Crescentic glomerulonephritis: a possible complication of streptokinase treatment for myocardial infarction

NEIL MURRAY,* JOHN LYONS,* MARGARET CHAPPELL†

From the *London Chest Hospital and †Royal Free Hospital, London

SUMMARY Twenty days after a streptokinase infusion given for myocardial infarction, a patient developed a group G streptococcal throat infection. Thirteen days later he presented with a serum sickness type illness and progressive renal failure. Renal biopsy showed crescentic glomerulonephritis.

Case report

A 56 year old man was admitted with a two hour history of retrosternal pain. The electrocardiogram demonstrated 2 mm ST segment elevation in the anterior leads suggestive of acute myocardial infarction. As part of a clinical trial he received an intravenous infusion of 1.8 million units of streptokinase (Kabikinase, Kabivitrum) over 60 minutes, after premedication with 100 mg of hydrocortisone. During the infusion ventricular fibrillation developed. This reverted to sinus rhythm with a single DC shock. There were no prolonged periods of hypotension. The electrocardiogram progressed to show T wave inversion but Q waves did not evolve. Creatine kinase concentration rose to a maximum of 267 U/l (normal <200 U/l) and the aspartate transaminase to 66 U/l (normal <40 U/l) on day 2 (streptokinase infusion given on day 0). During his stay in hospital he was treated with lignocaine, frusemide, amiloride, and metoprolol. He was mobilised and discharged on day 9.

Twenty days after the streptokinase infusion a sore throat developed and on day 33 he was re-admitted with swelling of the hands and feet and bilateral calf pain. He had a purpuric rash over the lower abdomen and legs and multiple splinter haemorrhages. There was no evidence of heart failure. Proteinuria and microscopic haematuria were present and urine microscopy showed hyaline casts. On admission plasma urea was 6.9 mmol/l, creatinine 115 µmol/l, sodium 136 mmol/l, and potas-

Fig 1 Photomicrograph showing crescentic glomerulonephritis. The section was stained with periodic acid Mallory Schiff reagent. The asterisk indicates cellular crescents; large arrow, atrophied tubules; small arrow, damaged tubular epithelium; arrowhead, collapsed glomerular tuft.

Requests for reprints to Dr Neil Murray, Department of Cardiology, Groby Road Hospital, Groby Road, Leicester LE3 9QE.

sium 5.1 mmol/l. An autoantibody screen was negative. The antistreptolysin O titre was >1000 (normal <100) and β haemolytic streptococci Lancefield Group G were cultured from a throat swab. Hypersensitivity to the streptococcal antigen was diagnosed. By day 44 plasma urea had risen to 19.1 mmol/l and creatinine to 464 μ mol/l. Oral prednisolone, 30 mg daily, and fluid restriction were started. Renal function continued to deteriorate and the plasma urea rose to 57 mmol/l. He became oliguric and peritoneal dialysis was started on day 49.

A renal biopsy was performed on day 61, 28 days after development of leg pains and purpura. All glomeruli in the biopsy showed large cellular crescents with an underlying segmental proliferative glomerulonephritis (fig 1). Capillary thrombi were present in a few loops and there was widespread necrosis and infiltration by polymorphonuclear leucocytes. No arteritis was seen. Tubular damage was severe, over a quarter of tubules being atrophied with interstitial fibrosis. There was moderate oedema and a

patchy interstitial inflammatory infiltrate. Electron microscopy showed segmentally distributed sub-endothelial and mesangial electron dense deposits with fusion of the epithelial foot processes (fig 2).

Cyclophosphamide (100 mg daily) was given in addition to prednisolone. He continued to require intermittent peritoneal dialysis for three weeks. After this dialysis was stopped and the plasma urea concentration remained steady at 20 mmol/l with an adequate urine output. He developed effort related chest pain which was eased by sublingual nitrates. In view of his renal failure, coronary angiography was not performed, and he was treated with a β blocker. He was discharged on day 105 when the plasma urea concentration was 18 mmol/l. Two days later he had a prolonged episode of chest pain and was readmitted with electrocardiographic evidence of a new anterior myocardial infarction. Further thrombolytic treatment was not given. On this occasion Q waves did evolve on the electrocardiogram and the creatine kinase concentration rose to 2661 U/l. He was mobilised without further pain. At discharge he was well. Plasma urea concentration was 19 mmol/l. Subsequently his renal function again deteriorated and he required further dialysis. A second renal biopsy specimen showed similar changes to the first but many crescents were now fibrous and there was more extensive tubular atrophy and interstitial fibrosis. Tissue was obtained for immunofluorescence studies and these showed segmentally distributed IgM, C3, and Clq.

Discussion

The development of crescentic glomerulonephritis as part of a serum sickness type illness after the administration of streptokinase and a subsequent streptococcal infection suggests a causal link with at least one of these antecedents. This patient had received other drugs, none of which have been reported as being associated with renal failure. Streptokinase, however, is antigenic, and bronchospasm, angioneurotic oedema, and anaphylaxis have been associated with its administration.^{1,2} Hypersensitivity to streptococcal antigens is also one of the commonest causes of proliferative glomerulonephritis.³

Renal failure has been reported after streptokinase and has been attributed to various aetiologies. Cholesterol embolisation of the renal circulation has been suggested and confirmed at necropsy.^{4,5} Thrombolysis is thought to remove a protective coat of thrombus overlying an ulcerated atheromatous plaque, allowing widespread diffuse embolisation of the underlying cholesterol crystals. Interstitial nephritis⁶ as well as "serum sickness" due to

Fig 2 Electronmicrograph showing crescentic glomerulonephritis. Ep, epithelial cell with fused foot processes. En, swollen endothelial cell. The arrow indicates subendothelial electron dense deposits.

immune complexes have also been suggested on clinical grounds but have not been proven by histological examination.

In this case the renal failure was shown to be caused by crescentic glomerulonephritis with an underlying segmental proliferative glomerulonephritis that apparently was the result of immune complex deposition. There are several possible pathogenic mechanisms to consider. First, this may have been an acute serum sickness type III hypersensitivity reaction to streptokinase. This has been postulated elsewhere⁷ and is supported by the accompanying purpura. In experimental serum sickness the lesions are evidently due to immune complexes and appear during the immune phase of antigen elimination, usually about 10 to 14 days after exposure to antigen. Typically the lesions are most severe at 13 days and heal rapidly, so that within two or three weeks the glomeruli appear normal.⁸⁻¹⁰ In most animals with these lesions antigen and immune complex concentrations have dropped almost to zero by 15 days. In the previously reported case, in which histological examination was not available, clinical manifestations appeared seven days after the start of streptokinase treatment.⁷ In our case the lesions did not appear until day 33. This delay is longer than would be expected, although probably not impossible so.

Secondly, the glomerulonephritis may have been a straightforward post-streptococcal phenomenon. The delay between the sore throat and the appearance of typical lesions is usually 1-4 weeks.¹¹ This is consistent with the 13 day delay seen in this case. While post-streptococcal glomerulonephritis is typically endocapillary in nature, a small proportion are of the crescentic type as demonstrated here.¹¹ Similarly, while purpuric rashes and splinter haemorrhages are uncommon, they do sometimes occur. On the other hand, the aetiological agent in post-streptococcal glomerulonephritis is almost invariably a group A rather than group G streptococcus. Furthermore, in this patient the typical subepithelial humps could not be identified on electron microscopy.

A third possibility is that the illness was due to a type III hypersensitivity reaction to the group G streptococcus after sensitisation by streptokinase. The evidence for this is circumstantial and the suggestion is speculative. This possibility should be

considered, however, because neither of the other two possibilities fully explain this case.

In this patient the renal failure may have been a simple post-streptococcal phenomenon and exposure to streptokinase may have been irrelevant. If, however, the glomerulonephritis was the result of some form of streptokinase hypersensitivity this is a serious complication of streptokinase treatment. New thrombolytic agents, such as tissue plasminogen activator, may not cause such allergic reactions. Experience with this agent is limited, however, and its possible antigenicity is as yet unknown.¹²

We thank Dr R Winwood for permission to report a patient under his care.

References

- 1 Bell WR, Meek AG. Guidelines for the use of thrombolytic agents. *N Engl J Med* 1979;301:1266-70.
- 2 Baumgartner TG, Glen Davis R. Streptokinase-induced anaphylactic reaction. *Clin Pharmacol* 1982;1:470-1.
- 3 Heptinstall RH. *Pathology of the kidney*. 3rd ed. Boston and Toronto: Little, Brown, 1983:387.
- 4 Rieben FW, Waldherr R, Oster P, Schettler G. Akutes Nierenversagen als Folge diffuser Cholesterinkristall-Embolisation unter Streptokinasetherapie. *Dtsch Med Wochenschr* 1979;104:1447-9.
- 5 Andrassy K. Discussion. p194. In: Ritz E, Bommer J, Andrassy K, Waldherr R. Acute renal failure, hypertension and skin necrosis in a patient with streptokinase therapy. *Am J Nephrol* 1984;4:193-200.
- 6 Pick RA, Joswig BC, Cheung AK, Cohen IM. Acute renal failure following repeated streptokinase therapy for pulmonary embolism. *West J Med* 1983;138:878-80.
- 7 Totty WG, Romano T, Benian GM, Gilula LA, Sherman LA. Serum sickness following streptokinase therapy. *AJR* 1982;138:143-4.
- 8 Heptinstall RH. *Pathology of the kidney*. 3rd ed. Boston and Toronto: Little, Brown, 1983:301-9.
- 9 Germuth FG. Comparative histologic and immunologic study in rabbits of induced hypersensitivity of serum sickness type. *J Exp Med* 1953;97:257-82.
- 10 Wilson CB, Dixon FJ. Antigen quantitation in experimental immune complex glomerulonephritis. I Acute serum sickness. *J Immunol* 1970;105:279-90.
- 11 Heptinstall RH. *Pathology of the kidney*. 3rd ed. Boston and Toronto: Little, Brown, 1983:395-401.
- 12 Sherry S. Tissue plasminogen activator (t-PA). Will it fulfil its promise? *N Engl J Med* 1985;313:1014-7.