RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS: TREATMENT WITH COMBINED IMMUNOSUPPRESSION AND ANTICOAGULATION WITH ARVIN

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SYNOPSIS

Five patients with rapidly progressive glomerulonephritis (RPGN) were treated with quadruple chemotherapy — i.e., prednisolone, cyclophosphamide , dipyridamole, and arvin followed by warfarin. Three patients demonstrated improvement in renal function. One patients with lupus nephritis died possibly due to overwhelming sepsis and severe cerebral involvement. One patient who presented with severe renal failure did not respond to the combination therapy. There was no significant side effect of arvin. The data suggests that defibrination with arvin in combination with prednisolone, dipyridamole, warfarin and cyclophosphamide has a role in RPGN. However, patients presenting with severe renal failure may not be improved.

INTRODUCTION

Rapidly progressive glomerulonephritis (RPGN) is a clinicopathological entity characterised by a rapid decline in renal function to uraemia within a few weeks or months, and associated with severe and diffuse glomerular lesions characterised by the formation of extensive occlusive epithelial-cell proliferation (crescents) (1).

In untreated patients this disease is almost uniformly fatal (2, 3). Treatment with combined immunosuppression and anticoagulation with heparin and or dipyridamole seem to have demonstrated a satisfactory response (1, 4-6). More recently high dosage 'pulse' steroid therapy and plasma exchange have been shown to give promising results (7).

The rationale for the use of anticoagulant therapy in RPGN is based on the evidence that coagulation mechanisms involving both fibrin and platelets are involved in the genesis or perpetuation of glomerular damage (8-12). Fibrin deposition is involved in the formation of extra-capillary crescents (8,10,12-14). Defibrination has been shown in experiments with rabbits to give a significant degree of structural and functional protection to glomeruli from the effect of nephrotoxic antibody (12).

In experimental nephrotoxic serum nephritis, the protective effects of arvin which is a defibrinating agent were strikingly superior to those of heparin (14). In contrast to heparin and warfarin, arvin was effective even in well-established experimental renal disease with significantly impaired renal function; renal function improved, fibrin deposition cleared partially or completely, and crescents decreased (15-17). Arvin administration may have a role in treatment of certain types of glomerulonephritis especially lupus nephritis in humans (18).

We describe here the response to a regimen of combined quadruple chemotherapy of prednisolone, cyclophosphamide, dipyridamole, and arvin followed by warfarin in five consecutive patients, who had RPGN with extensive crescents.

PATIENTS AND METHODS

Patients

The five patients described were admitted to the renal unit of General Hospital, Kuala Lumpur, between July 1982 and April 1984 because of rapidly deteriorating renal function or oligo-anuria requiring investigation and dialysis. The age range was 4 to 24 years. There were three males and two females. The patients were oligo-anuric on admission. Informed consent was obtained from each patient.

Clinical details on admission, symptoms and length of history, blood pressure, serum-creatinine, C3 and C4 components of complement, anti-streptolysin titre, antinuclear factor, the clinicopathological diagnosis and subsequent outcome are listed in table I.

TABLE 1: CLINICAL FEATURES OF PATIENTS AND COURSE OF DISEASE

Patient No.	Sex	Age (yrs)		History	Duration of illness (wks)	Presentation	BP (mm. Hg)	Creatinine Clearance (ml/min)	Serum Creatinine (umol/L) NR: 62-124		ASOT	C4 (mg/100 ml) NR: 20-50	C3 (mg/100 ml) NR: 50-120	ANF	Diagnosis	Follow-up (months)	Outcome
									Initial	Latest							
1	F	24	C	Orbital, ankle oedema	47	PRF N.S.	180/110	2	862	1246	<100	11.5	34.0	+ ve	SLE	2	Lost to follow-up
2	M	9	I	Fever, cough, haemoptysis, haematuria	13	PRF	100/70	14	206	937	<100	50.0	145.0	– ve	RPGN	19	Alive Recent rapid deterioration in renal function
	M	4	M	Influenza-like illness, sore-throat, orbital, ankle oedema	9	Oliguric	150/110	0.6	782	158	100	43.5	62.0	– ve	RPGN	26	Alive
4	F	7	C	Generalised oedema	7	Anuric	120/80	N.D.	698	57	400	38	10	– ve	Post Streptococcal GN	22	Alive
5	M	17	M	Orbital, ankle oedema	14	N.S.	130/80	N.D.	187	294	<100	10	16	+ ve	SLE	0	Dead

C = Chinese, I = Indian, M = Malay, PRF = Progressive renal failure, NS = Nephronic syndrome,
RPCN = Rapidly progressive glomerulonephritis, SLE = Systemic lupus erythematosus, ANF = Anti-nuclear factor, BP = Blood pressure,
ASOT = Anti-streptolysin titre, ND = not done.

Drug Therapy

Arvin: on the first day, 2 units/kg in 500 ml dextrose 5% was administered slowly intravenously over 6-12 hours. The initial infusion was given slowly to avoid the theoretical risk of massive intravascular fibrin formation. A second dose in like fashion was administered later on the first day. Arvin 2 units/kg, diluted in 10 ml normal saline, was given intravenously every 12 hour thereafter for another 13 days.

Prednisolone: was started at a dose of 60 mg/day and was subsequently tapered to 10-20 mg/day.

Cyclophosphamide: a single morning dose of 1.5-2.5 mg/kg was administered. This was reduced or stopped if the white-blood-cell-count fell below 3.5×10^3 per ul.

Dipyridamole: was given in a dose of 100 mg four times a day in adults, 10 mg per kg per day in children. This dose was achieved by gradual increments from a commencing dosage of 25 mg four times a day.

Warfarin: was given in doses to double the prothrombin-time. Warfarin was commenced after arvin had been discontinued.

Before, during, and after study, all concomitantly required medications, such as antihypertensive drugs and diuretic agents were continued.

Renal Biopsies (Table II)

Percutaneous or open renal biopsy specimens were obtained in all patients. All specimens were processed for light microscopy and immunoflourescence by conventional techniques. Only biopsy specimens showing more than ten glomeruli were accepted as adequate.

Monitoring

Response to therapy was followed by standard tests of renal function. The prothrombin time was determined as frequently as was necessary until it was stable. Similarly, white cell count and platelet count determination was done at regular intervals to detect leucopenia or thrombocytopenia.

CASE REPORTS

Patient 1 is a 24 year old Chinese female who had recurrent episodes of generalised oedema for which she had been treated with prednisolone elsewhere. She was found to have hypertension, chronic renal failure, albuminuria, and microscopic haematuria. Her serum creatinine was 862 umol/1 and her creatinine clearance was 2 ml/min. Her investigations supported a diagnosis of SLE. A renal biopsy showed membranoproliferative glomerulonephritis with extensive crescents. There was moderate degree of interstitial scarring and tubular atrophy. Combination therapy was commenced.

After seven weeks of therapy, it was felt that she had not responded and that she had reached end stage renal failure and her medications were ceased. Patient refused to consider the prospect of haemodialysis or renal transplantation and absconded.

Patient 2 is a 9 year old Indian male who presented with fever, cough, haemoptysis and haematuria for which he was treated as bronchopneumonia with acute glomerulonephritis elswhere. His blood pressure was 100/70 mm Hg., serum creatinine was 206 umol/1 and creatinine clearance was 14 ml/min. A renal biopsy showed numerous glomeruli with extensive crescent formation. There were many globally sclerosed glomeruli. He was diagnosed as having RPGN and combination therapy was commenced.

His serum creatinine which was 364 umol/1 at the onset of therapy decreased to 112 umol/1 at the end of arvin therapy. His daily urine output increased considerably from about 500 ml to 1000 ml after arvin was commenced. One month later, patient developed severe hypertension, his blood pressure being 220/120 mm Hg. Antihypertensive therapy was instituted. He also developed recurrent episodes of viral fever and hence cyclophosphamide was discontinued 2 months after commencement. Patient was subsequently discharged and has been followed-up for 19 months. Throughout his follow-up his blood pressure has been difficult to control. His serum creatinine began to increase gradually until it reached a level of 392 umol/1 at 16 months. Thereafter it rose rapidly to a level of 937 umol/1 at 19 months.

Patient 3 is a 4 year old Malay male who presented elsewhere with sorethroat, fever, generalised oedema

TABLE 2: HISTOLOGICAL FINDINGS

Patient No.	GLOMERULI							Interstitial Scarring	Tubular Atrophy	Immuno-floure-scence	Diagno
	Total No.	No. with Crescents	Nature of Crescent	No globally Sclerosed	Proliferative Changes	Necrosis	Hyaline Thrombosis				
1	10 (80%)	8	Predominantly Cellular	0	+	0	0	+ +	+ +	N.D.	SLE
2	102 (90%)	90	Predominantly Cellular	20	0	0	0	+	+	IgG, IgA, IgM, C3 Fibrin granular	RPGI
3	23 (90%)	21	Predominantly Cellular	9	0	0	0	+ +	+ +	IgG, C3, Fibrin granular (segmental)	RPGI
4	30 (80%)	24	Cellular and Fibrous	16	+	0	0	0	+	Fibrin only	PSGI
5	17 (50%)	9	Cellular	1	+	0	+	+	+	IgG, IgA, C3 linear	SLE

0 = nil, + = mild, + + = moderate, + + + = severe

associated with anuria and macroscopic haematuria of 5 days duration. His initial serum creatinine was 920 umol/1. He required repeated peritoneal dialysis and was subsequently referred to us for further management. His subsequent serum creatinine was 782 umol/1 and his creatinine clearance was 0.6 ml/min. He was oliguric for 12 days and was peritoneally dialysed. A renal biopsy showed 23 glomeruli of which 21 had predominantly cellular crescents and 9 were globally sclerosed. There was moderate degree of interstitial scarring with tubular atrophy. He was diagnosed as having RPGN and combination therapy was commenced.

Patient had been followed-up for 26 months and has maintained reasonable renal function, his latest serum creatinine being 158 umol/1. Warfarin was discontinued after about 7 months due to problems in control of his prothrombin time. Cyclophosphamide was reduced to 25 mg twice/week due to neutropenia. 16 months after commencement of therapy patient ceased medication on his own accord and did not turn up for follow-up. He was recalled and returned subsequently 2 months later and in view of reasonable renal function it was decided not to recommence his medication.

Patient 4 is a 7 year old Chinese female who presented with generalised oedema with progressive decrease in urine output associated with nausea and vomiting of one week duration. Her serum creatinine was 689 umol/1. Investigations supported a diagnosis of acute post-streptococcal glomerulonephritis (ASOT 1/400). She was anuric for 5 days and oliguric for 8 days and required dialysis. A renal biopsy showed 30 glomeruli of which 80% had cellular and fibrous crescents and 16 were globally sclerosed. Combination therapy was commenced.

Patient improved without complications. Her serum creatinine which was 282 umol/1 at the commencement of the therapy returned to normal levels and has remained so after 22 months, the latest serum creatinine being 57 umol/1. Her warfarin was ceased after 2 months due to problems related to control of her prothrombin time.

Patient 5 is a 17 year old male Malay, who presented with ankle and periobital oedema. Investigations supported a diagnosis of SLE. Despite initial treatment with prednisolone his renal function deteriorated. He developed staphylococcal and klebsiella pneumonia with septicaemia which was treated with antibiotics. A renal biopsy showed a diffuse proliferative glomerulonephritis with cellular crescents. There was mild hyaline thrombosis of the glomeruli with mild interstitial scarring and tubular atrophy. Combination therapy was started.

His basal pneumonia and septicaemia persisted despite antibiotic therapy and hence cyclophosphamide was ceased after one week. In view of his hypercatabolic state he was dialysed. 12 days after commencement of arvin therapy, he developed generalised fits. Arvin was withheld for 2 days until his fits were controlled and lumbar puncture and EEG showed no evidence of haemorrhage. CSF examination did not reveal any evidence of infection. EEG did not reveal any focal abnormality. Arvin was subsequently continued for 2 days. At the cessation of arvin therapy patient deteriorated rapidly and died. Unfortunately a post-mortem could not be done.

DISCUSSION

RPGN is defined clinically as a condition with a rapidly decreasing GFR on whatever evidence is available or a presentation in oliguria or anuria. The pathological criteria is an adequate biopsy containing at least ten glomeruli of which at least 50% are afflicted with enveloping crescents.

The patients described in this series fulfilled the clinico-pathological criteria described above. The conditions included idiopathic glomerulonephritis, SLE and acute post-streptococcal glomerulonephritis.

As immunological and coagulation mechanisms are involved in RPGN it has been suggested that crescentic nephritis be treated with anticoagulants (8) and agents which inhibit platelet function (5, 6). Kincaid-Smith et la. reported impressive results in patients with oliguric renal failure treated with heparin, dipyridamole, steroids, and immunosuppressive agents (4, 5). Since then others have reported reasonable results with combined immunosuppression and anticoagulants (1,6,19,20). Pollak VE et al. reported beneficial results of arvin in certain types of glomerulonephritis especially lupus nephritis (18).

In this series of five patients, three have responded well to therapy. Patient 3 has been followed up for 26 months and patient 4 has been followed up for 22 months. Both have continued to maintain their renal function. Patient 2 made considerable improvement initially, but after 2 months of therapy began to have gradual deterioration of renal function until the 16th month of therapy when his serum creatinine was 392 umol/1. Thereafter it rose rapidly to a level of 937 umol/1 at 19 months. It is interesting to note that the gradual decline in renal function was associate with the withdrawal of cyclophosphamide and hypertension that was difficult to control. Both these factors could have contributed to his gradual decline in renal function. His rapid decline in renal function could be due to both these factors as well as relapse of RPGN. Recurrence of RPGN after prolonged remission has been reported (21). Currently arrangements are being made for a repeat renal biopsy and possibly for a second course of arvin.

We have included a patient (No. 4) who had post-streptococcal glomerulonephritis, although there are many reports of a favourable outcome in this condition (3). However, not everyone share this view. Habib and Kleinknecht (22) have stated that end-stage renal disease will likely result, regardless of the etiology of the disease, when the number of glomeruli involved by crescent formation is more than 50% and that is more nearly certain when more than 80% of glomeruli are affected. They concluded that the outcome in children whose disease is of postinfection origin, therefore was sufficiently grave, even with treatment, to warrant a therapeutic trial. A review of 575 cases of RPGN indicated that there is no significant difference in the mortality of RPGN of different etiolgoy (7). Prognosis was found to be related to the percentage of glomeruli affected by crescent formation (7, 23, 24), with up to 100% mortality if involvement exceeds 80%. Some series have included patients with post-streptococcal etiology (1, 4). In view ofthe above observations and as our patient had severe renal failure (serum creatinine 698 umol/1), anuria for 5 days and oliguria for 8 days, we felt justified to treating the patient with the combination therapy.

The presence of oliguria is claimed to be of prognostic importance (1, 25). Brown et al (4) and Cameron et al (25) recommended that treatment should begin early, and before anuria developed, in order to assure maximum benefit of drug therapy. However, Kincaid-Smith et al (4) have reported recovery even in anuric patients treated with anticoagulants and immunosuppressive agents. Two of our patients who had oligo-anuria recovered and have maintained reasonable renal function after a follow-up of 14 to 18 months. Our results are in agreement with Kincaid-Smith et al (4) although the number involved is small.

The lack of response in patient 1 who had SLE could have been due to the severity of renal failure, the delay in presentation and the presence of 80% crescents with moderate degree of interstitial scarring. It has been the experience of Pollak VE et al that severe lupus nephritis with profound impairment of renal function has a bad prognosis (18).

Patient 5 died soon after completion of arvin therapy and it is therefore unable to evaluate the efficacy of the regime. It is difficult to postulate the cause of his death in the absence of a post-mortem. Overwhelming sepsis and florid cerebral lupus may have been contributory factors. Investigations performed did not indicate intracranial haemorrhage.

Under carefully controlled conditions, arvin administration appeared safe. Significant bleeding did not occur in defibrinated patients even with nephrotic syndrome or moderate to severe renal failure. Neutropenia occurred in two patients requiring cessation of cyclophosphamide in one patient and reduction of dose in the other. In the third patient, cyclophosphamide was ceased due to persistent infection. Septicaemia and pneumonia which occurred in one patient may have been contributed by prednisolone. Warfarin was discontinued in two patients due to problems related to control of prothrombin time and not due to haemorrhagic complications.

Our results suggest that treatment with combined immunosuppression and anticoagulation with arvin has a role in the management of RPGN. Under carefully controlled conditions, arvin administration is safe. We report that oligo-anuric patients have recovered with the combination regime. Patients presenting late in the course of the disease and those who are in severe renal failure do not seem to respond to treatment. It is therefore very important that these patients be diagnosed and treated as soon as possible. In view of the small number of patients involved in this series, further trials are necessary.

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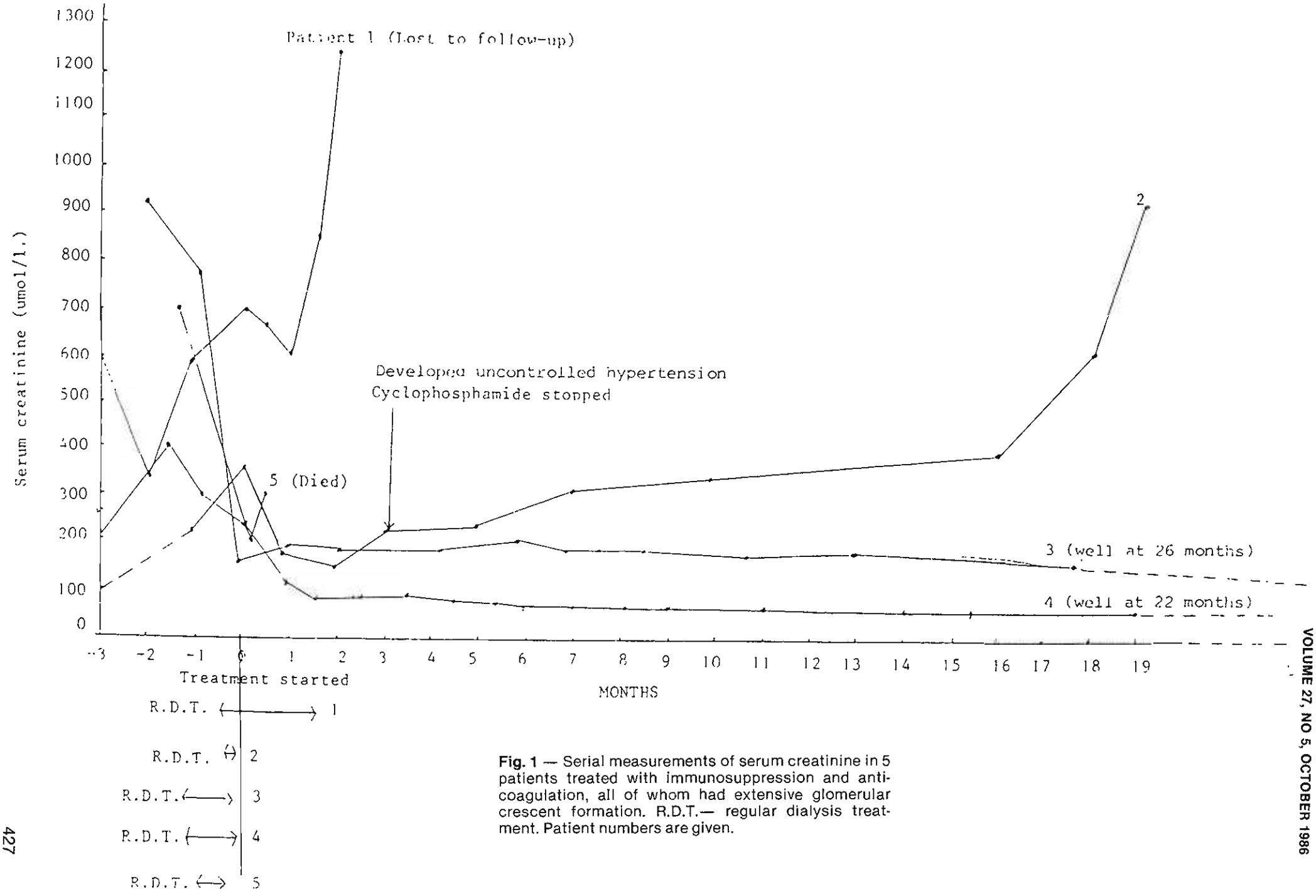

Fig. 1 — Serial measurements of serum creatinine in 5 patients treated with immunosuppression and anticoagulation, all of whom had extensive glomerular crescent formation. R.D.T.— regular dialysis treatment. Patient numbers are given.