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# A Case of Recurrent Proliferative Glomerulonephritis with Monoclonal IgG Deposits after Kidney Transplant Treated with Plasmapheresis

Andrea Ranghino<sup>a</sup> Michela Tamagnone<sup>a</sup> Maria Messina<sup>a</sup>  
Antonella Barreca<sup>b</sup> Luigi Biancone<sup>a</sup> Bruno Basolo<sup>c</sup>  
Giuseppe Paolo Segoloni<sup>a</sup> Gianna Mazzucco<sup>b</sup>

<sup>a</sup>Division of Nephrology Dialysis and Transplantation, Department of Internal Medicine, San Giovanni Battista Hospital and University of Torino, <sup>b</sup>Department of Biomedical Sciences and Human Oncology, University of Torino, and <sup>c</sup>Nephrology and Dialysis Unit, San Giovanni Bosco Hospital, Torino, Italy

## Key Words

Glomerulonephritis · Monoclonal IgG · Plasmapheresis · Recurrence

## Abstract

Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a rare and recently identified disease with a poor prognosis irrespective of the treatment. Recently, the possibility of recurrent or de novo PGNMID after kidney transplantation has been reported, which is associated with a better prognosis compared to PGNMID on native kidneys. Nevertheless, at present, due to the very few cases of recurrent PGNMID diagnosed, there is no proven effective treatment. Here, we report a case of recurrent PGNMID successfully treated with plasmapheresis, steroids and mycophenolate mofetil. Our report suggests that plasmapheresis might be a valid therapeutic option to treat recurrent PGNMID.

## Background

Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a rare and recently identified disease described by Nasr et al. [1] in 2004. The incidence of PGNMID in native kidneys is about 0.17% [2]. Diagnosis of PGNMID should be considered in the presence of monoclonal IgG deposition with a glomerular pattern that cannot be assigned to any of the established renal diseases related to dysproteinemia.

Histological patterns in PGNMID include membranoproliferative glomerulonephritis (GN; 56.8%), endocapillary proliferative GN (35.1%) and membranous GN (5.4%). In addition, crescents are described in 32% of cases [2]. By immunofluorescence (IF), the glomerular deposits are monoclonal and with positive staining for a single light-chain isotype and a single heavy-chain subtype IgG, frequently associated with C3 and C1q. Despite various therapeutic approaches, including steroids and immunosuppressive agents, the prognosis appears to be poor [2, 3]. Recently, the possibility of development of recurrent or de novo PGNMID after kidney transplantation has been reported [4, 5].

Here, we report a case of recurrent PGNMID in a transplanted patient treated with plasmapheresis, mycophenolate mofetil (MMF) and steroids.

## Case Report

A 66-year-old Caucasian woman was admitted to the hospital with fever, oliguria and hypertension developed 1 month after an episode of upper airway infection. On admission, blood pressure was 190/85 mm Hg, and body temperature was 37.4°C. The physical examination revealed pretibial edema, and the initial serum creatinine (sCr) was 3.2 mg/dl. Urinalysis showed dysmorphic erythrocytes 40 cells/400× field, leukocytes 40 cells/400× field and granular casts. Urine culture was negative, and the 24-hour proteinuria was 3.6 g. ANCA, ANA and Abs anti-dsDNA were negative, cryoglobulins were absent, and C3 was low. A renal biopsy revealed an unclassifiable endocapillary proliferative GN with cellular crescents (16/27 glomeruli; [fig. 1a, b](#)) and global sclerosis (3/27 glomeruli) associated with inflammatory infiltrate of the interstitium. IF staining showed diffuse IgG (2+), C3 (3+) and C1q (2+) deposits in the mesangium and in the subendothelial sites.

On the basis of the knowledge at the time of biopsy, a diagnosis of immune complex-mediated GN was made. Consistently, a therapy with steroid pulses (methylprednisolone 1 g/day, 3 boluses in total) and oral cyclophosphamide (50 mg/day) was started. Nevertheless, the treatment failed to improve renal function, and the patient started dialysis a few days later.

After 3 years, the patient underwent kidney transplantation from a deceased donor. Immunosuppressive treatment was based on basiliximab 20 mg on day 0 and day 4, tacrolimus (trough level 12–15 ng/ml in the first month, 10–12 ng/ml until the end of the third month, subsequently tapered to 8 ng/ml), MMF (1 g twice daily for the first month, then stopped) and steroids (maintenance dose 5 mg/day). At the time of discharge, the graft function was normal (sCr 0.69 mg/dl), and the proteinuria was absent.

Eighteen months after transplantation, sCr rose to 2 mg/dl with the appearance of proteinuria (3.3 g/day). ANCA, ANA, Abs anti-dsDNA and cryoglobulins were negative, and C3 was low. Interestingly, the renal biopsy revealed the same histological and IF patterns documented on native kidneys ([fig. 1c–e](#)). In addition, a positive IF staining for single light-chain isotype  $\kappa$  and the presence of large finely granular electron-dense deposits without structure on electron microscopy were detected ([fig. 1g](#)). A retrospective study of the native kidney biopsy showed identical IF positivity for single light-chain isotype  $\kappa$  ([fig. 1f](#)) and the same electron microscopy finding with large mesangial and parietal electron-dense deposits ([fig. 1h](#)). A bone marrow biopsy excluded a lymphoproliferative disorder.

Overall, these findings allowed us to diagnose PGNMID on the graft and, consequently, to revise the diagnosis made on the native kidneys due to the similarity of the morphological features. On the basis of this revision, a diagnosis of recurrent PGNMID was made. The lack of proven effective therapeutic approaches for PGNMID and the failure of the therapy previously used on native kidneys led us to treat the patient with plasmapheresis and immunoglobulin (0.5 g/kg/day) in association with steroid pulses (methylprednisolone 4 mg/kg/day, 850 mg in total) and MMF 1.5 g/day. After the treatment, sCr and proteinuria dropped to 1.1 mg/dl and 0.2 g/day, respectively.

A protocol biopsy performed 3 months later showed a focal and segmental mesangial proliferation with disappearance of the endocapillary proliferation and cellular crescents ([fig. 2a, b](#)). Nevertheless,

IF staining for IgG, C3, C1q and single light-chain isotype  $\kappa$  remained positive only in the mesangium (fig. 2c, d).

Six months later, the patient was hospitalized in the intensive care unit because of a respiratory failure requiring endotracheal intubation associated with a worsening of the graft function and fever. A CT scan of the chest revealed a severe pulmonary vascular congestion. Due to the unresponsiveness to the diuretic, hemodialysis was started together with empiric antibiotic therapy. A renal biopsy was not performed because of the increased risk of bleeding due to the abnormal coagulation tests. Thus, treatment with steroid pulses (methylprednisolone 500 mg/day for 3 days) was started in order to treat a possible episode of acute rejection and/or a further recurrence of PGNMID. Because of the failure of the steroid treatment and the persistence of a life-threatening disease, the immunosuppressive therapy was stopped.

In the following 2 weeks, the patient showed a persistence of symptoms and signs putatively related to an acute rejection (fever, anuria and high arterial resistance index with absence of renal artery stenosis measured by Doppler ultrasonography) in combination with a significant worsening of the respiratory failure in the context of an ongoing multiple organ failure. The persistence of life-threatening conditions along with the absence of functional improvement of the graft following a rescue therapy with steroid pulses led us to consider that the resume of the immunosuppressive treatment involved too much risk for the patient.

Therefore, in order to give the patient the best chance of survival, after more than 3 weeks without improvements in graft function, we decided to perform a transplant nephrectomy. Unexpectedly, the histology of the graft displayed a large number of normal glomeruli and only few glomeruli (4%) with a low degree of mesangial and/or extracapillary proliferation without signs of acute rejection (fig. 2e, f). A severe tubular necrosis was also present. Few days after transplant nephrectomy, the patient's clinical conditions improved, and she is still doing well after 1 year of follow-up.

## Discussion

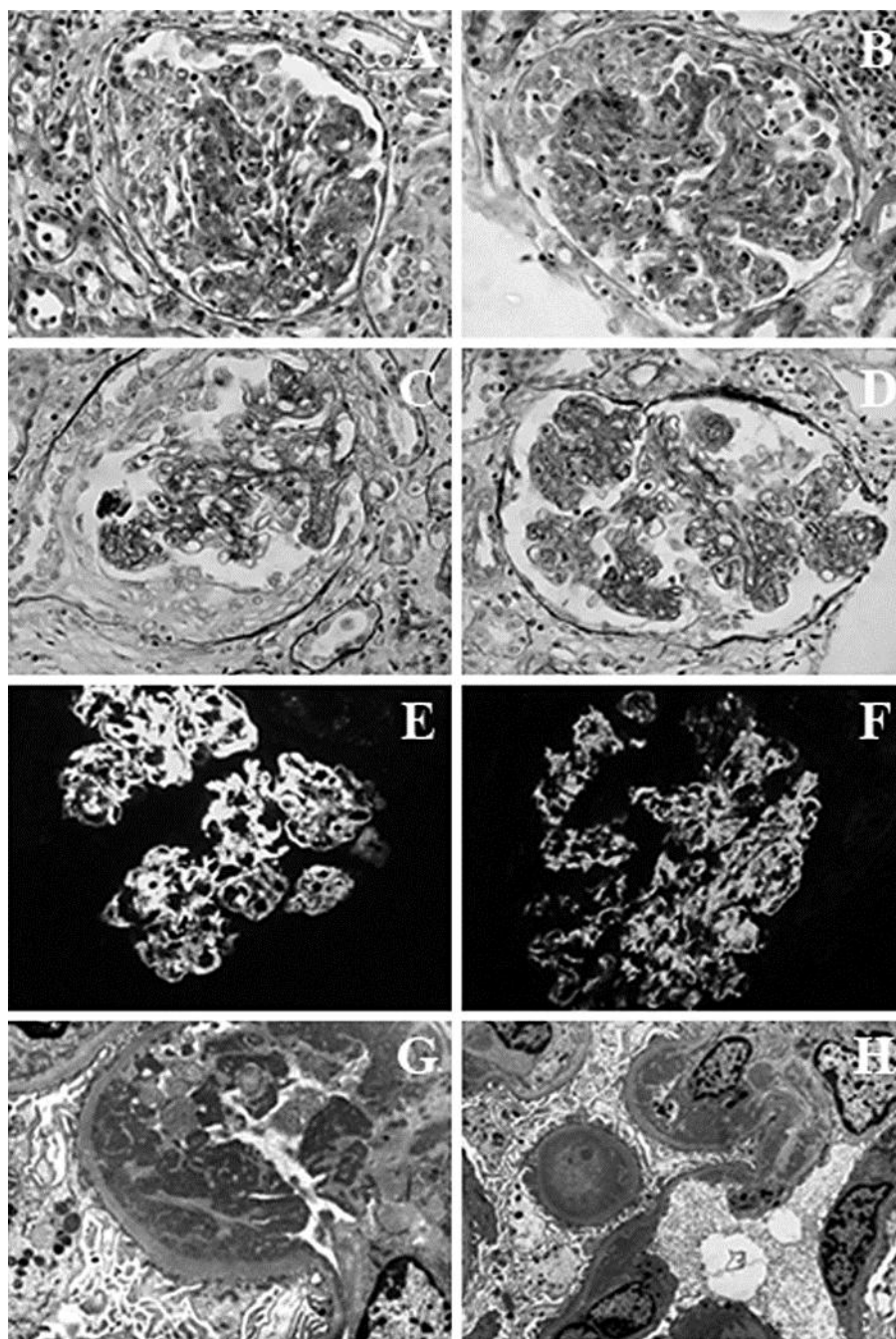
PGNMID is a rare entity described for the first time in 2004 [1]. Clinically, the disease includes proteinuria, hematuria and frequent renal insufficiency [2]. The prognosis of PGNMID in native kidneys is poor (25% of the patients undergo dialysis less than 3 years after the diagnosis) [2]. Recently, 6 cases of recurrent PGNMID have been described after kidney transplantation [4, 5]. These cases seem to have a better prognosis compared to the disease in native kidneys, probably due to the use of an immunosuppressive therapy [4]. Nevertheless, there are only a few patients with recurrent PGNMID, and the therapeutic approaches variegated (steroids, cyclophosphamide and rituximab) [4, 5]. At present, there is no proven treatment for recurrent PGNMID. Recently, Albawardi et al. [5] described the possibility of de novo PGNMID on kidney allograft with a late onset compared to the recurrent disease. In addition, 2 cases of PGNMID associated to chronic lymphocytic leukemia have been described. These cases were successfully treated with rituximab, suggesting that the depletion of CD20+ lymphocytes might be effective [6]. In our case, symptoms related to glomerular damage (proteinuria and worsened graft function) confirmed by renal biopsy developed later compared to the mean age of recurrent PGNMID reported in the literature (18 months vs. 3.8 months, respectively) [4]. A possible pathogenesis of PGNMID suggested by Nasr et al. [2] involved a clonal proliferation of B lymphocytes or plasma cells that hypersecrete abnormal IgG capable of self-aggregation and deposition in the glomerulus. According to this hypothesis, we treated the patient with plasmapheresis in order to remove the abnormal IgG. In addition, to reduce the proliferation of the B cells, we introduced MMF. Treatment with plasmapheresis could also be considered applicable in our case because of the presence of cellular crescents

found in 18% of the glomeruli [7]. Even though rituximab could be a rational therapeutic approach for PGNMID, we thought that in our case rituximab was not justified as first-line treatment because of (i) the high risk of fatal infectious disease associated with the use of rituximab in transplanted patients [8], (ii) the potential risk of new onset of CD20-negative lymphoma and solid tumors [9, 10] and (iii) the absence of a primitive lymphoproliferative disorder.

Our case suggests that plasmapheresis associated with MMF and steroids might be a valid therapeutic option in the induction of clinical and histological remission of PGNMID. The reappearance of slight glomerular signs compatible with an initial relapse of PGNMID 6 months after treatment raises the question whether more courses of plasmapheresis are needed in order to maintain a lasting remission.

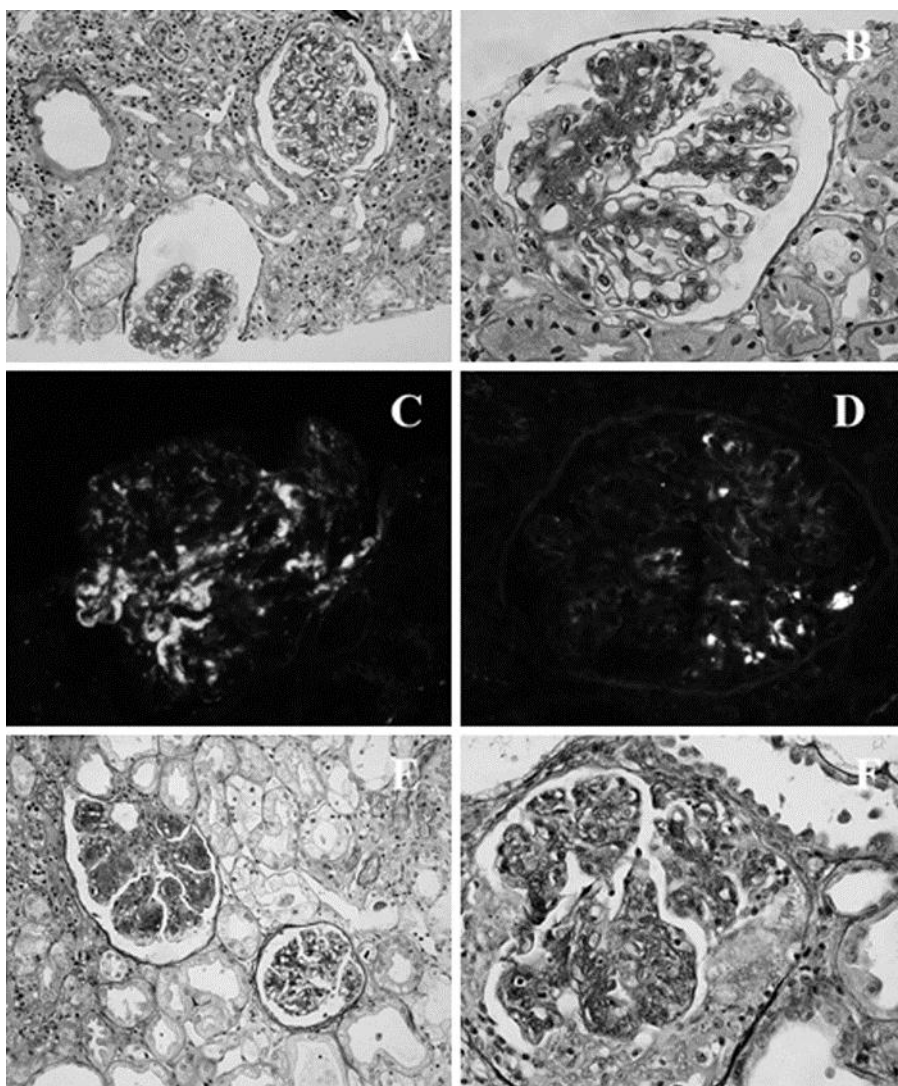
### **Disclosure Statement**

None of the authors have a conflict of interest to declare.



**Fig. 1.** **A, B** Histology of the native kidney. The glomeruli show segmental cellular crescent (**A, B**) and diffuse endocapillary hypercellularity (**B**). **C, D** Histology of the graft (first biopsy). The glomeruli show the same pattern found on the native kidneys with extracapillary proliferation (**C**) and endocapillary proliferation (**D**; periodic acid-Schiff; original magnification  $\times 400$ ). **E** IF performed on the graft (first biopsy) shows a strong granular capillary staining of the glomerulus in the mesangium and in the subendothelial sites (IgG, original magnification  $\times 400$ ). **F** A similar pattern was found on the native kidney (single light-chain isotype  $\kappa$ , original magnification  $\times 400$ ). **G** Electron microscopy from the first transplant biopsy shows large granular subendothelial electron-dense deposits (original magnification  $\times 5,200$ ). **H** Electron microscopy of the native kidney shows the same pattern with subendothelial and mesangial electron-dense deposits (original magnification  $\times 3,000$ ).





**Fig. 2.** **A, B** Histology of the graft (second biopsy) after plasmapheresis treatment show less disease activity. The glomeruli show only a segmental mesangial hypercellularity (periodic acid-Schiff; original magnification  $\times 400$ ). **C, D** IF performed on the graft (second biopsy) displays only a slightly segmental mesangial staining of the glomerulus (IgG, original magnification  $\times 400$ ). **E, F** Representative images of the histology of the graft after transplant nephrectomy showing one normal glomerulus and one with mesangial hypercellularity (**E**), and one glomerulus with segmental cellular crescent (**F**; periodic acid-Schiff; original magnification  $\times 400$ ).

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