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ORIGINAL ARTICLE

Nephritic factor and recurrence in the renal transplant of membranoproliferative glomerulonephritis type II

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Abstract Animal models suggest a role for nephritic factor in the pathogenesis of glomerular disease, but evidence for a role in human disease is lacking. To assess its role, we applied a recently developed method that allows measurement of low levels of nephritic factor activity to stored serum specimens from three patients who had membranoproliferative glomerulonephritis (MPGN) type II. All three had had renal transplants, and one lost two of three transplants from recurrent disease. Evidence for a role for nephritic factor in human disease was a positive correlation between the level of nephritic factor activity and both the severity of recurrence and an increase in serum creatinine concentration. However, the hypocomplementemia was never severe; C3 levels of 49–76 mg/dl and nephritic factor levels of 89 U/ml were associated with severe recurrences. We have previously seen severe disease with mild hypocomplementemia. In contrast, patients with partial lipodystrophy often have severe hypocomplementemia and, presumably, high levels of nephritic factor yet have a mild glomerulonephritis. Disease severity and nephritic factor levels thus appear to be inversely related. The disease is progressive when only moderate amounts of nephritic factor have been circulating and C3 only mildly depressed.

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Introduction

Evidence has accumulated over the last several years that supports a causal role for nephritic factor (NF) in the genesis of glomerulonephritis. Patients with inborn or acquired abnormalities of the complement system that, like NF, cause active convertase to circulate, frequently develop a nephritis resembling membranoproliferative glomerulonephritis (MPGN) type II (reviewed in [1]). Active convertase in the circulation means that the amplification loop is uncontrolled, and a result is that C3 is depleted to a variable extent. Additional evidence that NF is nephritogenic comes from studies of experimental animals. Animal nephritis models result when the complement proteins are manipulated so that normal control of the amplification loop is lost [2].

The failure of clinicians over nearly four decades to recognize that NF has a role in producing MPGN is in part because precise methods for its measurement have not been readily available. Those measurements that have been made have not been supportive of the concept that it is nephritogenic. Schwertz et al. [3, 4] measured NF activity in 50 patients with MPGN type II in a multicenter study. The method was that of Rother [5], the method which, extensively modified, was used in our study. NF was absent in 20% of the patients, and when present, it did not correlate with the clinical course. Leibowitch et al. [6] studied 11 posttransplant patients with MPGN type II. Two of the patients had no NF demonstrable yet had intra-

membranous dense deposits. NF was measured by crossed immunoelectrophoresis.

In many studies, the role of NF in nephritogenesis has been assessed by using the level of C3 as a surrogate for NF. C3 levels were considered to have a reciprocal relationship to NF activity. A number of observers have found little or no relationship between C3 levels, and hence NF activity, and the clinical course [7–9].

A method for measuring NF activity, recently developed in this laboratory [10], has been used on stored serum specimens from three patients with MPGN type II who had renal transplants. The study seeks to answer several questions: Will the concept that NF is nephritogenic be supported by actual measurement of NF in patients? What levels of NF are nephritogenic? How well can NF activity be predicted by the C3 level? What events affect the level of NF?

Methods

NF activity was measured on serum specimens that had been stored for many years at –80°C. All NF measurements were made on this aged serum, but the majority of the C3 measurements were by radial immunodiffusion when the serum was fresh. The few C3 measurements on aged serum were by the Dade BN-Prospec apparatus.

As with other autoantibodies, NF was found to be very stable. Its activity was undiminished when high dilutions of serum containing NF underwent five cycles of freezing and thawing. Also, levels of NF activity on aged specimens of serum from patients other than those reported herein have been of the same order of magnitude as those from similar patients seen recently.

Measurement of NF was by a screening method developed by Rother [5]. The method was extensively modified, but the principle remained the same. Serum containing NF is incubated with sheep red blood cells suspended in normal human serum (NHS) for 20 min at 30°C. During this time, C3b is deposited on the red cells by the NF-stabilized convertase. After addition of C5 in the form of ethylenediaminetetraacetic acid (EDTA) rat serum, the red cells hemolyze during a 1.5-h incubation at 37°C. The amount of hemolysis, measured spectrophotometricly, is considered to be proportional to NF activity. The method thus does not measure NF directly but, rather, the C3b produced by both NF-stabilized and unstabilized convertase, the latter formed in small quantity by the bystander C3, which is activated by the stabilized convertase. The plot of optical density (OD) minus the blank (the corrected OD) of the supernatant versus the volume of NF-containing serum in the reaction mixture describes a straight or slightly curved line, which goes through the origin. This allows NF activity to be measured in arbitrary U (U) and eliminates the need for extensive washing of the cells, a part of the original Rother method [5].

Modifications of the Rother method were mainly directed at reducing the variability of replicates. They consisted of sequestering the sample from the cell-serum mixture so that all tubes could be mixed at the same time, thus avoiding mixing by vortexing and increasing the gelatin concentration in the buffers.

Two serial dilutions of a serum with a high level of NF activity were included in each run as calibrators, as were blanks consisting of diluted normal human serum. The calibration line is a plot of the corrected OD of the calibrators versus the U of NF activity assigned to the calibrators. The method is capable of detecting NF activity in 16 nanoliters of a serum that contains NF in high concentration. Interday coefficients of variation ranged from 7.4% to 13.5%, mean 11.5% (ten measurements on each of five specimens), and intraday coefficients of variation ranged from 7.4% to 12.6%, mean 9.7% (ten measurements on each of five specimens).

Applying the method to aged serum from normal subjects gave corrected ODs varying between +0.1 and –0.1. These correspond approximately to NF activity levels of +10 and –10 U/ml. A few serum samples contained false NF, with levels in terms of true NF activity as high as 30 U/ml. The C3 concentration in these sera was always in the normal range. A distinguishing feature of false NF was that the corrected ODs of serial dilutions were erratic and did not go through the origin.

NF activity levels of up to 500 U/ml have been found in the serum of a few patients with MPGN type II and as high as 2,400 U/ml in patients with MPGN type III.

Results

Patient 1

Patient 1 was 12 years old at the time of his first transplant. Receiving prednisone after onset at age 8 years, he improved, but subsequently relapsed and developed end-stage renal disease (ESRD). Details of his course can be found in earlier publications ([11, 12]; patient 1). His mother donated the allograph kidney, and his immunosuppressive therapy was azathioprine and prednisone. NF and C3 levels during his posttransplant course are given in Figs. 1, 2, 3 and 4. Table 1, in which his course has been divided into nine periods, summarizes the data of these figures.

Bilateral native nephrectomies were done 2 weeks before the transplant. While anephric and on peritoneal dialysis, NF activity was high relative to later values, averaging 167 U/ml. The C3 level was appropriately low at 25 mg/dl

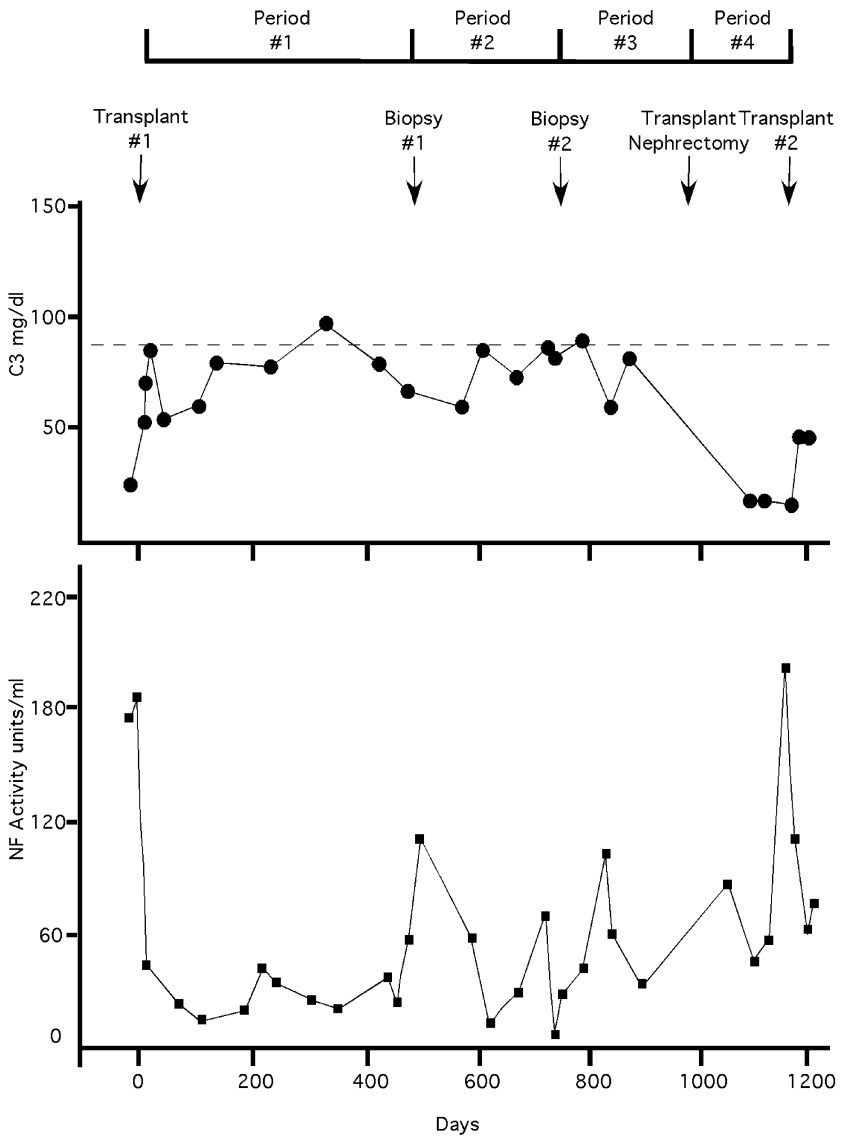

Fig. 1 Patient 1. Events after the first transplant. Nephritic factor activity (*small closed squares*) and serum C3 levels (*closed large circles*) are plotted against time in days. Indicated are the times of transplant, transplant biopsies, and transplant nephrectomy. Periods correspond to those in Table 1. The *dashed horizontal line* denotes the lower limit of the normal range for C3

(Fig. 1 and Table 1). NF activity rapidly fell posttransplant to reach 48 U/ml on the 12th day. On day 485, the transplant was biopsied. In the year before that biopsy (period 1 in Table 1), NF activity was relatively stable, varying between 22 and 42 U/ml, with a mean of 38 U/ml. The C3 level was slightly below the lower limit of the normal range (mean 74 mg/dl). Many of the urine samples during this period contained trace to 1+ amounts of protein and a small amount of occult blood. The biopsy showed mild proliferation of glomerular cells and a slight reduction in the number of open capillary lumens. Labeled anti-C3 gave a 1+ to 2+ linear fluorescence. Immunoglobulin G (IgG) was absent. The morphology was compatible with a mild recurrence of his MPGN type II.

A second biopsy was obtained 263 days after the first. During this interval (period 2, Table 1), NF activity increased on two occasions (Fig. 1). Two weeks after the first biopsy, the level was 115 U/ml. The event provoking this increase is not known. The second increase to 61 U/ml occurred 2 weeks before the second biopsy and corresponded in time to a respiratory infection, thought to be viral in origin, which was accompanied by a fever to 102.6°F. Over the 263 days before the second biopsy, NF activity, including the spikes, average 89 U/ml, considerably higher than before the first. It is noteworthy that the C3 level did not respond to the NF activity increase and remained at the lower limit of the normal range (mean 76 mg/dl). The biopsy showed that the disease had increased in severity. Open capillary lumens had fallen to an estimated 20%, and 30% of the glomeruli were involved with crescents, and 20% were nonfunctional because of scarring. Tubular atrophy and interstitial fibrosis were graded 1+.

During period 3, from the second biopsy until the transplant nephrectomy (Fig. 1), it was necessary to start

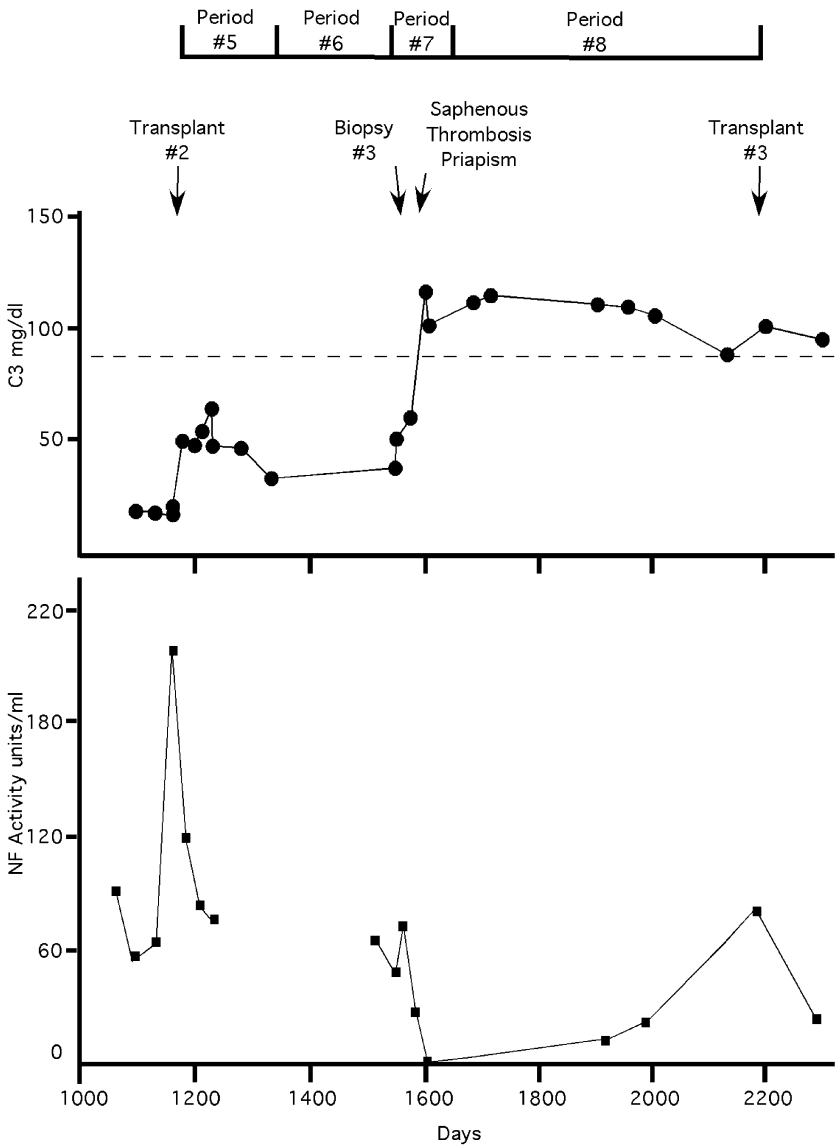

Fig. 2 Patient 1. Events after the second transplant. Nephritic factor activity and serum C3 levels are plotted as in Fig. 1 against days since the first transplant. Indicated are times of second and third transplants, transplant biopsy, and complications. Periods correspond to those in Table 1

dialysis. Peritoneal dialysis was started 110 days into this period and changed to hemodialysis after 44 days. About 2 weeks before peritoneal dialysis was started, there was another spike in NF activity to 107 U/ml. In 18 days, the level had dropped to 43 U/ml. Overall, NF activity was lower in this period compared with the previous (mean 50 vs. 89 U/ml), but the C3 level was again unchanged.

Because he was anephric, hemodialysis, which had started on day 854, continued during all of period 4. NF activity during this period averaged considerably higher than in the previous period, and now the C3 level was commensurately lower. There was a remarkable increase in NF activity to 212 U/ml of unknown cause in the last 7 days of this period just before he received his second transplant (Fig. 1).

At the start of period 5 (Fig. 2), he received a second kidney, this one of cadaveric origin, and his immunosuppression therapy included azathioprine, prednisone, and antilymphocyte globulin. NF activity started falling immediately and in 1 month had gone from 212 to 66 U/ml. During the remaining 20 weeks of this period, the average NF activity level was 89 U/ml, comparable to that in period 2 when there was a severe recurrence (Table 1). During this time, the C3 was relatively low, averaging 49 mg/dl, the urine was intermittently abnormal, and the serum creatinine was elevated between 1.1 and 1.3 mg/dl.

For the 28 weeks of period 6, data for NF activity and C3 levels are not available. The serum creatinine ranged from 1.0 to 1.3 mg/dl. The urine, however, became increasingly abnormal. During period 7, because of increasing signs of recurrence, the second transplant was biopsied. Histopathology, as before, showed marked glomerular proliferation and crescents. The kidney had been in place for a little over 1 year. Three weeks after this biopsy,

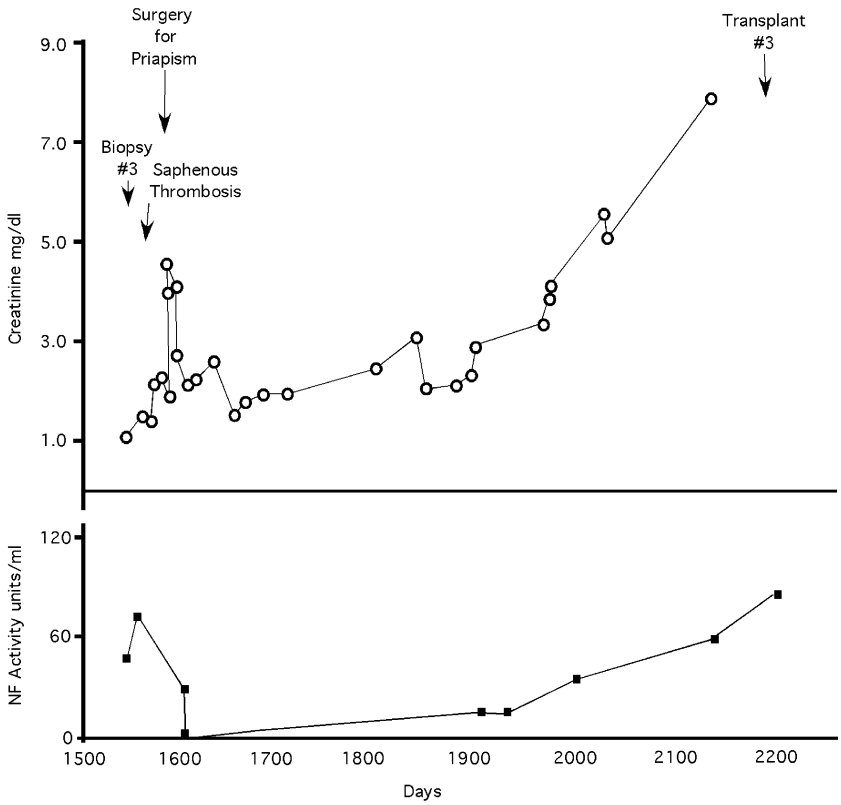

Fig. 3 Patient 1. Nephritic factor activity (*small closed squares*) and serum creatinine levels (*large open circles*) during periods 7 and 8 plotted against days since the first transplant. Times of third biopsy, third transplant, and complications are indicated. Note relatively constant creatinine levels, while nephritic factor activity is low, and increasing creatinine levels as nephritic factor activity increases

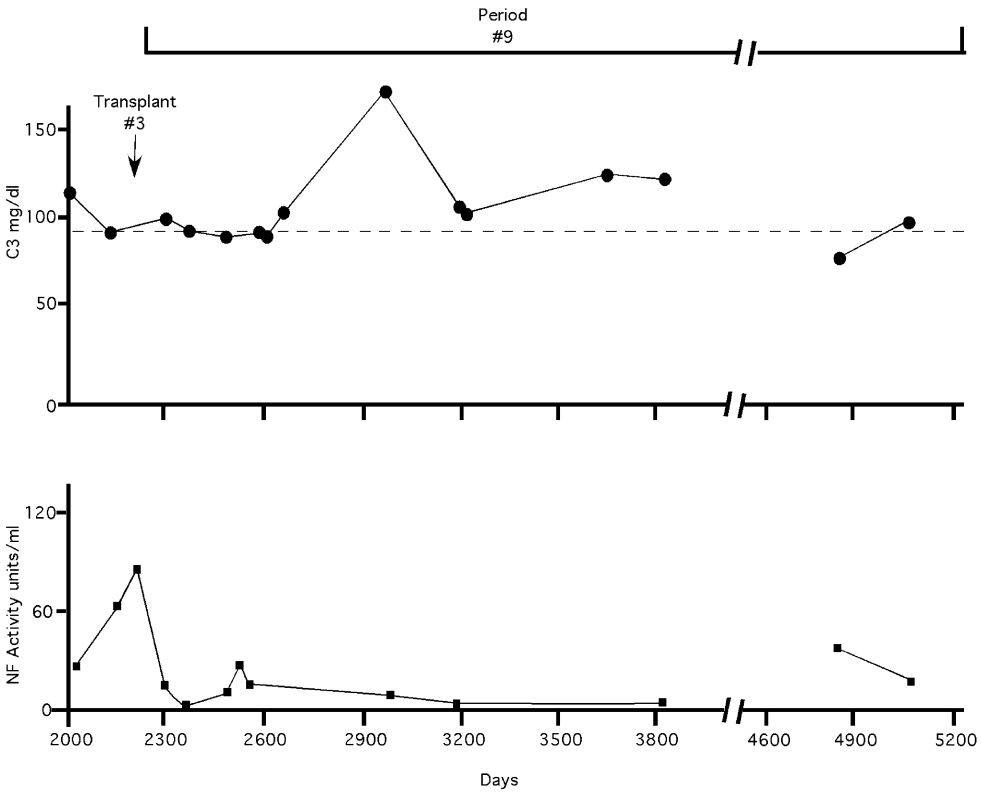

Fig. 4 Patient 1. Events after the third transplant. Nephritic factor activity and C3 levels are indicated as in Fig. 1. Graph encompasses period 9 (see Table 1)

Table 1 Course of patient 1 divided into nine periods

Period no. (duration, weeks)	Inclusive days and events	NF activity U/ml	Serum C3 mg/dl (range)	Clinical status
1 (68)	0–476 1st transplant to 1st biopsy	Mean, 38	Mean, 74 (70–83)	Biopsy evidence of mild recurrence
2 (38)	477–740 1st biopsy to 2nd biopsy	Mean, 89 (mean, 24 excluding two spikes)	Mean, 76 (62–89)	Biopsy evidence of severe recurrence
3 (33)	741–970 2nd biopsy to transplant nephrectomy	Mean, 50 (mean, 34 excluding one spike)	Mean, 76 (63–89)	Function continues to deteriorate
4 (26)	971–1,154 transplant nephrectomy to 2nd transplant	Mean, 101 (mean, 65 excluding terminal increase)	Mean, 22 (20–23)	On dialysis
5 (25)	1,155–1,328 after 2nd transplant	Mean, 89 (mean, 76 excluding posttransplant increase)	Mean, 49 (27–78)	Laboratory evidence of recurrence
6 (28)	1,329–1,523	No data	No data	Laboratory evidence of recurrence
7 (8)	1,524–1,578 to priapism	Mean, 52	Mean, 58 (42–61)	Biopsy 3 @ day 1,546 = severe recurrence
8 (87)	1,579–2,191 priapism to 3rd transplant	Mean, 13 during the first year, rising to 54 by 3rd transplant	Mean, 109 (90–118)	Laboratory evidence of recurrence (see Fig. 3)
9 (400)	2,192–5,054 after 3rd transplant	Fell from 54 to 8 in 100 days. Usually very low thereafter	Mean, 105 (76–163)	No recurrence for 14 years

he developed thrombosis of his right superficial saphenous vein. This was initially treated successfully but complications developed later. One of these, priapism, developed 12 days after the thrombosis and eventually had to be relieved surgically.

The eighth period encompasses the 1.7 years from the episode of priapism until the third transplant (Fig. 2). At the start of this period, NF activity spontaneously fell, initially to 2 U/ml, averaging 13 U/ml for all the following year. With the fall in NF activity, the C3 level promptly rose to well within the normal range. As shown in Fig. 3, during the year in which his NF level was low (first part of period 8), his serum creatinine remained relatively constant, but during the remaining 8 months of this period, both the serum creatinine and NF activity rose, with the serum creatinine reaching 8 mg/dl. However, NF activity rose to only 61 U/ml, considerably less than before the previous two transplants.

A search of the chart for a therapeutic modality that might have caused NF to fall to low levels was not revealing, and it seems very unlikely that heparinization, reportedly of value in the treatment of MPGN [13] but used in this patient for only 4 days ending 24 days before the NF level fell, would have been responsible.

Although he was very uremic at the end of period 8 (Fig. 2), he was not dialyzed because cadaveric kidneys from an anencephalic infant became available. His immunosuppression therapy again was azathioprine, prednisone, and antilymphocyte globulin. Posttransplant, NF activity fell to reach 8 U/ml in about 100 days (Fig. 4). It is of interest that the level fell even though at the time a number of surgical procedures were necessary on his right thigh, including repair of the femoral artery, evacuation of a hematoma, and drainage of an abscess. The level of NF activity remained generally low thereafter. A brief spike to 34 U/ml was recorded about 300 days posttransplant, and a level of 39 U/ml was present 8 years posttransplant. There were no clinically evident recurrences after his third transplant, so presumably, NF activity never attained the 40–90 U/ml range that earlier in his course was associated with severe recurrences. As would be expected from the absence of recurrences, most C3 levels obtained in the 8 years after this transplant were in the normal range. After day 3,400, he was seen only occasionally. These kidneys lasted for 14 years, at which time financial problems made it impossible for him to obtain medication and subsequently he refused all treatment.

Patient 2

Patient 2 had onset of nephritis at age 6 years. Details of his course were given previously ([12]; patient 2). Receiving prednisone and cyclophosphamide, he improved and was well for 4 years, except for continuing proteinuria. The relapse at age 10 years, did not respond to medication, and at age 11 years, he received a kidney from his father (Fig. 5). In the 12 weeks before the transplant, the C3 level was rising rapidly, but data for NF activity are not available for either the immediate pretransplant or for the immediate posttransplant periods. However, about 4 months after

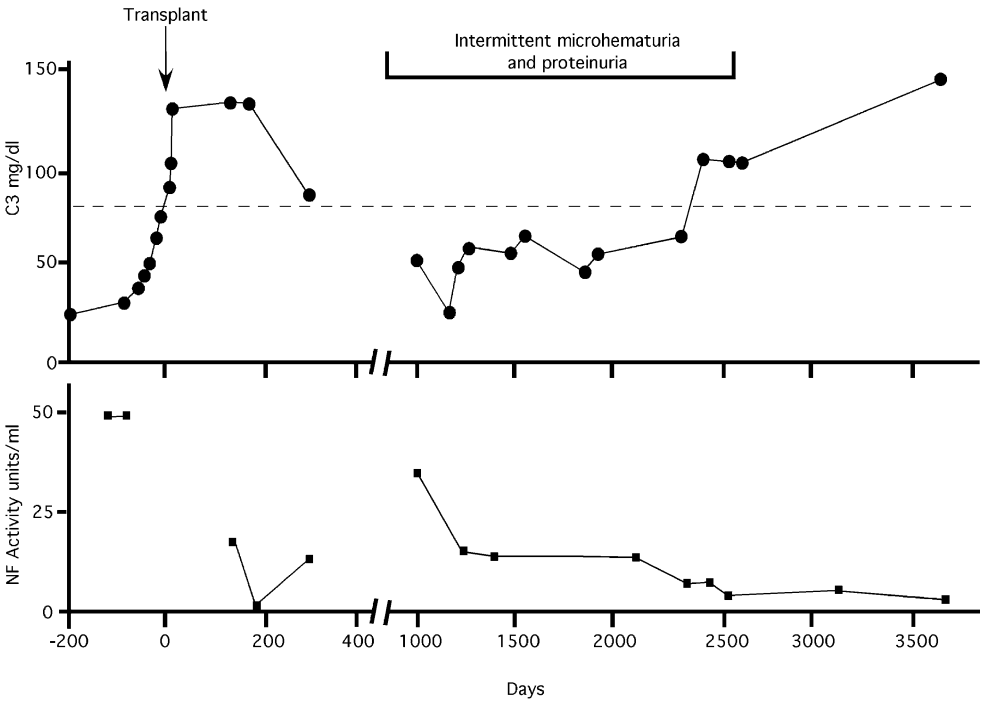

Fig. 5 Patient 2. Nephritic factor activity and serum C3 levels before and after his renal transplant plotted as in Fig. 1. Time of mild recurrence of disease, producing intermittent urinary abnormality, is indicated. Note differences in scale on the abscissa

transplant, NF activity was low and the C3 normal. At this time, he developed cytomegalovirus hepatitis, and his urine showed trace amounts of protein for 1 month. Data are not available for the next 2 years, but he recovered uneventfully from the hepatitis and was clinically well. Approximately 3 years after transplant, microhematuria and trace proteinuria were occasionally present. During the next 1,000 days, of 18 urinalyses, 12 showed a trace to 1+ amounts of protein, and intermittently occult blood was present. During this time, the C3 level was depressed, ranging from 24 to 72 mg/dl, and NF activity was in the 14–16 U/ml range. Although his medical regimen was not altered, NF activity eventually fell to the 4–6 U/ml range, and both the C3 level and urine became normal. Over the next 3 years, NF activity ranged from 4–7 U/ml, and there was no evidence of a recurrence. Over the 27 years to the present, he has been well.

Patient 3

Patient 3 developed nephritis at age 4.5 years and ESRD at age 17.5 years. NF activity was low pretransplant and was unaffected by nephrectomies or dialysis 2 weeks before transplant (Fig. 6). The C3 level was depressed more than would be predicted from the level of NF activity. Data for NF activity are not available for about 12 weeks posttransplant, but during this time, her C3 level was mildly depressed. On the 75th day, she began complaining of leg

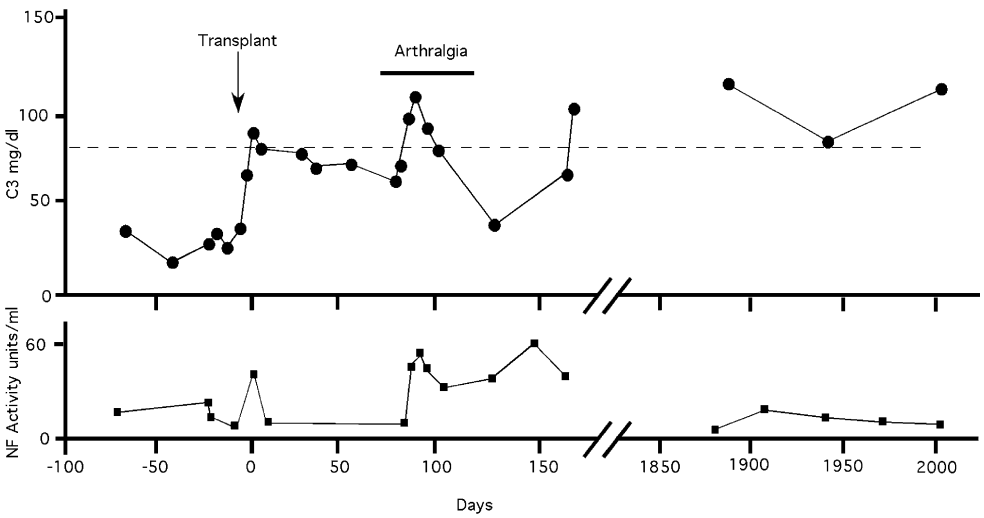

Fig. 6 Patient 3. Nephritic factor activity and serum C3 levels plotted as in Fig. 1 before and after renal transplantation. An episode of arthralgia is indicated. Note differences in scale on the abscissa

and back pain, and 10 days later was admitted for diagnostic studies. After she had been symptomatic for 17 days, NF activity rose from the 10–20 range to the 31–62 U/ml range and remained elevated for 83 days. She was symptomatic for a total of 50 days, but the NF elevation continued for 50 more days. The C3 level initially fell very slowly in response to the NF increase. The cause of her arthralgia was not determined. When seen 5 years after the transplant, NF activity was still very low, and C3 was in the normal range. Over this 5-year period, there was no sign of a relapse. She kept the kidney for 17 years. The cause of its loss is unknown.

Discussion

A number of criticisms can be made of this study. Not only is it essentially of a single patient, but the serum specimens were not collected according to a protocol. Specimens that would be informative are missing. In addition, because specimens were collected in a somewhat random manner, they may not be truly representative. These deficiencies should be borne in mind in judging the data. It should, however, be noted that the observations do have a number of internal consistencies, and the observations in several respects parallel those made on MPGN type II patients with their native kidneys.

Several observations on these patients appear valid and can be summarized as follows. The observations support the conclusions derived from animal studies that a perturbation of the complement system such as that produced by NF can be nephritogenic. They suggest that spikes of NF activity produce glomerular damage but they are not adequate to ascertain the cause of these spikes. The level of C3 responds slowly to changes in NF activity, and in individual serum specimens, the correlation between NF and C3 is poor. Most importantly, the data reinforce unpublished observations from this laboratory that low levels of NF activity and the resulting only moderate depression of C3 are more nephritogenic than very high levels of NF and very low levels of C3. A basis for this seeming paradox will be proposed.

Several observations in the study confirm the nephritogenicity of NF. Most striking was the course of patient 1. After his third transplant, the level of NF activity seemingly spontaneously dropped and remained low, except for mild elevations that were apparently not sustained, and for 14 years, his disease did not recur. In contrast, after each of his two previous transplants, NF activity had been higher for long intervals, and the kidneys each survived for only 2 years.

Another observation suggesting that NF is nephritogenic is the rough correlation between its level and the severity of the recurrence. Thus, in patient 1, a mean NF activity level of 38 U/ml was accompanied by a very mild nephritis (period 1), whereas it took levels approaching 90 U/ml to produce a severe nephritis (Table 1).

A correlation between NF activity and glomerular damage also can be seen in period 8 of patient 1. This patient had damaged glomeruli from a recurrence immediately posttransplant. Suddenly, however, NF activity fell and remained low for a year. During that year, the glomerulonephritis did not progress, as attested by rather constant serum creatinine levels (Fig. 3). As NF activity subsequently rose, the serum creatinine rose in parallel.

Although the data is meager, the above suggests that at these comparatively low levels of NF activity, a 30% or greater increase will amplify a recurrence, taking it from mild to severe. Thus, in patient 1 period 1, the recurrence was mild, with NF activity averaging 38, but severe in period 3, when NF activity averaged 50.

The averages calculated for NF activity in Table 1 correlated best with the presence and severity of the recurrences if values during spikes were included. It will be noted that the table contains averages that both include and exclude the spikes. If further study confirms that spikes greatly augment nephritogenesis, it becomes important to know their origin. One spike occurred concurrently with a respiratory infection in period 2. NF activity went to 61 U/ml. Two other episodes of respiratory infection are mentioned in the chart, but corresponding spikes were not seen, perhaps because blood was not drawn at the right time. A spike to 75 U/ml occurred 7 days after the beginning of the saphenous vein thrombosis. Earlier specimens are not available. Several spikes were unaccounted for. It is attractive to assume that the spikes are part of an acute-phase reaction. This seems logical for the spike accompanying a respiratory infection in period 2, but its applicability to the increase in NF activity occurring with the arthralgia experienced by patient 3 is not clear. The elevation occurred some time after the arthralgia started and continued for a time after she became asymptomatic. Thus, the correlation between the two is poor. A protocol study will be necessary to determine the effect of intercurrent infections on NF activity.

Even more problematic are the elevations in NF activity seen in the days before a transplant. In the 2 weeks before the first transplant in patient 1, NF activity was consistently elevated to as high as 187 U/ml. The week before the second transplant, the level reached 212 U/ml. For the month before the third transplant, data are lacking. Several questions can be asked about this phenomenon. Does the elevated NF activity occur in all patients pretransplant? These data are not available for patient 2, and the levels are not recorded as elevated in patient 3. Thus, the elevations may be unique to patient 1. Their origin is not known, although in patient 1, they may be in some way related to

both hemo- and peritoneal dialysis. It could also be asked whether there should be concern if NF activity is high at the time of transplant. Would the elevation initiate a recurrence in the newly transplanted kidney? The data suggest that this should be a concern. If one assumes from the data of Table 1 that a NF activity level of approximately 90 U/ml can cause a severe recurrence, one would not have predicted an early recurrence after the first transplant when this level was present or exceeded for only 12 days. After the third transplant, this level was never attained. However, after the second, when there was an early recurrence, the level was above 89 for 26 days. Although data are meager and confined to experience with one patient, they do raise a concern about transplanting patients with moderate levels of NF activity.

The above-mentioned fall in NF activity after the first and second transplants could well be an effect of the high posttransplant doses of immunosuppressive agents. This regime after the second transplant contained antilymphocyte globulin but only azathioprine and prednisone after the first. The slow fall in NF activity after the second transplant suggests that the antilymphocyte globulin used did not influence the level of NF activity.

It was shown many years ago [14] and again recently [10] that C3 and NF activity levels correlate poorly. A poor correlation was also seen in several instances in our study. Thus, in periods 1, 2, and 3 in patient 1, C3 levels remained relatively constant as NF activity rose and the recurrences became more severe. On the other hand, there are a number of places where C3 changes were appropriate for the changes in NF. It should be noted also that on occasions in which the C3 level did change in a direction appropriate to the change in NF activity, the response could be very slow. The decoupling of C3 and NF activity levels, when considered in the light of the great speed with which C3 is converted by stabilized convertase in vitro [15], suggests that in vivo there are a number of factors modulating this conversion.

One of the important contributions of this study is the recognition that relatively low levels of NF activity can produce severe glomerular damage. This has also been noted in this clinic in patients with their native kidneys. Two had persistently low levels of NF activity with only moderately depressed C3 levels. One developed ESRD in 2.5 years and the other in 14 years. In contrast, another patient had, over many years, NF activity levels at times reaching 500 U/ml and very low C3 levels. Her renal function remained normal despite several pregnancies. It is well known that patients with partial lipodystrophy can be severely hypocomplementemic for long periods without manifesting MPGN [16].

A basis for the inverse correlation between the level of NF activity and the severity of the nephritis becomes apparent when events in the mesangium are considered. An inflammatory reaction in the mesangium leading to mesangial sclerosis is thought to be basic to the disease and that NF, by generating C3b from native C3, could be the proximate cause of the inflammation. C3b bears a metastable binding site with a half life measured in milliseconds [17], which, nevertheless, forms a strong bond with a number of structures [18]. Clusters of bound C3b can activate C5 to form the membrane attack complex, C5b-9 [19], which causes cellular injury. The fraction of C3b that does not reach a binding site is converted to inactive C3b (iC3b) and further to C3c and C3dg.

C3 and NF enter the mesangium via fenestrae in the endothelial cells as constituents of plasma [20]. Two factors could determine the fraction of the entering C3 that is converted to C3b and eligible to bind to and injure mesangial structures. Most important would be the ratio of NF to C3. NF is not altered by its reaction with convertase and recycles [21]. Therefore, its concentration in the mesangium should closely approach that of plasma, regardless of the rate of mesangial flow. C3, on the other hand, is depleted by the stabilized convertase. Depletion would be rapid if its concentration is low and that of NF high. Thus, severely hypocomplementemic patients would have low rates of mesangial C3b deposition, and therefore, their nephritis would be mild. On the other hand, C3 would persist in the mesangium at all mesangial flow rates if NF is low and, as a result, C3 relatively high. Thus, relatively low NF levels (as seen in patient 1, periods 2 and 5, Table 1), by insuring the constant presence of C3 in the mesangium, would foster C3b deposition and therefore be more damaging. A second factor would be the degree of loculation of the mesangium. With increasing proliferation, loculation would increase. Assuming mesangial flow continues, the result would be that the distance between the site of C3b formation by a stabilized convertase and a site where the C3b could bind would diminish, resulting in fewer C3b molecules decaying and more depositing. Thus, the proliferative effect of the high rate of C3b deposition produced by high C3 and relatively low levels of NF activity would in itself foster more C3b deposition and augment disease progression.

The effectiveness of low levels of NF in producing nephritis probably explains the two patients of Leibowitch et al. [6] who developed intramembranous-dense deposits posttransplant without signs of complement activation. The crossed immunoelectrophoresis used by the authors to measure NF is relatively insensitive to low levels.

If moderately low levels of NF are most nephritogenic, it would follow that therapy, which only partially reduces the level of NF activity in the severely hypocomplementemic patient, could activate the disease. If this proves to be the case, either the dose should be such that NF rapidly disappears or some other therapy should be developed.

As a final comment, it would be gratifying to say that management of patient 1 would have been easier and success would have come quicker if NF measurements had been available. This, however, seems unlikely, in view of the therapeutic modalities available at that time. NF measurements will be most valuable for testing therapies that have the potential of eliminating this autoantibody. The availability of such therapy would make NF measurement essential in the management of these patients.

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