al.*, 1959). Haematuria is also known to occur in sickle-cell trait, sickle-cell haemoglobin C disease, sickle-cell thalassaemia, and a variety of combinations of haemoglobin S with other abnormal haemoglobins. The present report of four cases of haematuria in sickle-cell haemoglobinopathies is prompted for two reasons. Firstly, detection of blood in the urine of young adults in an environment endemic for schistosomiasis need not always indicate the presence of the infection. Of more practical importance is the surgical diagnostic problem sometimes posed by gross haematuria simulating renal neoplasm. Awareness of the possibility that this symptom may exist in sickle-cell haemoglobinopathy makes careful appraisal necessary, to avoid the inadvertent sacrifice of an apparently normal-functioning kidney.

Case 1

A 30-year-old female trader had had persistent haematuria for five weeks, at first mild, but later gross and alarming. There were no associated urinary findings. Her blood pressure (B.P.) was 120/85 mm. Hg. Both kidneys were easily felt. Her blood group was O-positive, sickling was present, and her genotype AS. The clotting-time (Biggs and Macfarlane, 1957) was 8 minutes and bleeding-time (Duke, 1910) 3 minutes. Haemoglobin (Hb) 7.3 g./100 ml. ; packed-cell volume (P.C.V.) 22% ; mean corpuscular haemoglobin concentration (M.C.H.C.) 33% ; white blood count (W.B.C.) 6,600/cu. mm. ; platelets 138,000/cu. mm. Her blood urea, electrolytes, and liver-function tests were all normal. Total serum proteins were 7.8 g./100 ml., and on electrophoresis showed a diffuse increase in the globulin fraction. Urinary specific gravity (S.G.) was 1008 and the specimen contained many red cells. At cystoscopy bleeding was observed from the left ureteric orifice. Intravenous pyelography (I.V.P.) showed good function bilaterally, but extending from three calices on the left was some contrast in small medullary cavities (Fig. 1). Her haematuria cleared gradually within a fortnight and she has since remained well and active.

Case 2

A tailor aged 47 was subject to recurrent episodes of painless haematuria for two months. Examination revealed severe anaemia (Hb 3.0 g./100 ml.). His urine contained a trace of albumin and its S.G. was 1006 ; red blood cells were detected at microscopy, but there were no casts. Blood group was O-positive, sickling was present, and his genotype AS. His blood urea was 16 mg./100 ml. Cystoscopy showed blood spurting from the left ureteric orifice. Left ureteric catheterization was followed by a retrograde pyelogram, after which a nephrectomy was performed. Naked-eye appearance of the kidney showed marked congestion of the vessels close to the papillae, with softening of the central and apical portions of the pyramid ; there were blood clots in the renal pelvis. Microscopy did not reveal any abnormalities in either glomerular or tubular morphology. He remained well for five years, but has lately developed proteinuria and hypertension. The latter event has been complicated by congestive heart failure, but this has responded well to digoxin, thiazides, and reserpine. At the time of writing he remained practically symptom-free.

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Case 3

A 37-year-old housewife gave a three-year history of recurrent attacks of haematuria, each episode lasting a few days. She had been so impressed by the transient nature of her symptom that she had not thought it necessary to seek medical attention. Indeed, all her previous admissions into hospital were for obstetric reasons, and during her last admission her ankles were noticed to be swollen, she had proteinuria and microscopic haematuria, and her B.P. was 140/100 mm. Hg. She was eventually delivered of a full-term live foetus, but at postnatal attendances these features persisted. Her red cells showed sickling, genotype AS. Blood-clotting and bleeding times were normal. Hb 11 g./100 ml. ; P.C.V. 33% ; M.C.H.C. 33% ; W.B.C. 3,500/cu. mm. Her blood urea was 23 mg./100 ml. and total serum proteins were 8.0 g./100 ml. Urine: S.G. 1010 ; midstream sample contained a few red cells but numerous white cells. Culture of this yielded a mixed growth of coliform organisms, and a week's course of nitrofurantoin cleared her urinary infection. I.V.P. showed evidence of cavitation involving the central and apical parts of the right upper calicine configuration extending into the medulla.

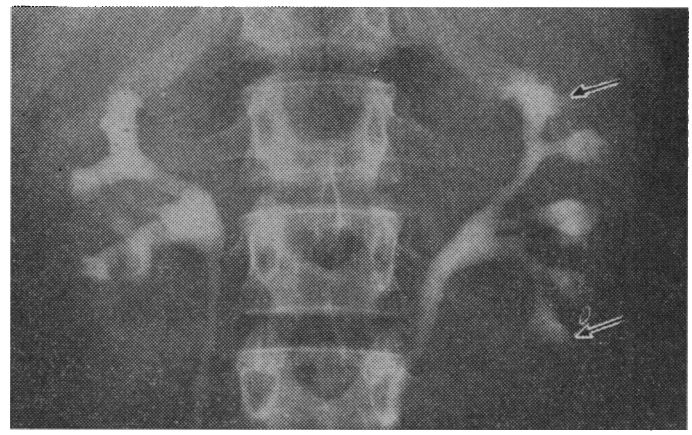

FIG. 1.—Case 1. Intravenous pyelogram (sickle-cell trait). On the left side dye extends from calices into small medullary cavities.

Case 4

A steward aged 37 had haematuria for two days. This was associated with frequency of micturition (three times at night), but there was no dysuria. Examination showed a well-built man with minimal pallor of his mucous membrane and tenderness in the right loin. B.P. 125/80 mm. Hg. Urine S.G. 1010, and midstream specimen contained many red cells and a trace of protein. His blood group was O-negative and genotype SS. I.V.P. showed changes in the right upper group of calices consistent with the medullary form of papillary necrosis (Fig. 2). Within a week his haematuria cleared completely and he has remained well for five years.

Discussion

Ischaemic infarction of the medullary pyramids has been known to occur since Friedreich's (1877) original description in a man with hydronephrosis due to an enlarged prostate. It was not until many decades afterwards (Günther, 1937) that its association with diabetes mellitus was recognized, becoming familiar to latter-day pathologists as necrotizing papillitis. In

the past decade there have been widespread reports, notably from Switzerland and Scandinavia, of a great increase in the numbers of cases of renal papillary necrosis after excessive use of phenacetin compounds (Lindeneg *et al.*, 1959; Harvald, 1963).

It is estimated that about 4% of those individuals possessing the S gene suffer from haematuria at some time during their

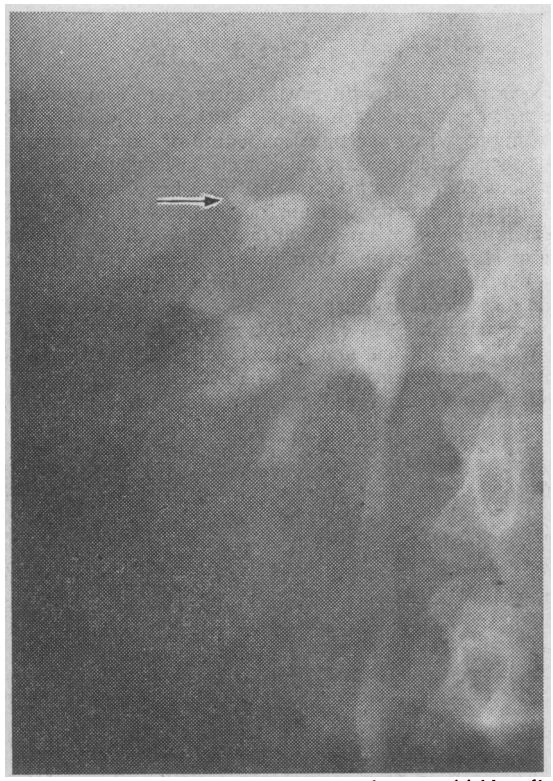

FIG. 2.—Case 4. Intravenous pyelogram (sickle-cell anaemia) On the right side the upper group of calices show changes consistent with papillary necrosis.

lives (Allen, 1964). Harrow *et al.* (1963) described renal papillary necrosis in five patients with sickle-cell trait. The true incidence of renal papillary necrosis in each of the various types of haemoglobinopathy is unknown. The scant reference in the literature to haematuria in patients homozygous for the S gene seems paradoxical, since the disorder is thought to be brought about by the presence of S haemoglobin. However, the relative frequency of this symptom in the trait may be more apparent than real. Firstly, the trait is far more common in the general population than the anaemia, and, secondly, the presence of haematuria as a lone symptom in the most innocuous of the genotypes naturally attracts more attention. The incidence of haematuria in haemoglobin SC disease is somewhere between these two extremes (River *et al.*, 1961).

In more than half of all cases of papillary necrosis so far reported diagnosis was made during life by histological examination of papillae voided in the urine. Examination of renal biopsy specimens has not been rewarding. In three of the four cases reported above radiological investigation involving the use of contrast medium in I.V.P. revealed definitive ring changes in the renal papillae, formation of cavities in the pyramids or at the papillae, or an outline of concretions formed around necrotic fragments.

The pathogenesis of renal papillary necrosis in these states remains obscure. Its early association with diabetes and chronic obstructive renal disease suggested antecedent pyelonephritis. Support for this view was strengthened by the observation that phenacetin itself would cause an interstitial nephritis. The blood supply to the renal papillae derives from two sources: the vasa recta from the juxtamedullary region, and branches from the plexus of spiral vessels in the calix. Baker (1959) has shown how vulnerable these vessels are in diabetic arterial disease, infection, or back pressure on the calices. Whether primary vascular spasm occurs, as suggested by Kimmelstiel (1948), to account for ischaemic infarcts in sickle-cell crises is unknown. Perillie and Epstein (1961) found that sickling occurred in SS and AS subjects if the red blood cells were exposed to a hypertonic medium. It is well known that the counter-current system responsible for the concentration of urine produces a graded increase in osmolarity and lowering of oxygen tension from the base of the medulla to the tips of the papillae. It thus seems likely that increased viscosity and stasis would more readily affect the vasa recta supplying the papillary tips, leading to local ischaemia and tissue destruction.

Summary

Four cases of haematuria of varying severity associated with a sickling tendency are reported. Of these, three had sickle-cell trait and one sickle-cell anaemia. In three patients the radiological changes observed in the kidneys were those of renal papillary necrosis; in the remaining case the macroscopic appearance of the kidney from which the bleeding arose was suggestive of this lesion.

The conditions associated with renal papillary necrosis are reviewed. Hyperosmolarity in the region of the papillary tips is thought to predispose to sickling of red cells in neighbouring small vessels with subsequent ischaemic necrosis.

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