*Quarterly Journal of Medicine, New Series, XLVI, No. 182, pp. 151–62, April 1977*

# Addison's Disease with Renal Microangiopathy and Renal Failure (a New Syndrome)

Y. SACHDEV, A. R. MORLEY, R. WILKINSON, AND R. HALL

*From the Departments of Medicine and Pathology, Royal Victoria Infirmary, Newcastle upon Tyne*

Accepted 29 April 1976

SUMMARY

**A syndrome comprising Addison's disease, renal microangiopathy and renal failure is described in two patients. The renal lesions manifested despite corticosteroid replacement therapy and were characterized by glomerular damage and thrombo-microangiopathic changes in afferent arterioles and intralobular arteries. Both patients died as a result of their renal disease.**



## INTRODUCTION

Addison's original description (1855) of primary adrenocortical failure consisted of 11 cases with either idiopathic adrenal failure, tuberculosis of the adrenal gland or metastatic tumour in the adrenals. Idiopathic adrenal failure and tuberculous adrenal infection are still the two main causes of primary adrenocortical insufficiency. A diagnosis of idiopathic (autoimmune) Addison's disease is usually made by the exclusion of other known causes of adrenal destruction, by the detection of antibodies to adrenocortical tissue (Irvine, Stewart, and Scarth, 1967) and occasionally by measurement of urinary epinephrine output in response to 2-deoxy-D-glucose (Wegienka, Grasso, and Forsham, 1966). The histological appearance of the adrenal glands is also characteristic.

It is known that patients with autoimmune Addison's disease are remarkably prone to other autoimmune disorders of the organ specific type (Goudie, Anderson, Gray, and Whyte, 1966; Blizzard, Chee, and Davis, 1967; Irvine *et al.*, 1967; Frey, Vogt, and Nerup, 1973). The association of autoimmune thyroid disease (Schmidt, 1926; Brenner, 1928; Wells, 1930; Sloper, 1953; Carpenter, Solomon, Silverberg, Bledsoe, Northcott, Klinenberg, Bennett, and Harvey, 1964; Gharib, Hodgson, Gastineu, Scholz, and Smith, 1972) premature gonadal failure (Turkington and Lebovitz, 1967; Irvine, Chan, Scarth, Kolb, Hartog, Bayliss, and Drury, 1968); pernicious anaemia and subclinical atrophic gastritis (Meecham and Jones, 1967; Turkington and Lebovitz, 1967; Irvine and Barnes, 1975); diabetes mellitus (Ogle, 1886; Faber and Grønbaek, 1956; Beeven, Nelson, Renold, and Thorn, 1959;

Wehrmacher, 1961; Solomon, Carpenter, Bennett, and Harvey, 1965; Tzagournis and Hamwi, 1967; Irvine, 1968; Irvine and Barnes, 1972; and Frey *et al.*, 1973) and idiopathic hypoparathyroidism (Irvine and Barnes, 1972) with autoimmune Addison's disease is well documented. The combination of autoimmune Addison's disease with mucocutaneous candidiasis (Kenny and Holliday, 1964; Block, Pachman, Windhorst, and Goldfine, 1971); systemic lupus erythematosus (SLE) (Larson, 1961; Eichner, Schambelan, and Biglieri, 1973) and diffuse cerebral sclerosis (Sharr, 1975) has also been described. Irvine and Barnes (1972) reported cases of focal glomerulonephritis and of renal tubular abnormality in association with Addison's disease. The association of idiopathic Addison's disease with renal microangiopathy and renal failure has not been reported so far as we are aware. Two unrelated patients with Addison's disease who later developed renal microangiopathy and renal failure are described.

*Case 1*

A 27-year-old woman was admitted to hospital in a collapsed state after an attack of acute gastroenteritis. She was pale and dehydrated yet had increased pigmentation of the oral mucosa and axillae. Her plasma 11-hydroxycorticosteroid (11-OHCs) level at 9 a.m. was 90 nmol/l and this did not change after intramuscular (IM) synacthen (250 $\mu$g tetracosactrin). There was an impaired adrenocortical response to insulin-induced hypoglycaemia (Table 1). Plasma sodium was 123 mmol/l; potassium 6·4 mmol/l; and chloride 90 mmol/l. A diagnosis of Addison's disease was made and she was treated with intravenous saline and hydrocortisone. The following tests showed no abnormalities: tuberculin test, sputum culture for acid fast

TABLE 1. *Hypothalamic pituitary adrenal axis (at the time of first admission)*

| Plasma 11-hydroxycorticosteroid (11-OHCs) (nmol/l) | | | |
|---|---|---|---|
| Time | Normal range | *Case 1* | *Case 2* |
| 9 a.m. | 190 to 720 | 90 | 64 |

Synacthen stimulation test (intramuscular) (250 $\mu$g tetracosactrin):

| Time in minutes | Plasma 11-OHCs (nmol/l) *Case 1* | *Case 2* | Comments |
|---|---|---|---|
| 0 | 100 | 64 | Normal response is characterized by a maximum increment of more than 300 nmol/l and a maximum value greater than 550 nmol/l. |
| 30 | 102 | 65 | |
| 60 | 80 | 55 | |

Standard insulin tolerance test:

| Time in minutes | Blood glucose level (BGL mmol/l) *Case 1* | *Case 2* | Plasma 11-OHCs (nmol/l) *Case 1* | *Case 2* | Comments |
|---|---|---|---|---|---|
| 0 | 4·9 | 5·5 | 80 | 70 | Symptomatic hypoglycaemia at 30 minutes. No significant adrenocortical response to insulin induced hypoglycaemia. |
| 30 | 1·5 | 1·8 | 90 | 80 | |
| 60 | 3·2 | 3·4 | 86 | 75 | |
| 90 | 3·5 | 3·9 | 85 | 75 | |
| 120 | 4·0 | 4·5 | 90 | 70 | |

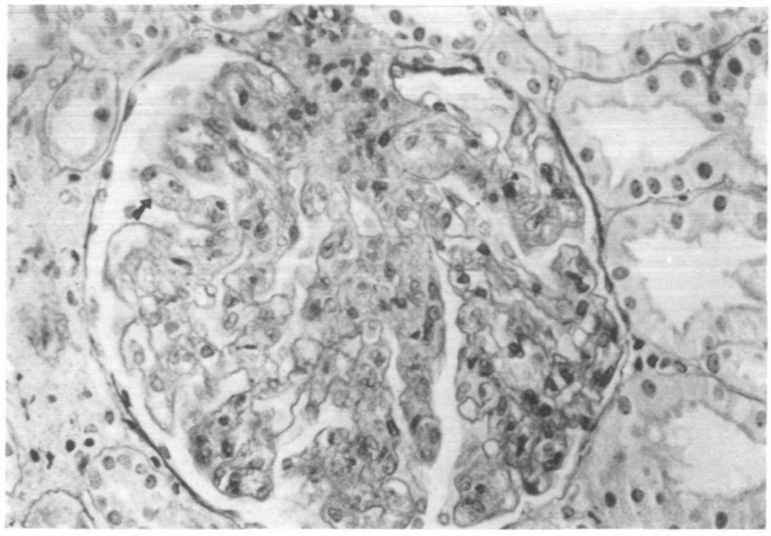

FIG. 1. *Case 1.* Glomerulus showing lobularity, mesangial increase and partial reduplication of basement membrane. Periodic acid Schiff ×256.

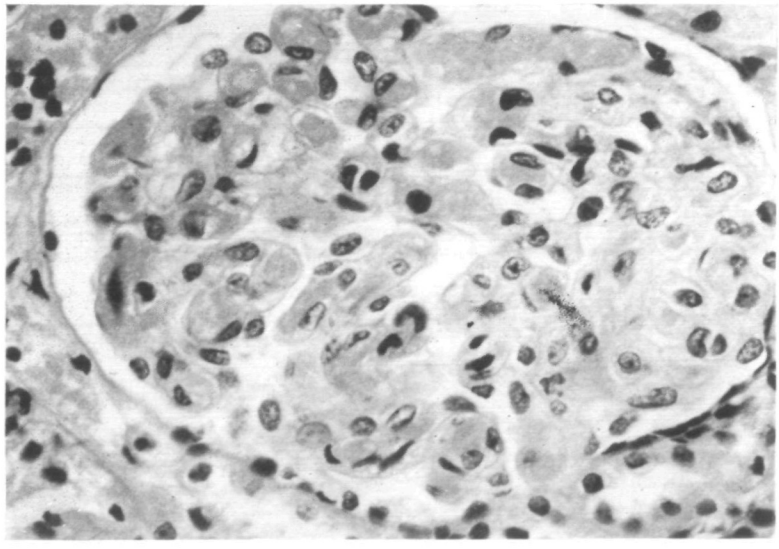

Fig. 2. *Case 1.* Glomerulus with all capillary loops occluded by fibrin-like material. Haematoxylin and Eosin ×383.

bacilli (AFB), LE cell phenomenon, antinuclear factor, chest and abdominal radiographs. Adrenal, ovarian, thyroid and gastric antibodies were not detected.

Her condition improved and she was discharged on replacement therapy with hydrocortisone and fludrocortisone. Five weeks later she presented with progressive lethargy, right sided pleuritic pain and was found to have a haemolytic anaemia with a positive Coomb's test. She improved with large doses of prednisolone (60 mg daily). Three weeks later, however, while still receiving high doses of prednisolone, she developed generalized oedema, albuminuria (1·5 g/24 hour) with granular and cellular casts. The blood urea was increased to 40 mmol/l and serum creatinine to

220 μmol/l. Renal biopsy showed glomerular enlargement with lobularity and occasional capsular adhesions (Fig. 1). Overall glomerular cellularity was increased with endothelial and mesangial cell hyperplasia and occasional neutrophils. The glomerular basement membrane was occasionally split. In a few glomeruli (Fig. 2), the capillary loops were blocked by hyaline eosinophilic material with the tinctorial characteristics of fibrin. There was focal tubular atrophy with dilatation of the proximal convoluted tubules and an occasional mitotic figure. Several afferent arterioles (Fig. 3) were blocked by hyaline material and endothelial cell proliferation. Immunofluorescent examination (Table 2) revealed widespread, almost linear deposition of fibrin within glomerular capillaries and occasional small segmental deposits of IgM. Tubular casts contained IgA and fibrin.

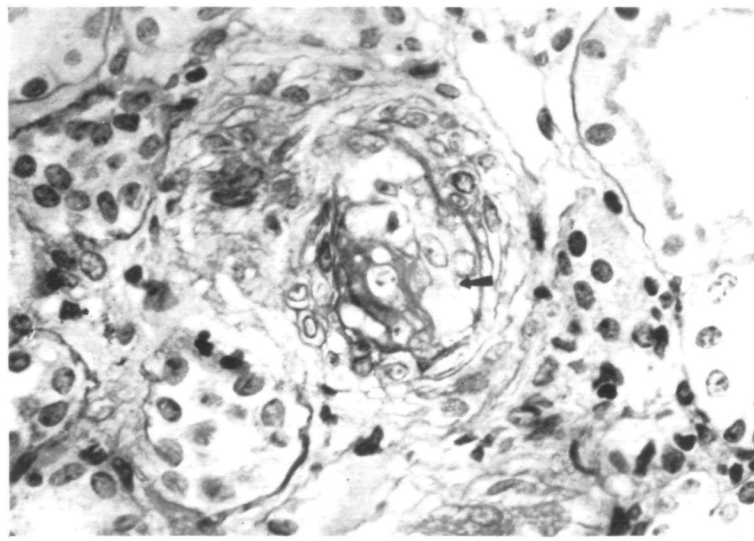

FIG. 3. *Case 1.* Small artery showing intimal proliferation and occlusion. Periodic acid Schiff ×383.

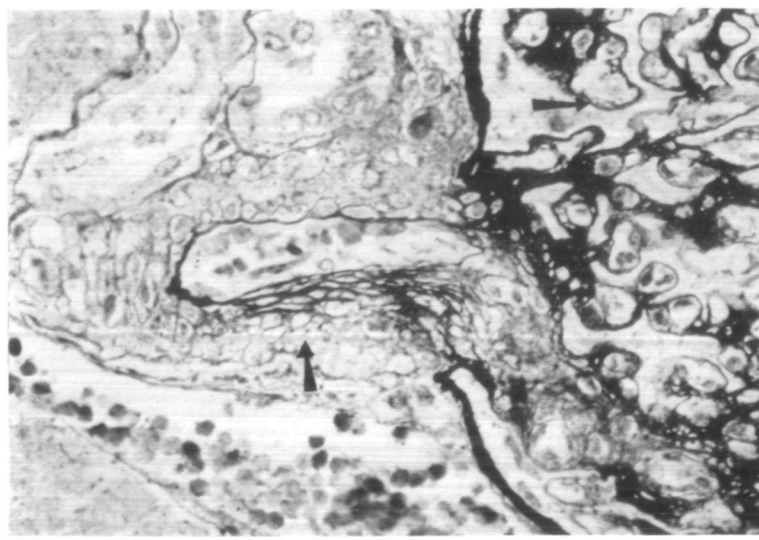

FIG. 4. *Case 1* (autopsy). Hyperplastic afferent arteriole, and partial reduplication of glomerular basement membrane. Periodic acid silver methenamine ×383.

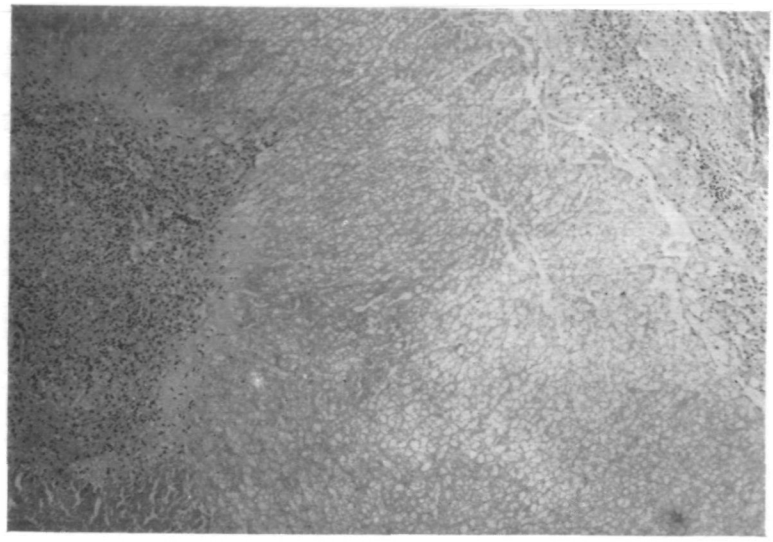

FIG. 5. *Case 1.* Right adrenal gland showing fibrinoid necrosis. Haematoxylin and Eosin ×40.

The patient was treated symptomatically and azathioprine 100 mg/day was added to the steroid therapy. She made a transient improvement but soon deteriorated and died six months later. Autopsy examination revealed normal shaped kidneys (70 g each) with moderate cortical atrophy. The glomeruli were enlarged and there was capillary loop thickening, patchy reduplication of the basement membrane and an increase in mesangial matrix. About 10 per cent of glomeruli showed the basement membrane wrinkling of obsolescence. A striking feature was the hyperplasia of afferent arterioles (Fig. 4). Several afferent arterioles were blocked by hyaline material and endothelial proliferation. The adrenal glands (Fig. 5) were small and hard showing coagulation necrosis of both cortex and medulla. Other organs were normal.

*Case 2*

A 47-year-old woman presented with drowsiness, lethargy and general debility. She was pale, febrile (38·5 °C) and had abnormal pigmentation of the mucous membranes and axillae. Plasma 11-OHCs was 64 nmol/l and did not rise in response to synacthen (Table 1). Serum sodium was 120 mmol/l; potassium 5·3 mmol/l and chloride 90 mmol/l. A diagnosis of Addison's disease was made and she was treated with hydrocortisone and fludrocortisone. Adrenal, ovarian, thyroid and gastric antibodies were not detected. There was no clinical, biochemical or radiological evidence of tuberculosis or other underlying cause for her adrenal failure. She remained well for two years after which she developed features of chronic renal failure with generalized oedema, anaemia (Hb 8 g/dl), raised blood urea (26 mmol/l) and serum creatinine (860 μmol/l). The LE cell test and Wasserman reaction (WR) were negative (WR had been positive 23 years previously remaining so for three years and had then become negative without therapy). The VDRL and antinuclear factor tests were weakly positive. Adrenal and other antibodies were not detected and the serum complement was normal. The platelet count was 160 000/mm$^3$, and the plasma fibrinogen 0·29 g/l (normal 0·15 to 0·4 g/l) and the fibrin degradation products 100 μg/ml (normal less than 10 μg/ml).

A renal biopsy showed dilated Bowman's capsules with hyaline eosinophilic material. Glomerular lobularity was increased. Many glomerular capillary loops

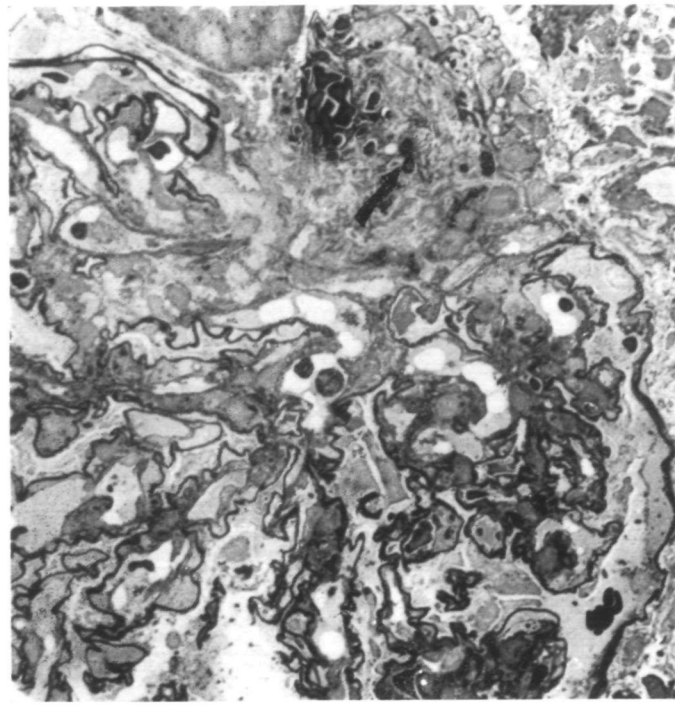

FIG. 6. *Case 2.* Increased mesangial matrix, wrinkled basement membrane, 'fibrinoid' necrosis of afferent arteriole with red cell extravasation. Periodic acid silver methenamine ×500.

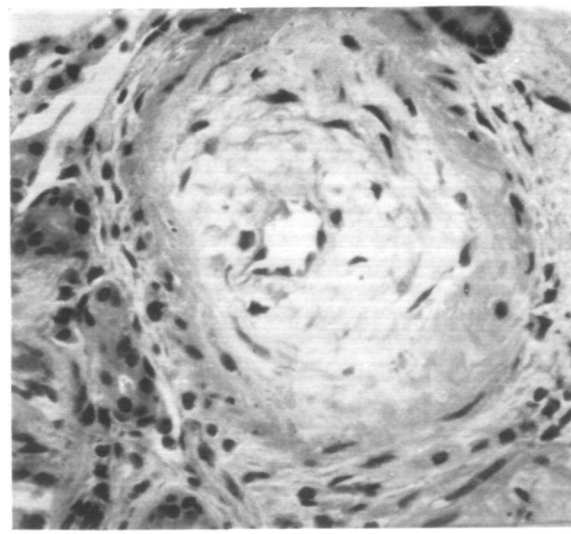

FIG. 7. *Case 2.* Interlobular artery narrowed by loose subintimal fibroblastic proliferation. Haematoxylin and Eosin ×308.

were narrowed and the basement membrane was wrinkled (Fig. 6). Occasional loops were completely thrombosed. Several afferent arterioles showed loose intimal proliferation and were blocked by fibrin. Twenty per cent of the glomeruli were entirely sclerosed. There was widespread tubular atrophy and dilatation. Many

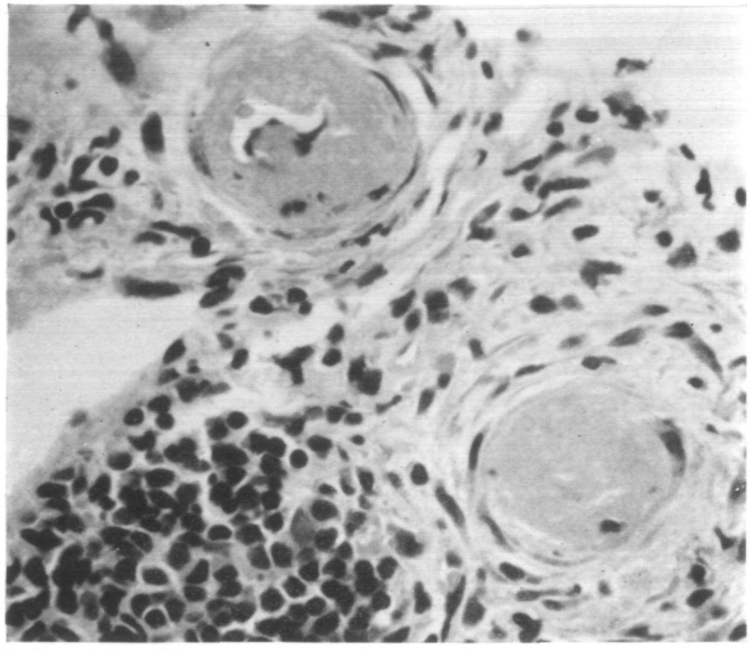

FIG. 8. *Case 2.* Arterioles containing fibrin thrombus. Haematoxylin and Eosin ×460.

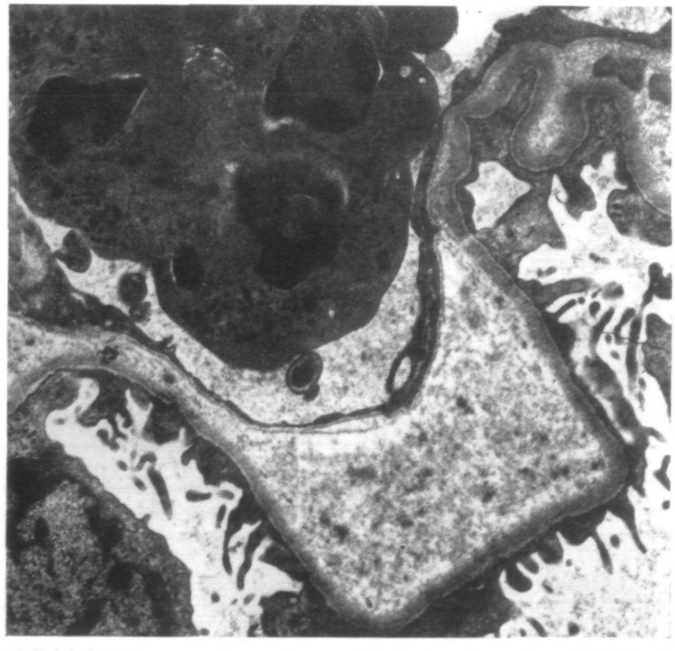

FIG. 9. *Case 2.* Wrinkled basement membrane with electron translucent thickening of lamina interna. Electron micrograph ×8,000.

tubules contained hyaline casts and a few red cell casts. The tubular epithelium was irregular and flattened and showed occasional mitotic figures. There was oedema of the interstitial tissue which was diffusely infiltrated by lymphocytes and plasma cells. The interlobar and intralobular arteries and afferent arterioles were equally

TABLE 2. *Summary of immunofluorescent findings*

| | | Glomerular deposits | | | | | Deposition in other renal tissues |
|---|---|---|---|---|---|---|---|
| | | IgA | IgG | IgM | βic/βia | Fibrin | |
| *Case 1* | Biopsy 19.9.73 | — | — | Segmental ++ | — | Generalized 'linear' ++ | Casts IgA ++ No vascular deposits |
| | P.M. 23.11.73 | Segmental + | — | Segmental + | — | Focal diffuse ++ | Casts IgA ++ Fibrin ++. No vascular deposits |
| *Case 2* | Biopsy 15.2.74 | — | — | — | — | — | Casts IgA +++ Arteries (media). Fibrin ++ |
| | P.M. 27.6.75 | — | — | Segmental ++ | — | Segmental ++ | Fibrin ? + in a few arterioles |

affected showing fibrinoid necrosis, thrombosis, intimal proliferation and obstruction (Figs 7 and 8). There was no evidence of vasculitis. Immunofluorescent examination showed some patchy deposition of fibrin and IgM in arteriolar and arterial walls, but no significant glomerular deposition of IgA, IgG, IgM or complement (Table 2). Electron microscopy (Fig. 9) confirmed wrinkling of the basement membrane and deposition of an electron-translucent material which contained irregular strands of electron-dense material between the endothelial cells and the basement membrane. The lumen contained occasional neutrophils. The basement membrane was of uniform thickness and there were no intramembranous or subepithelial deposits; the mesangial matrix was increased and the mesangial cell processes extended beneath the endothelial cells. The foot processes were extensively fused.

The patient was subjected to peritoneal dialysis because of resistant oedema with some symptomatic relief. Corticosteroid therapy was continued. She improved initially but a year later developed aortic regurgitation and after gradual deterioration in health she died of chronic renal failure six months later. Autopsy demonstrated small coarsely granular kidneys with atrophic cortices. The adrenal glands were small (total weight 4·5 g) hard and nodular showing coagulation necrosis. Fibrinous vegetations were present on the aortic, mitral and tricuspid valves and there was widespread pericarditis with fibrosis. The lungs were congested and a small area of consolidation was present in the left lower lobe. Apical and posterior pleural adhesions were present. Histological studies revealed necrosis of both adrenal glands with cholesterol crystals, haemosiderin, and spotty calcification. The kidneys were reduced in size (right 120 g, left 85 g) with a finely granular cortex. There was widespread glomerular atrophy with dilatation of Bowman's capsule in the subcapsular glomeruli. Many glomeruli were sclerosed and this was associated with narrowing of afferent arterioles by fibroblastic intimal proliferation. Similar narrowing of the arcuate arteries was seen but the lobular arteries were not involved.

## DISCUSSION

The clinical picture in both patients was characterized by adrenocortical insufficiency, progressive involvement of different systems, microangiopathy and renal failure. There was no evidence of tuberculosis or other known disorders which could have led to the adrenocortical failure which must, therefore, be classified as idiopathic. The adrenal glands showed coagulation necrosis and there was little lymphocytic infiltration. The picture is consistent with ischaemic necrosis of the adrenals although it was not possible to demonstrate direct evidence of vascular obstruction. Adrenal and other antibodies were absent (other than the previously positive WR and weakly positive ANF in *Case 2*). The common renal lesion was diffuse microangiopathy. The renal histological features seen in both patients were enlargement of some glomeruli with increased lobularity and deposits of hyaline eosinophilic material. There was patchy splitting of the basement membrane in one patient and both had a large number of obsolescent glomeruli. Renal arterioles and some of the intralobular arteries showed fibroblastic intimal proliferation, fibrinoid necrosis and thrombosis. Fibrin deposits in the afferent arterioles and glomerular capillaries suggested intravascular coagulation. There was no evidence of vasculitis nor of any deposition of immunoglobulins or complement. Thus immunologically-mediated glomerulonephritis appeared unlikely (de Wardener, 1973).

The other possible conditions with histological similarities are accelerated (malignant) hypertension, polyarteritis nodosa (PAN), systemic lupus erythema-

tosus (SLE), and systemic sclerosis (SS). All these conditions were considered but seemed unlikely to explain the whole picture. The clinical profile ruled out the possibility of hypertensive renal failure. The arteritis specific for PAN is characterized by vasculitis, thrombosis and arterial aneurysm formation (Arkin, 1930); while the glomeruli show capillary microthrombi, focal fibrinoid necrosis, polymorphic capsular infiltration and crescent formation (Rose, 1957; Patalano and Sommers, 1961; Benitez, Matthews, and Mallory, 1964). All these features were absent in our patients. In SLE immune deposits may be found in the epithelial surface of the basement membrane, intramembranously or subendothelially. Light microscopy shows localized basement membrane thickening, wire loop lesions and glomerular necrosis (Churg and Grishman, 1953); and with the electron microscope, three different categories of renal involvement can be recognized (Pollak, Pirani, and Schwartz, 1964). All these histological features were absent in these patients as were the characteristic deposits of anti-DNA immune complex. In SS the renal involvement is usually apparent late in the clinical course of the disease and the most striking feature is the rapid onset of hypertension (Rodnan, Schreiner, and Black, 1957; Khoo and Stump, 1960), though both structural and functional pathological changes are common and can be seen in the early stages (Calvert and Owen, 1956; Fisher and Rodnan, 1958). The positive WR in *Case 2* was considered to be a transient manifestation of a disturbed autoimmune mechanism. The enlargement of the juxtaglomerular apparatus (JGA) in *Case 1* is of interest. The sodium loss and hypotension resulting from adrenal necrosis might lead to increased renin output. Tribe and Heptinstall (1965) have shown prominent granularity of the JGA in rats in which the adrenals were removed 20 days before death.

Intravascular coagulation and fibrin deposits seen in the renal histology suggested the diagnosis of thrombotic microangiopathy (Symmers, 1952) or microangiopathic haemolytic anaemia (MAHA) (Brain, Dacie, and Hourihane, 1962). The basic factor in the pathogenesis of haemolysis in this condition appears to be direct contact between the red cells and the diseased blood vessels resulting in red cell fragmentation. Considerable evidence has been presented indicating that red cell fragmentation may be caused by fibrin strands deposited in the damaged vessels (Bull, Rubenberg, Dacie, and Brain, 1968). Sevitt, Naish, Baker, Bulpitt, Archer, Nelson, and Peters (1973) however suggest that fibrin deposits do not play any significant part in the red cell damage.

The two common clinical conditions characterized by MAHA are the haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). In both these conditions there is usually considerable haemolysis but the Coomb's test is negative and the blood picture shows burr cells, helmet cells and other fragmented red cells (Schwartz and Motto, 1949). The hallmarks of HUS are haemolysis due to fragmented cells, thrombocytopenia and biochemical and pathological evidence of intravascular coagulation (Gasser, Gautier, Steck, Siebermann, and Oechslin, 1955; Gianantonio, Vitacco, Mendilaharzu, Gallo, and Sojo, 1973). In TTP the most characteristic lesion is the occlusion of small arteries and arterioles by microthrombi (Moschcowitz, 1925; Singer, 1954); but the brunt of the disease does not necessarily fall on the kidneys. In the HUS there is impairment of renal function

and the histological changes are characteristic. The clinical and histological picture of our patients is different from those of typical HUS and TTP and is difficult to classify in any previously described syndrome. To the best of our knowledge, the association of Addison's disease with a microangiopathy of the intravascular coagulation variety with renal failure has not yet been described and appears to present a new syndrome.

REFERENCES


ADDISON, T., 1855. *On the Constitutional and local effects of diseases of the suprarenal capsules*. D. Highley, London.

ARKIN, A., 1930. *Amer. J. Path.* **6**, 401.

BEEVEN, D. W., NELSON, D. H., RENOLD, A. E., and THORN, G. W., 1959. *New Engl. J. Med.* **261**, 443.

BENITEZ, L., MATTHEWS, M., and MALLORY, G. K., 1964. *Arch. Path.* **77**, 117.

BLIZZARD, R. M., CHEE, D., and DAVIS, D., 1967. *Clin. exp. Immunol.* **2**, 19.

BLOCK, M. B., PACHMAN, L. M., WINDHORST, D., and GOLDFINE, I. D., 1971. *Amer. J. med. Sci.* **261**, 213.

BRAIN, M. C., DACIE, J. V., and HOURIHANE, D. O'B., 1962. *Brit. J. Haemat.* **8**, 358.

BRENNER, O., 1928. *Quart. J. Med. N.S.* **22**, 121.

BULL, B. S., RUBENBERG, M. L., DACIE, J. V., and BRAIN, M. C., 1968. *Brit. J. Haemat.*, **14**, 643.

CALVERT, R. J., and OWEN, T. K., 1956. *Lancet* **ii**, 19.

CARPENTER, C. C. J., SOLOMON, N., SILVERBERG, S. G., BLEDSOE, T., NORTHCOTT, R. C., KLINENBERG, J. R., BENNETT, I. L., and HARVEY, A. McG., 1964. *Medicine (Baltimore)* **43**, 153.

CHURG, J., and GRISHMAN, E., 1953. *Amer. J. Path.* **29**, 199.

DE WARDENER, H. E., 1973. *The Kidney*, 4th edn. p. 252. Churchill Livingstone, London.

EICHNER, H. L., SCHAMBERLAN, M., and BIGLIERI, E. G., 1973. *Amer. J. Med.* **55**, 700.

FABER, V., and GRØNBAEK, P., 1956. *Acta endocr.* **22**, 145.

FISHER, E. R., and RODNAN, G. P., 1958. *Arch. Path.* **65**, 29.

FREY, H. M. M., VOGT, J. H., and NERUP, J., 1973. *Acta. endocr.* **72**, 401.

GASSER, C., GAUTIER, E., STECK, A., SIEBERMANN, R. E., and OECHSLIN, R., 1955. *Schweiz. med. Wschr.* **85**, 905.

GHARIB, H., HODGSON, S. F., GASTINEAU, C. F., SCHOLZ, D. A., and SMITH, L. A., 1972. *Lancet* **ii**, 734.

GIANANTONIO, C. A., VITACCO, M., MENDILAHARZU, F., GALLO, G. E., and SOJO, E. A., 1973. *Nephron* **11**, 174.

GOUDIE, R. B., ANDERSON, J. R., GRAY, K., and WHYTE, W. G., 1966. *Lancet* **i**, 1173.

IRVINE, W. J., STEWART, A. G., and SCARTH, L., 1967. *Clin. exp. Immunol.* **2**, 31.

—— 1968. *Proc. roy. Soc. Med.* **61**, 271.

—— CHAN, M. M. W., SCARTH, L., KOLB, F. O., HARTOG, M., BAYLISS, R. I. S., and DRURY, M. I., 1968. *Lancet* **ii**, 883.

—— and BARNES, E. W., 1972. *Clinics. Endocrinology and Metabolism* **1**, 549.

—— —— 1975. *Clinical Aspects of Immunology*, 3rd edn. Ed. P. G. H. Gell, R. R. A. Coombs, and P. J. Lachmann, p. 1301. Blackwell Scientific Publications, Oxford.

KENNY, F. M., and HOLLIDAY, M. A., 1964. *New Engl. J. Med.* **271**, 708.

KHOO, E. C., and STUMP, T. A., 1960. *Ann. intern. Med.* **52**, 717.

LARSON, D. L., 1961. *Systemic lupus erythematosus*. Little, Brown and Co., Boston.

MEECHAM, J., and JONES, E. W., 1967. *Lancet* **i**, 535.

MOSCHCOWITZ, E., 1925. *Arch. intern. Med.* **36**, 89.

OGLE, J. W., 1886. *St. George's Hospital Rep.* **1**, 157.

PATALANO, V. J., and SOMMERS, S. C., 1961. *Arch. Path.* **72**, 1.

POLLAK, V. E., PIRANI, C. L., and SCHWARTZ, F. D., 1964. *J. Lab. clin. Med.* **63**, 537.

RODNAN, G. P., SCHREINER, G. E., and BLACK, R. L., 1957. *Amer. J. Med.* **23**, 445.

ROSE, G. A., 1957. *Brit. med. J.* **ii**, 1148.

SCHMIDT, M. B., 1926. *Verh. dtsch. Ges. Path.* **21**, 212.

SCHWARTZ, S. O., and MOTTO, S. A., 1949. *Amer. J. med. Sci.* **218**, 563.

SEVITT, L. H., NAISH, P., BAKER, L. R. I., BULPITT, C. J., ARCHER, D. F. J., NELSON, D. A., and PETERS, D. K., 1973. *Brit. J. Haemat.* **24**, 503.
SHARR, M., 1975. *J. Neurological Sciences.* **24**, 305.
SINGER, K., 1954. *Advanc. intern. Med.* **6**, 195.
SLOPER, J. C., 1953. *J. Path. Bact.* **66**, 53.
SOLOMON, N., CARPENTER, C. C. J., BENNETT, I. L., and HARVEY, A. M., 1965. *Diabetes* **14**, 300.
SYMMERS, W. ST. C., 1952. *Brit. med. J.* ii, 897.
TRIBE, C. R., and HEPTINSTALL, R. H., 1965. *Brit. J. exp. Path.* **46**, 339.
TURKINGTON, R. W., and LEBOVITZ, H. E., 1967. *Amer. J. Med.* **43**, 499.
TZAGOURNIS, M., and HAMWI, G. J., 1967. *Metabolism* **16**, 213.
WEGIENKA, L. C., GRASSO, S. G., and FORSHAM, P. H., 1966. *J. clin. Endocr.* **26**, 37.
WEHRMACHER, W. H., 1961. *Arch. intern. Med.* **108**, 114.
WELLS, H. G., 1930. *Arch. Path.* **10**, 499.