Recurrent glomerulonephritis

G. A. COLES
M.D., M.R.C.P.

Department of Renal Medicine, Welsh National School of Medicine, K.R.U.F. Institute of Renal Disease, Cardiff
Royal Infirmary, Cardiff, Wales, United Kingdom

Summary

A patient with seven attacks of acute glomerulonephritis is described. Following each attack renal function returned to normal. Investigations strongly suggested immune complex disease as the cause of the nephritis but extensive tests failed to define the antigen. The possibility of an exogenous self-administered antigen is considered.

KEY WORDS: glomerulonephritis, immune complex, antigen.

Introduction

Immune complexes are well recognized as being capable of causing glomerulonephritis. A large number of antigens have been implicated in human disease but in the majority of patients with presumed immune complex nephritis the aetiology remains unknown (Wilson, 1979). This report describes a patient who had had seven attacks of acute nephritis of probable immune complex aetiology with complete clinical recovery following each episode. The antigen concerned remains a mystery.

Case report

The patient, a 29-year-old housewife, was first seen in July 1972 for arthropathy. Subsequently, she had seven attacks of acute glomerulonephritis as judged by the presence of haematuria, proteinuria and urinary casts. The clinical course is summarized in Table 1. All the attacks were preceded by arthralgia for a few days. On five occasions swollen, painful joints were present during the episode. The attacks in September 1972, February 1975, July 1976 and September 1976 were also preceded by vomiting for one or two days. She complained of two days sore throat before admission in June 1976, September 1976 and March 1977. Blood pressure remained normal in all the episodes but in two of them, February 1975 and June 1976, facial oedema was present on admission. Temperature was not elevated on any occasion. Following each admission her

symptoms and signs resolved. In particular, the urinary abnormalities disappeared, blood urea raised fell to normal and creatinine clearance rose to 80 ml/min or more. Proteinuria, though present on each attack, was mild, the maximum being 1.8 g/24 hr in June 1976. Between these episodes she often complained of arthralgia and rashes but there was nothing to find on examination. Before the episodes in July 1972 and February 1975 she had received ampicillin.

In July 1975, between attacks 2 and 3, she had a full assessment. Renal function was normal and there was no abnormality in the urine. Renal biopsy showed no abnormality on light or immunofluorescent microscopy. Electron microscopy showed only focal epithelial cell podocyte fusion.

In December 1975 she complained of a rash and joint pains. Her platelets were 63×10^9 /litre but her urine was normal. The platelets rose to 144×10^9 /litre in January 1976 but progressively fell to 35×10^9 /litre in May the same year. They rose after the attack of nephritis in June 1976 but fell again during the episode in July the same year. Subsequently they returned to normal. In none of the episodes were there any fragmented red cells on blood film.

Renal biopsy performed during the attack in June 1976 showed a focal proliferative glomerulonephritis. Immunofluorescence demonstrated a faint, patchy deposition of IgG in the glomeruli. A further biopsy in the July 1976 episode revealed a diffuse proliferative glomerulonephritis affecting endothelial and mesangial cells (Fig. 1). There was marked fibrin deposition in the glomerular capillary loops. Electron microscopy showed deposits on the epithelial side of the basement membrane (Fig. 2). Immunofluorescence revealed marked segmental granular deposition of IgG (Fig. 3). Smaller amounts of IgA, C3 and fibrin were also found. In none of the biopsies was there any vasculitis or significant interstitial change.

Throat swabs were taken on each admission but only once, in June 1976, grew a β -haemolytic streptococcus. A throat swab taken in March 1977

TABLE 1. Summary of the clinical and biochemical data for each episode of nephritis (haematuria, proteinuria and urinary casts)

Date	Sept. 1972	Feb. 1975	June 1976	July 1976	Sept. 1976	Mar. 1977	Apr. 1978
Arthropathy	—	+	+	+	+	+	—
Oliguria	+	+	—	+	—	—	—
Maximum blood urea—mmol/litre (mg/100 ml)	33 (198)	18 (108)	7 (42)	48 (288)	14 (84)	4 (24)	4 (24)
Treatment	Aspirin Indomethacin	Aspirin	Nil	Pulse Steroids	Pulse Steroids	Penicillin	Penicillin

+ Present.

— Absent.

FIG. 1. Renal biopsy during episode five (July 1976). There is marked endothelial and mesangial proliferation with some polymorphonuclear leucocytes present in the glomerulus. (HE, $\times 200$).

grew *Haemophilus parahaemolyticus*. Following this she was placed on long-term penicillin.

In June 1976 she had a dilatation and curettage for lower abdominal pain but nothing abnormal was found. Later the same year in October when seen in the clinic she alleged she had haematuria. She produced a dark brown coloured sample. This gave only a trace positive result for blood but was subsequently found to contain phenol.

During one of her admissions her husband produced some 18 different drugs which she had consumed at some time. These included antibiotics, analgesics and vitamin preparations. She failed to attend clinic after July 1978.

Immunological studies

Plasma levels of C3, C4 and factor B were estimated by automated immunoprecipitation using a Technicon AIP system. Serial values for C3 are shown in Fig. 4. There was a close correlation between clinical disease and low C3 levels. C4 fell to 90 mg/litre in December 1975 and again to 90 mg/100 ml in July 1976 in association with a low C3. On all other occasions C4 was normal as was factor B. Total haemolytic complement was normal between the June and July 1976 episodes. Cryoglobulins were sought during three attacks of nephritis in 1976 and were isolated in two of them (July and September). Analysis of the precipitate showed IgG

FIG. 2. High power electron microscopic appearances of part of a glomerulus taken from the same biopsy as shown in Fig. 1. There are sub-epithelial electron dense deposits (arrowed) ($\times 20,000$).

FIG. 3. Immunofluorescent microscopy of the same renal biopsy as in Figs 1 and 2. There is segmental deposition of IgG within the glomerular tufts ($\times 500$).

FIG. 4. Serial values of serum C3 compared to the clinical features. N = nephritis; U = uraemia; A = arthropathy alone; P = purpura alone; B = Biopsy.

but no paraprotein. The total amount of cryoprecipitate was not quantified. Serum immunoglobulins were measured on several occasions and were normal. Repeated tests for anti-nuclear factor and rheumatoid factor were negative. Anti-streptolysin O titre was never raised. Antibodies to common viruses were looked for but no significant titres appeared at any time. Self-induced disease was considered. The patient had previously worked in a hospital and may have had access to antisera. In view of the similarities of her illness to serum sickness, antibodies to foreign serum proteins were assayed using double diffusion in agar over 72 hr. Convalescent and acute sera showed no reaction to horse, sheep or rabbit serum. Lymphocyte transformation tests to ampicillin, penicillin, streptomycin, aspirin, paracetamol and codeine were negative. A normal response to phytohaemagglutinin was, however, obtained. An antiserum to the isolated *Haemophilus parahaemolyticus* was raised in a rabbit. After absorption with normal human kidney the antiserum was layered on cryostat sections of the biopsy obtained in July 1976. There was no reaction even after pre-treatment in an acid-citrate buffer.

Discussion

This woman has had seven distinct episodes of acute glomerulonephritis with apparently complete healing on each occasion. Second attacks of acute post-streptococcal glomerulonephritis are well recognized (Ramberg, 1947; Bernstein and Stillerman, 1960; Roy, Wall and Etteldorf, 1969). Sometimes an apparent second or further attack may be an acute exacerbation of an underlying chronic disease (Vernier *et al.*, 1959). Mendoza *et al.*, (1975) described a patient with membrano-proliferative glomerulone-

phritis with several attacks of acute nephritis or a rheumatic fever-like disease. Renal function returned to previous levels after each episode. However, protein and red cells were always present in the urine between attacks. In our patient there was no evidence of a recurring streptococcal aetiology and the absence of urinary abnormalities between attacks plus the normal histological findings between episodes 2 and 3 exclude any underlying chronic process.

Dickneyes *et al.* (1977) described a patient with two attacks of glomerulonephritis in association with chronic pancreatitis but there was no evidence of any other disease process in our patient.

Recurrent acute renal failure can be caused by other conditions such as interstitial nephritis (Saltissi, Pusey and Rainford, 1979) but the biopsies effectively exclude any alternative diagnosis to glomerulonephritis. The absence of fragmented red cells excludes recurrent haemolytic uraemic syndrome.

Systemic lupus erythematosus could remit particularly with the use of steroids. Unfortunately, a DNA binding antibody assay was not available so this diagnosis cannot be entirely excluded. However, the clinical course of several remissions without steroids and the absence of any immunoglobulin deposition in the glomeruli between attacks makes this diagnosis highly unlikely.

There appears to be no record of a similar clinical picture in the literature. Besides the seven attacks of nephritis, she had one episode of isolated arthropathy and one of purpura which were probably immunologically mediated. On several occasions the clinical picture was similar to serum sickness. The results of immunofluorescence, complement studies, the deposits seen on electron microscopy and isolation of cryoglobulins all point to this patient having suffered from recurrent immune complex disease with activation of the classical complement pathway. Although cryoglobulins were looked for in only three of the episodes and immunofluorescence was performed in two, it is reasonable to assume the other attacks also had an immune complex aetiology. Small amounts of cryoglobulins can be isolated from sera from otherwise normal subjects. However, in the two episodes in this patient when cryoglobulins were found, the nephritis was worse, as judged by deterioration in renal function, than in the episode where they were not detected, suggesting they might have been of pathogenic significance.

Episodes of recurrent immune complex disease raise the possibility of immune deficiency of which, however, there was no evidence in this patient. In particular, the total serum haemolytic complement, C3, C4, factor B and immunoglobulins were all normal between episodes. Furthermore, the patient did not suffer from recurrent infections.

All attempts to find the antigen have so far proved

unsuccessful. Drugs were considered but apparently these have not preceded the latter episodes and lymphocyte transformation tests were negative to those listed. In view of the apparently complete remissions it is likely that the antigen was exogenous in origin and healing in hospital has occurred because the antigen was no longer present. The social background of this patient was sufficiently disturbed that self-induced disease has to be considered, although the patient herself denied this possibility. Boulton Jones *et al.* (1974) described a patient with self-induced immune complex glomerulonephritis but the clinical course was one of a slow progression to renal failure.

To date treatment of this patient has been empirical. Pulse steroids were tried in view of the report by Cole *et al.* (1976) of successful reversal of rapidly progressive glomerulonephritis. However, it is likely recovery has occurred not because of the use of steroids or any other drug but because of withdrawal of the antigen.

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References

- BERNSTEIN, S.H. & STILLERMAN, M. (1960) A study of the association of group A streptococci with acute glomerulonephritis. *Annals of Internal Medicine*, **52**, 1026.
- BOULTON-JONES, J.M., Sissons, J.G.P., NAISH, P.F., EVANS, D. & PETERS, D.K. (1974) Self-induced glomerulonephritis. *British Medical Journal*, **3**, 387.
- COLE, B.R., BROCKLEBANK, J.T., KIENSTRA, R.A., KISSANE, J.M. & ROBSON, A.M. (1976) Pulse methylprednisolone therapy in the treatment of severe glomerulonephritis. *Journal of Pediatrics*, **98**, 307.
- DICKNEYES, J.P., WOLFSON, W., KOWELL, A. & DORNFIELD, L. (1977) Reversible crescentic glomerulonephritis following an acute exacerbation of chronic relapsing pancreatitis. *Archives of Internal Medicine*, **137**, 1065.
- MENDOZA, N., MANDALENAKIS, N., KAUTER, A., PIRANI, C.L. & POLLAK, V.E. (1975) Chronic membrano-proliferative glomerulonephritis. A patient with recurrent episodes simulating rheumatic fever and acute nephritis. *American Journal of Medicine*, **59**, 251.
- RAMBERG, R. (1947) The prognosis for acute nephritis. *Acta Medica Scandinavica*, **127**, 396.
- ROY, S., WALL, H.P. & ETTELDORF, J.N. (1969) Second attacks of acute glomerulonephritis. *Journal of Pediatrics*, **75**, 758.
- SALTISSI, D., PUSEY, C.D. & RAINFORD, D.J. (1979) Recurrent acute renal failure due to antibiotic induced interstitial nephritis. *British Medical Journal*, **1**, 1182.
- VERNIER, R.L., WORTHEN, H.G., WANNAMAKER, L.W. & GOOD, R.A. (1959) Renal biopsy studies of the acute exacerbation in glomerulonephritis. *American Journal of Diseases of Children*, **98**, 653.
- WILSON, C.B. (1979) Immunopathologic evaluation of renal diseases. In: *Renal Disease* (Ed by Black, D. & Jones, N.F.) 4th edn, p. 139, Blackwell Scientific Publications, Oxford.

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