PGNMID and anti-CD38 monoclonal antibody: a therapeutic challenge

Nefrologo in corsia

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ABSTRACT
Monoclonal gammopathy of renal significance (MGRS) designates disorders induced by a monoclonal protein secreted by plasma cells or B-cell clones in patients who do not meet the diagnostic criteria for multiple myeloma or other B-cell malignancies. Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a form MGRS.
Until now, no guidelines to decide the best therapeutic approach to manage PGNMID exist, and most patients progress to End Stage Renal Disease (ESRD) without therapy. Recently, daratumumab has showed an acceptable improvement in proteinuria and renal function in patients with PGNMID.
We report the clinical outcome and the histological renal evolution and treatment complication of our patient, who was initially treated with a combination regimen including bortezomib, dexamethasone, and cyclophosphamide and then with anti-CD38 monoclonal antibody-based regimen.

PAROLE CHIAVE: monoclonal gammopathy of renal significance, proliferative glomerulonephritis with monoclonal immunoglobulin deposits, histological evaluation, pharmacological therapies, case report

Introduction

Monoclonal gammopathy of renal significance (MGRS) designates disorders induced by a monoclonal protein secreted by plasma cells or B-cell clones in patients who do not meet the diagnostic criteria for multiple myeloma or other B-cell malignancies. MGRS was defined by the *Kidney* and Monoclonal Gammopathy Research Group (IKMG) in 2012 [1] and is classified by the site of the dominant immunoglobulin deposition or even by the ultrastructural findings on renal biopsy. It is important to mention that while light chains and truncated heavy chains can affect all renal compartments, intact immunoglobulin molecules are limited to the glomerulus [1–2].

Renal damage due to nephrotoxic monoclonal immunoglobulin (MIg) or its light- or heavy-chain fragments include some disorders, such as cast nephropathy, amyloidosis, MIg deposition diseases, immunotactoid glomerulopathy, proliferative GN with monoclonal Ig deposits, light-chain proximal tubulopathy, and the rare entities of crystal-storing histiocytosis and crystalglobulinemia. C3 glomerulonephritis and *Thrombotic* Microangiopathy (TMA) due to dysregulation of the alternative complement pathway can be seen as a result of indirect mechanisms induced by immunoglobulins [2].

Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a form of monoclonal gammopathy of renal significance (MGRS) often leading to end-stage kidney disease [3]. In 70% of cases no blood or bone marrow monoclonal immunoglobulins are detected [3].

In PGNMID, deposits are detected in the glomeruli, especially in mesangial and subendothelial space and occasionally in the subepithelial space [4]. In most patients, PGNMID is IgG3-driven, but it can also be IgA-driven or IgM-driven [5].

Plasma cell-derived PGNMID (usually IgG) is treated with bortezomib-based chemotherapy; B-cell-derived PGNMID is usually treated with a rituximab-based regimen [6]. The patients with PGNMID may have plasma cell clones that produce monoclonal proteins, which elicit inflammation. Recently daratumumab showed an acceptable improvement in proteinuria and renal function in patients with PGNMID [7].

Herein we report the clinical outcome and the histological renal evolution and treatment complication of our patient, who was initially treated with a combination regimen including bortezomib, dexamethasone, and cyclophosphamide and then with anti-CD38 monoclonal antibody.

Case report

We report the case of a 66-year-old white man with a history of JAK2 mutation-negative essential thrombocythemia, on cytoreductive therapy with anagrelide, who presented with proteinuria in the nephrotic range. At presentation urinalysis showed 40 RBCs/µL, albuminuria 100 mg/dl and proteinuria 4.3 gr/day. Serum creatinine was 1.8 mg/dL, calcium 8.7 mg/dl, hematuria with 40 RBC, serum immunofixation did not detect any abnormalities and protein electrophoresis showed hypogammaglobulinemia, IgG 508 mg/dl, negative Bence Jones and negative urine immunofixation revealed monoclonal IgA k (87 mg/24 h) and a mild increase in serum kappa free light chain with normal kappa/lambda ratio. A kidney biopsy was performed (Figure 1) and showed a 30% of fibroepithelial crescent cell, 4% epithelia crescent cell and single fibrinoid necrosis. Immunofluorescence showed positive diffuse staining for IgA (3+), C3 (2+) and k-light chain (3+) involving the basal membrane in intramembranous and subepithelial region and the mesangium, with negative staining for λ-light chain and for heavy chain. The ultrastructural evaluation

highlighted subendothelial and mesangial electron dense deposits. Therefore, we reached a diagnosis of proliferative glomerulonephritis with monoclonal IgA-kappa deposits without interstitial fibrosis, with mild tubular atrophy [7].

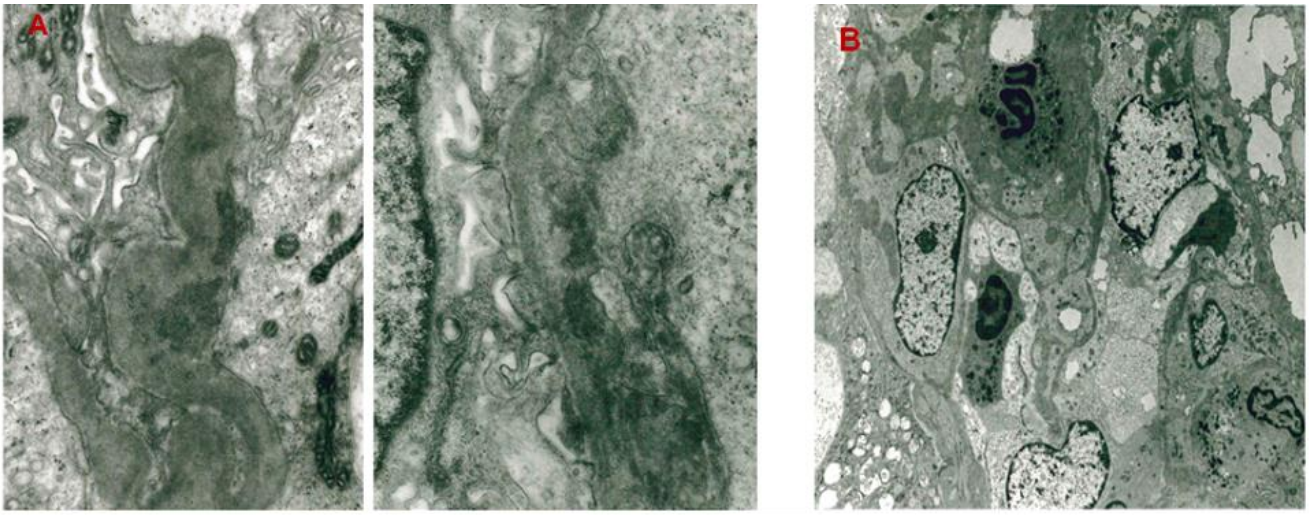

Figure 1: Renal Biopsy. Photo A: electron microscopy, electron-dense deposits with focally variegated texture (without evidence of well-developed microtubules or fibrils) located in subendothelial area (original magnification ×14,000); photo B: electron microscopy: endocapillary hypercellularity filled by swollen endothelial cell, monocyte and neutrophil granulocyte (original magnification ×1900)

Bone marrow aspiration and biopsy with fluorescence in situ hybridization detected essential thrombocythemia with mild fibrosis MF-1 and presence of 8% κ-restricted plasma cells, considered as monoclonal gammopathy of undetermined significance (MGUS). Whole-body, CT bone scan showed erosive lesions of the temporal bone extended for 3 cm, non-ossifying fibromas (NOF) of the distal epiphysis of the right femur. Consequently, the diagnosis of MRGS was made and chemotherapy with CyBorD regimen (Bortezomib, Dexamethasone and cyclophosphamide) was started. The treatment schedule included 8 cycles of Bortezomib, Dexamethasone and cyclophosphamide with the following doses: cyclophosphamide 350 mg per os on days 1, 8, 15 + bortezomib 1.3 mg/m2 subcutaneously on days 1, 8, 15, 22 + dexamethasone 20 mg per os on days 1, 8, 15,22, each of these for 35 days.

Acyclovir, fluconazole and trimethoprim-sulfamethoxazole was added to the therapy as prophylaxis and after 4 weeks trimethoprim-sulfamethoxazole was withheld due to an allergic reaction.

After the first 4 cycles of therapy, a mild renal improvement was achieved. The serum creatinine decreased to 1.4 mg/dl with a partial reduction of proteinuria up to 3100 mg/24h and a reduction of monoclonal IgA k from 87 to 50 mg/24h. After 6 months of chemotherapy, osteolytic lesions on the sphenoid greater wing were detected on CT bone scan. After 8 cycles of CyBorD chemotherapy, at the 12th month of follow up: monoclonal IgA remained constant and under 50 mg/24h in urine immunofixation; serum free kappa light chain concentration was 32.9 mg/l and serum free light chain lambda was 14.7 mg/l (k/λ ratio = 2.2); a non-monoclonal component was detected in protein electrophoresis, while mild deterioration of renal function (cr: 2.3 mg/dl) without reduction of proteinuria was observed.

During the first 12 month of follow up no adverse effects related to the cytotoxic therapy were observed. At this time another evaluation with BMA and CT bone scan was programmed. The bone marrow aspirate and the biopsy were examined with light microscopy, immunohistochemistry, and flow cytometry, showing the presence of 10% κ-restricted plasma cells, considered as MGUS, with mild fibrosis MF-1. No new bone lesions were detected in the CT scan.

Based on radiological and histological findings, associated with progressive renal impairment (an increase of serum creatinine up to 4.1mg/dl with constant proteinuria nearly 4 gr/day), the second line treatment with Daratumumab-Lenalidomide plus Dexamethasone (D-Rd) was scheduled.

D-Rd regimen chemotherapy was started, despite the stable hematologic disease. The Daratumumab regimen consisted in an intravenous (IV) dose of 16 mg/kg once a week for 8 weeks, followed by the same dose once every 2 weeks plus lenalidomide and dexamethasone (for eight additional doses).

After one month of therapy with D-Rd regimen (4° administration) the patient was admitted to our hospital because of a rapidly progressive loss of renal function and nephrotic syndrome. Lower extremities petechiae were found on physical examination, with pitting edema in the lower limbs.

At admission, ultrasound examination evidenced the normal size of the inferior vena cava with a 40% collapsibility index, and mild bilateral pleural effusion; both kidneys had normal size and normal parenchymal thickness, with normal arterial and vein vascularization without hydronephrosis. Blood and urinary exams showed a progressive renal impairment with increase of creatinine up to 8.7 mg/dl and urea around 270-290 mg/dl, proteinuria increased to 5.5 gr/24h, Hb 8 gr/dl, albumin 1.9 gr/dl, calcium 6.9 mg/dl, magnesium1.3 mg/dl, sodiuria 47 mmol/l, creatinuria 114 mg/dl, procalcitonina 0.4 (normal range <0.5). They also evidenced normal complement C3 and C4 levels, negative cryoglobulins, and Ig levels 130 mg/dl. Protein electrophoresis detected monoclonal gammopathy IgAK 1.7%, 0.06 g/dl, negative rheumatoid factor; serum k free light chain concentration was 21.8 and lambda was 10.8 mg/l (k/λ ratio 2.01). Urinary immunofixation showed IgAk less than 50 mg/24h with microscopic hematuria and 300 mg/dl albuminuria. Skin punch biopsy was performed, revealing acute cutaneous vasculitis.

At this time, based on the deterioration of the renal function and despite the mild hematologic improvement during the first cycle of chemotherapy, ultrasound-guided percutaneous renal biopsy was performed again. The renal biopsy was examined with light microscopy and immunofluorescence. Light microscopy showed an increase of sclerosis up to 70%, 30% of fibroepithelial crescent cell and mild leucocyte interstitial infiltration. Immunofluorescence showed positive staining for IgA (2+) and C3 (1+) and k-light chain (2+) involving mesangial, subendothelial and intramembranous regions.

Given the rapidly progressive renal failure and the presence of fibroepithelial crescent cells in the renal biopsy, accompanied by acute cutaneous vasculitis, in a patient with IgA monoclonal gammopathy, the following renal rescue therapy was programmed: IV cyclophosphamide 500 mg once every 2 weeks for 4 doses adjusted for renal insufficiency and IV metilprednisolone 125/day for 3 days, followed by oral prednisone 50 mg with rapid tapering

On the other hand, the chemotherapy was continued with daratumumab IV at a dose of 16 mg/kg once weekly for 8 weeks, followed by 16mg/kg every two weeks for 8 weeks, plus oral dexamethasone 20 mg (only in the day of chemotherapy, withholding prednisone).

After nearly three weeks of therapy (after the 2nd administration of Daratumumab-dexamethasone and the 2 nd administration of cyclophosphamide) the patient was admitted because of fever, cough and hemoptysis. A CT scan at admission revealed extended consolidation diffused in the entire right lung lobe, characterized by ground glass opacities mixed with parenchymal consolidation and air bronchogram (Figure 2).

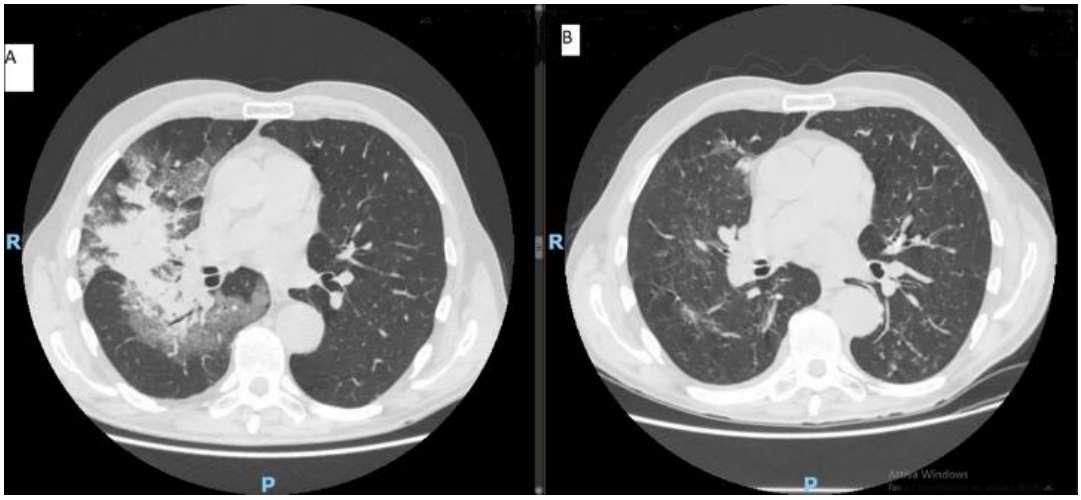

Figure 2: Pneumonitis before (A) and after (B) treatment

Serological assessment, sputum and blood cultures were done to identify the type of organism causing the infection and upon admission a broad-spectrum antibiotic therapy with meropenem and teicoplanin associated with a new triazole antifungal, voriconazole, was started. After one week of therapy, there was an improvement in the clinical symptoms. Therapy with voriconazole was continued because of positive serum aspergillus-specific antibody. On the other hand, CMV PCR exam resulted positive (58000 cp/ml) and antiviral therapy with IV ganciclovir (1.25 mg/kg/dose 3 times weekly) was started.

After roughly 7 days of antibiotic therapy, in consideration of the adequate reduction of systemic inflammatory markers with sustained renal failure (creatinine 8.4 mg/dl and urea 320 mg/dl), a central venous catheter (CVC) was inserted in the internal jugular vein and the patient underwent 6 hemodialysis sessions with the HFR Supra Bellco filter system to achieve an acceptable and persistent reduction of free light chains, as the effect of chemotherapy was still persisting.

After 22 days of hospitalization, as a result of febrile neutropenia, antibiotic therapy was continued and filgrastim (granulocyte colony-stimulating factor) was applicated subcutaneously. Suspecting that the neutropenia was induced by ganciclovir and in consideration of the negative PCR CMV test, the induction therapy was withheld. After a mild improvement of the renal function, the CVC was removed, and the creation of surgical arteriovenous fistulas (AVFs) was planned.

Following 4 days of granulocyte colony-stimulating factor therapy, the neutrophils count increased up to the normal range and the fever disappeared; therefore, maintenance therapy with oral valcyte was started and maintained for the following two weeks.

After nearly 35 days of hospitalization, Acinetobacter baumanii was found in sputum culture and was successfully treated with inhaled colistin at a dose of 1000000 UI three times a day for 5 days.

The patient was discharged with serum creatinine reduced from 8.4 mg/dl to 6 mg/dl and urea from 298 mg/dl to 150 mg/dl; CRP and procalcitonin were in the normal range, with negative cultural tests. One month after discharge, laboratory exams showed a further reduction of creatinine, down to 5.2 mg/dl, while urea remained steady around 150 mg/dl; CRP, procalcitonin and complete blood count were all in the normal range. The patient did not need hemodialysis and we decided to continue chemotherapy with Daratumumab-dexamethasone (Table I).

		Time	Creatinine mg/dl	ProteinuriaGr/ 24h	SIF	UIF	SE	KLC	k/λ ratio	IgG mg/dl
	T0	Before treatment	1.8	3	neg	IgAK 87mg/24h	hypogammaglobulinemia		0.94	
CyBorD	T1	End of 1th cycle	1.89	3.2	neg	IgAK:50.3 mg 24h	hypogammaglobulinemia normal, without MC		0.9	508
	T4	End of 4th cycle	1.4	2.5	neg	IgAK<50 mg 24h	hypogammaglobulinemia normal, without MC		1.02	
	T6	End of 6th cycle	2.1	4.2	neg	IgAK<50 mg 24h	hypogammaglobulinemia normal, without MC			
	T7	End of 7th cycle	2.05	4	neg	IgAK<50 mg 24h	hypogammaglobulinemia normal, without MC	28.16 mg/l	1.8	336
	T8	End of 8th cycle	2.3 mg/dl	3.5	neg	IgAK<50 mg 24h	hypogammaglobulinemia normal, without MC	32.9 mg/l	2.2	
2 month follow up		1th month	2.9	3.4	neg	IgAK<50 mg 24h		35.05	1.6	362
		2th month	4.4	5.9	MC IgAK	IgAK<50 mg 24h	MC 0.17 g/dl, 3.3 %	43	2.08	319
Anti CD38 monoclonal based chemotherapy	T1	After 1th cycle of D.Rd	6.8	4.4	MC IgAK	IgAK<50 mg 24h	MC 0.06 g/dl, 1.7 %	21	2.01	130
		Second renal biopsy								
	T2	After 2 cycles of D-d and first administration of CYC	6.1	4.2	MC IgAK	IgAK<50 mg 24h		17.3	1.2	91
		1 month follow up without therapy	5.4	3.2	MC IgAK	IgAK<50 mg 24h		11.3	0.9	540
		Resumption of D-d after infection resolution								

Table I: The disease progression (CyBorD: Bortezomib, Dexamethasone and cyclophosphamide; D-Rd: daratumumab-lenalidomide plus dexamethasone; SIF: serum immunofixation; UIF: urine immunofixation; SE: serum electrophoresis; KLC: kappa light chain)

Discussion

The clinical presentation of kidney involvement in MGRS is ambiguous and, according to the IKMG recommendations, a kidney biopsy is mandatory for the correct diagnosis and management [1]. A peculiar aspect of MGRS is that kidney lesions are associated with low-grade plasma cell dyscrasias or lymphoproliferative disorders in the absence of multiple myeloma (MM) or other hematologic malignancies. PGNMID occurs specially is the sixth decade of life and is rarely seen in younger patients. Unlike other MGRS, abnormal monoclonal immunoglobulin in serum or urine or even in bone marrow is detected only in 30 % of the PGNMID [8]. Daratumumab is a human immunoglobulin G (IgG) kappa monoclonal antibody anti-CD38 cells [9]. Given the good results of daratumumab in the treatment of patients with refractory MM, it has recently been used in renal disease secondary to PGNMID. The hypothesis is that there is a correlation between kidney injury and monoclonal proteins produced by plasma cells. Therefore, removing the pathologic clone can result in a renal response [10]. Recently, Zand et al. have evaluated, in an open-label, phase 2 trial, daratumumab's safety and efficacy in 11 adults with PGNMID. Daratumumab was administrated intravenously (16

mg/kg) once a week for 8 weeks, then every other week for eight additional doses. One patient did not complete the first infusion. During the 12-month follow up, six patients had a partial response, and four had a complete response. The trial concluded there was a significant improvement in proteinuria and a stabilization of kidney function in patients with PGNMID on daratumumab [7]. Until now, no guidelines to decide the best therapeutic approach to manage PGNMID exist, and most patients progress to End Stage Renal Disease (ESRD) without therapy [3, 11]. We have described a case of MGRS secondary to PGNMID treated at first with 8 cycles of CyBorD chemotherapy. After one year, monoclonal IgA remained constant, with a deterioration of renal function without reduction of proteinuria. At this time, considering both the findings in BMA and CT bone scan and the progressive renal impairment, we chose a second-line treatment with anti-CD38 monoclonal antibody, which showed good results according to a Mayo Clinic study Unfortunately, during the first month of this second-line therapy (with daratumumab-lenalidomide-dexamethasone) the patient was hospitalized because of a rapidly progressive renal failure, despite stable hematologic disease. A second renal biopsy showed sclerosis in up to 70% of the glomeruli and 30% of fibroepithelial crescent cells. This was associated to acute cutaneous vasculitis, and the rescue therapy of choice included intravenous cyclophosphamide and oral prednisone; the treatment with daratumumab, without lenalidomide, was continued. Unfortunately, after three weeks, all therapies were withheld because of infective complications and sever febrile neutropenia. The most common side effects associated with daratumumab are neutropenia (37%), thrombocytopenia (23%), anemia (16%), pneumonia (10%), infusion-related reactions (6%), upper respiratory tract infection (5%), and fatigue (5%) [12]. Some studies find daratumumab to be adequately safe, with an acceptable improvement in proteinuria during the first month of infusion. However, in the case we have described, severe pulmonary infection and life-threatening febrile neutropenia was observed within three months of therapy, with progressive renal impairment. It is possible that the severe pulmonary infection was detected because of the withholding of prophylaxis treatment with trimethoprim-sulfamethoxazole (due in turn to an allergic reaction), but it is also possible that the risk was increased by the association of anti-CD38 monoclonal antibody with alkylating agents. In our case, despite using the therapeutic regimen targeting plasma cell clones responsible for kidney injury, no improvement was achieved, even with the reduction of M-spike protein.

Conclusion

The management of PGNMID remains unclear, and treatment is based on expert consensus, depending on the underlying clone and the risk of renal impairment progression. While low-risk patients without detectable monoclonal disease are treated only with supportive care, chemotherapy is indicated for patients with monoclonal immunoglobulins and a high risk of renal impairment. Histological evaluation guides all therapeutic decisions, according to the pattern and degree of kidney injury. Once MGRS is diagnosed, the collaboration between nephrology and hematology specialist is recommended to find the most adequate therapy. The case we have described, of PGNMID with the presence of mild monoclonal IgA k in urine immunofixation, did not respond to first-line therapy with CyBorD regimen, nor to second-line regimen with Daratumumab (anti CD38). According to our experience, further research is needed to assess the management and outcome of PGNMID.

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