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Autologous Stem Cell Transplant for the Treatment of Type I Crystal Cryoglobulinemic Glomerulonephritis Caused by Monoclonal Gammopathy of Renal Significance (MGRS)

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INTRODUCTION

Cryoglobulins (CGs) are immunoglobulins that precipitate at temperatures below 37 °C and dissolve again after rewarming. Cryoglobulinemia may be asymptomatic or cause end-organ damage by CG precipitation in small- to medium-sized blood vessels.[1] In their seminal work, Brouet *et al*.[2] classify cryoglobulinemias into 3 subgroups according to CG composition and clonality. In type II cryoglobulinemia there is a mixture of monoclonal IgM with rheumatoid factor activity and polyclonal IgG. In type III, CGs consist of polyclonal IgM and IgG.[1] Type II and III cryoglobulinemias are also referred to as mixed cryoglobulinemias and are often caused by chronic hepatitis C infection and less frequently by autoimmune diseases or other viral infections (hepatitis B infection, HIV).[3]

CGs in type I cryoglobulinemia are monoclonal Igs (MIg), also known as paraproteins, commonly IgG, IgM subtypes, or free light chains. The underlying pathological process is a plasma cell or B-cell lymphoproliferative disease, such as multiple myeloma (MM), Waldenström macroglobulinemia, chronic lymphocytic leukemia, or other B-cell non-Hodgkin lymphoma. However, in approximately 40% of symptomatic cases, the plasma cell or B-cell clone is too small to fulfill the diagnostic criteria of MM or overt lymphoma. The term monoclonal gammopathy of undetermined significance (MGUS) used for these cases is a misnomer, as the MIg causes disease regardless of the size and tumor burden.[4] For cases with renal involvement, the International Kidney and Monoclonal Gammopathy Research Group introduced the term monoclonal gammopathies of renal significance (MGRS).[5] The updated MGRS definition includes monoclonal gammopathies that cause renal disease but have low tumor burden and thus treatment from the hematological standpoint is not imminently indicated.[6] These patients may have fewer than 10% plasma cells in bone marrow biopsy, smoldering myeloma, or low-grade lymphomas.[7] MGRSs are not of undetermined significance, and their relevance to renal pathology has opened the use of clone-directed therapies targeting the nephrotoxic MIg-producing clone, with an aim to preserve renal function.[8] Retrospective studies to date suggest that clone-directed therapy improves renal outcomes.[9]

MGRS encompasses a wide spectrum of renal histopathological entities caused by a nephrotoxic MIg, including ever rarer subtypes such as type I cryoglobulinemic glomerulonephritis.[S1,S2] Historically, MGRS may have gone underdiagnosed and patients not offered optimal treatment, unlike their counterparts fulfilling consensus myeloma or lymphoma diagnostic criteria.[S3] Here, we report a case of severe type I crystal cryoglobulinemic glomerulonephritis caused by MGRS, for which treatment with myeloma induction therapy and autologous stem cell transplantation (ASCT)

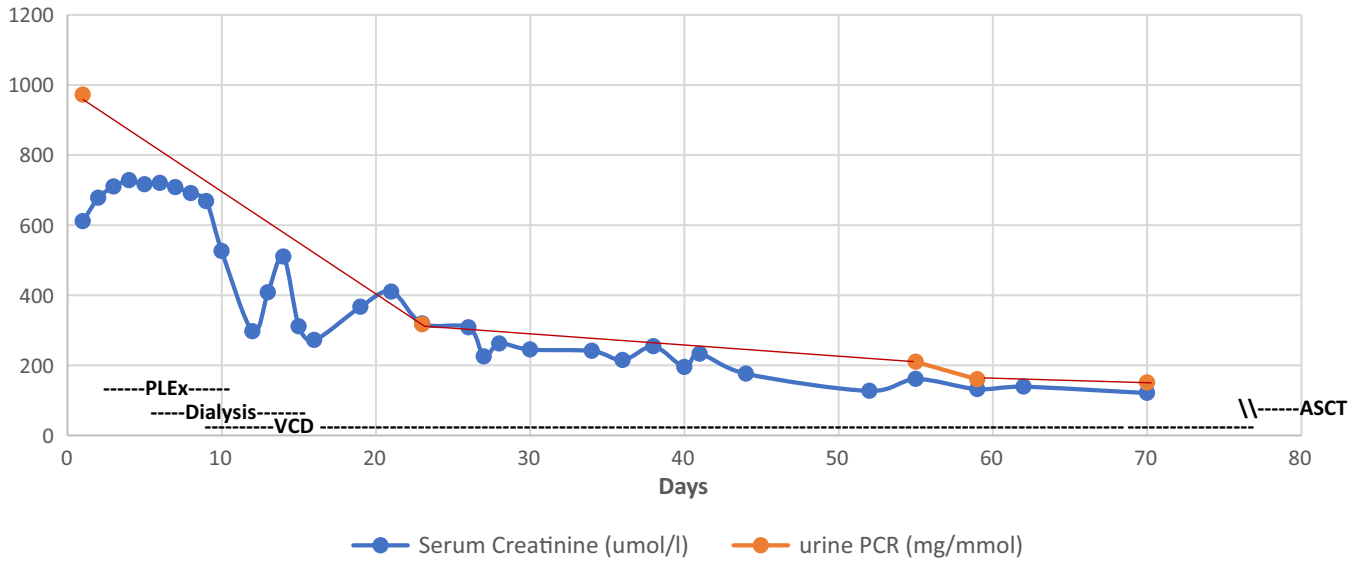

Figure 1. Serum creatinine and urine protein-to-creatinine ratio. ASCT, autologous stem cell transplantation; PLEx, plasma exchange; VCD, bortezomib, cyclophosphamide, and dexamethasone.

induced long-lasting complete hematological response and renal function preservation.

CASE PRESENTATION

Presentation

A 35-year-old female patient presented in July 2015 with a 2-month history of fatigue and 1-week history of myalgias, vomiting, and a vasculitic painful rash in palms and feet. She was previously diagnosed with ankylosing spondylitis in 2014 and treated with adalimumab due to poor response to nonsteroidal anti-inflammatory drugs. Initial investigations showed anemia with hemoglobin 73 g/l, mean corpuscular volume 79.2 fl, white blood cells 10.6 $\times$ 10^9/l, platelets 285 $\times$ 10^9/l and neutrophils 9.0 $\times$ 10^9/l. She had acute kidney injury and nephrotic range proteinuria, with serum creatinine 728 μmol/l, urea 25.5 mmol/l, albumin 24 g/l, and urine protein-to-creatinine ratio 972 mg/mmol. Serum lactate dehydrogenase and bilirubin were normal. A renal ultrasound showed normal-sized kidneys. Because of the severity of the renal dysfunction and hyperkalemia at presentation, the patient received hemodialysis pending further investigations and in preparation for a renal biopsy (Figure 1).

Renal and Hematological Investigation

Antinuclear, antineutrophil cytoplasmic, and anti-glomerular basement membrane antibodies were negative, and hepatitis B virus DNA and C virus RNA and Human Immunovirus DNA polymerase chain reactions were negative. Complement C3 and C4 levels were normal. Renal biopsy performed on day 2 showed a membranoproliferative pattern of glomerulonephritis with intraluminal capillary thrombi that stained weakly on periodic acid–Schiff and showed IgG kappa restriction on immunofluorescence (Figure 2). On electron microscopy, in addition to nonorganized subendothelial and intraluminal electron-dense deposits, some of the intraluminal material had a "grid-like" substructure with weak periodic acid–Schiff staining typical for crystal globulin. Cryoprecipitate was detected in serum and immunofixation demonstrated IgG kappa monoclonal cryoglobulin. Serum protein electrophoresis showed an IgG kappa paraprotein measuring 10 g/l, with normal IgM and IgA levels. The serum free light chain ratio of 3.2, was mildly raised, as expected for renal function (kappa level 245.5 mg/l and lambda 77.1 mg/l). Bence-Jones protein was not detected. The patient underwent further hematological workup with bone marrow aspirate and trephine biopsy showing a normocellular bone marrow with excess of plasma cells (8%–10%). The plasma cells were CD138+, CD56+, CD20−, CD117−, and Cyclin D1−, and demonstrated kappa light restriction with a kappa-lambda ratio of 4:1. Fluorescence hybridization analysis showed t(4;14) IGH/FGFR3. Computed tomography–positron emission tomography scan excluded bone lytic lesions or other fluorodeoxyglucose-avid disease.

Treatment and Follow-up

The patient received treatment with 7 sessions of plasma exchange and started on VCD chemotherapy with bortezomib 1.3 mg/m^2 subcutaneous injection twice weekly, oral cyclophosphamide 500 mg weekly, and dexamethasone 20 mg as per standard 21-day protocol. Within 2 weeks after admission, the patient was dialysis independent. She completed 6 cycles of VCD chemotherapy with partial response (paraprotein

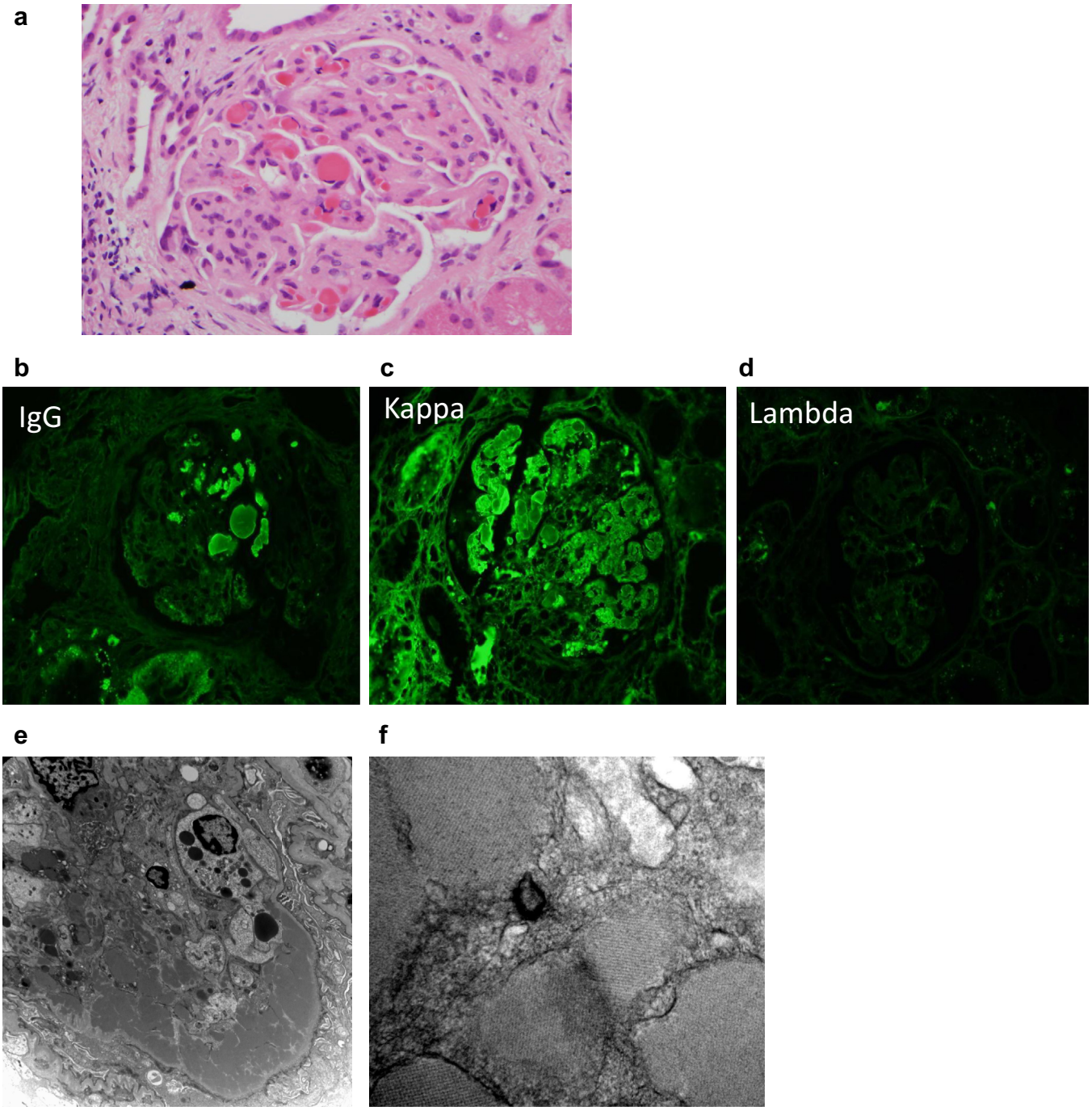

Figure 2. Renal biopsy findings. (a) Light microscopy showing a membranoproliferative pattern glomerulonephritis with intraluminal thrombi (hematoxylin-eosin, original magnification ×400). Immunofluorescence showed positive staining in thrombi and segmentally along capillary walls staining for IgG (b) and kappa light chain (c). Stain for lambda light chain (d) was negative (all original magnification ×400). (e) Electron microscopy showing subendothelial and intraluminal electron-dense deposits (original magnification ×6000). (f) Electron microscopy showing a grid-like structure to some of the deposits, typical of crystal globulins (original magnification ×60,000).

3 g/l, kappa serum free light chain 36.6 mg/l, lambda 24.1 mg/l, ratio 1.52). She had successful stem cell mobilization with granulocyte colony-stimulating factor alone and proceeded with Melphalan 200 mg/m^2 conditioned ASCT in February 2016. She achieved stringent complete response, negative for minimal residual disease by flow cytometry. Four years after treatment, the patient remains asymptomatic in stringent complete response with a serum creatinine 85 μmol/l (Chronic Kidney Disease–Epidemiology Collaboration 75 ml/min per 1.73 m^2), urine protein-to-creatinine ratio of 80 mg/mmol.

DISCUSSION

We report a case of severe type I crystal cryoglobulinemic glomerulonephritis caused by MGRS

Table 1. Studies on type I cryoglobulinemia

Study: Author (year) Country reference	Terrier *et al.* (2013) France[S7]	Neel *et al.* (2014) France[S14]	Harel *et al.* (2014) France[S8]	Sidana *et al.* (2017) USA[S9]
Number of patients	64	36	64	102
Mean age (yr)	65.4 ± 11.4 (range, 38–89)	63 (range, 41–85)	62	Median 59 (range, 31–91)
Female, *n*/*N* (%)	36/64 (56)	16/36 (44.4)	33/64 (51.5)	47 (46)
Follow-up	Mean, 46.2 ± 42.0 mo	Mean, 70 mo (median, 63 mo)	Median, 6.75 yr (range, 1–20 yr)	Median 4.2 yr (95% CI, 3.2–5.7)
MGUS, *n* (%)	28 (44)	13 (36)	26 (41)	39 (41)
Hematological malignancy, *n* (%)	36 (56)	23 (64)	38 (59)	55 (59)
- MM	12	4	2	20 (14 SMM/6 MM)
- Waldenström myeloma	13	12	16	18
- CLL	2	1	5	–
- MZL	6	6	2	–
- Other	3	0	2	17
- Indolent MM	–	–	11	–
Light chain				
- Kappa	NR	72%	41/64 (54%)	NR
- Lambda	NR	28%	23/64 (56%)	NR
- Urine light chain	NR	9/31 (29%)	NR	NR
Monoclonal Ig isotype				
- IgG	NR	11 (30%)	38/64 (59%)	50/90 (53%)
- IgM	NR	25 (70%)	26/64 (41%)	37/90 (39%)
- Other	NR	N/A	N/A	Biclonal IgG and IgM 5 (5%)
Skin involvement	55 (86%)	21 (58.3%)	33 (51%)	64 (63%)
- Purpura	44 (69%)	16	8	43 (42%)
- Acrocyanosis	19 (30%)	NR	12	25 (25%)
- Necrosis	18 (28%)	NR	16	–
- Ulcers	17 (27%)	NR	0	35 (34%)
Joint involvement, *n*/*N* (%)	18/64 (28)	7/36 (20)	4/64 (6)	24/102 (24)
Neurological involvement				
- CNS	NR	NR	6/64	3/102
- Peripheral neuropathy	28 (44%)	17/36 (47%)	9/64 (14%)	33/102 (32%)
Renal involvement, *n*/*N* (%)	19/64 (30)	11/36 (30.5)	13/64 (20)	14 (14)
- Proteinuria	NR	7	13	14
- Nephrotic syndrome	NR	NR	8	NR
- Creatinine, µmol/l	Median 80 (59–800)	Mean 314	NR	NR
- eGFR, ml/min	68 ± 26 ml/min	NR	NR	NR
- eGFR <60 ml/min	21/64 (33%)	NR	NR	NR
- Renal impairment	N/A	8/36	6/13	11/102
Type of renal pathology	18/64 biopsied	10/36 biopsied	9/64 biopsied	13/102 biopsied
- MPGN	17/18	7/10	9/9	9/13
- C3GN	1/18	0	–	0
- Thrombi	0	2	Glomerular thrombi 7/9	1
- Other	0	1 cast nephropathy	–	3
Normal C3 and C4	NR	NR	26/48	NR
Complement level C3	Median 0.89 (0.30–1.93)	NR	NR	NR
Complement level C4	Median 0.09 (0.01- 0.34)	NR	NR	NR
Low C3	16/45 (36%)	NR	9/24 (low c3 and C4)	NR
Low C4	38/47 (81%)	NR	22/24	NR
Cryoglobulin level	Median 1.55 (0.1–10.4)	Median 0.8 g/l	NR	Median 7.5%
RF activity	NR	3/12 (25%)	NR	NR
Treatment	Data for 64 patients	Data for 34 patients	Data for 64 patients (treatment at any time)	Data for 89 patients (1st-line treatment)
	(1st-line treatment)	(1st-line treatment)	No treatment 18/64	No treatment 16/89
	No treatment 8/64	No treatment 4/34	Prednisolone alone NR	Steroids alone 10
	Prednisolone 49/64	Noncytoreductive 6/34	Plasmapheresis 12/64	Plasmapheresis 22/89
	Plasmapheresis 9/64	Plasmapheresis 9/34	Alkylating agents 19	Alkylating agents 19
	Alkylating agents 16/64	Single-alkylating 8/34	Anthracycline 1	Rituximab 11
	Polychemotherapy 9/64	Potent cytoreductive 12/34	Immunomodulatory 9	Alkylating and RiX 12
	Rituximab 7/64	Rituximab 4/34	Bortezomib 10	Azathioprine/MMF 3

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Table 1 | (Continued) Studies on type I cryoglobulinemia

Study: Author (year) Country reference	Terrier *et al.* (2013) France[S7]	Neel *et al.* (2014) France[S14]	Harel *et al.* (2014) France[S8]	Sidana *et al.* (2017) USA[S9]
	Azathioprine/MMF 3/64		HDM+ASCT 4	PIs or IMIDs 16
	Bortezomib-based 2/64		Rituximab 8	HDM+ASCT 6
	Fludarabine 1/64		Rituximab and CP 3	
Sustained remission	15	NR	NR	Improved $n = 47$
Nonresponder	13	NR	NR	
Responder–relapser	25	Most of the patients	NR	
ESRD	NR	2	NR	NR
Deaths	4 (7%)	9 (25%)	15	24
- Sepsis/infection	2	4	5	NR
- Hemopathy	1	0	6	NR
- Unknown cause	1	0	1	NR
- Cardiovascular	0	4	0	NR
- Hemorrhage	0	1	0	NR
- Cancer (solid tumor)	0	0	3	NR
Survival rates, %				77% at last follow-up
1-yr	97	NR	NR	
2-yr	NR	NR	87	
3-yr	94	NR	NR	
5-yr	94	82	83	
10-yr	87	60	68	

C3GN, C3 glomerulonephritis; CI, confidence interval; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CP, cyclophosphamide; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; GN, glomerulonephritis; HDM+ASCT, high-dose melphalan and autologous stem cell transplant; IMID, immunomodulatory; MM, multiple myeloma; MPGN, membranoproliferative glomerulonephritis; MZL, marginal zone lymphoma; N/A, not applicable; NR, not reported; PI, proteasome Inhibitors; RF, rheumatoid factor; RiX, rituximab; SMM, smoldering myeloma; VCD, bortezomib, cyclophosphamide, and dexamethasone.

with excellent long-term outcome after VCD chemotherapy and high-dose Melphalan with ASCT. To our knowledge, this is the first report of ASCT in the era of MGRS with detailed and long-term follow-up.

Type I cryoglobulinemia is rare and appears to be less common than mixed cryoglobulinemias, with studies reporting a wide variation accounting for 4% to 40% of patients with cryoglobulinemias.[2,S4–S9] Older retrospective studies did not delineate monoclonal type I cryoglobulinemia, which has been poorly described as an entity. Nonetheless, the disease has distinct clinicopathological characteristics, etiopathogenetic mechanisms, and differences in management compared with mixed cryoglobulinemias.[S10] Crystallization and aggregation of monoclonal cryoglobulins are temperature and concentration dependent, causing symptoms frequently in distal extremities where temperature is lower, and in kidneys where ultrafiltration increases their concentration. Moreover, monoclonal cryoglobulins lack rheumatoid factor activity and the associated cryocrit is much higher than for mixed cryoglobulinemias, reaching up to 50%. As a result, cutaneous manifestations are caused by hyperviscosity and vascular occlusion by the cryoprecipitate rather than immune-complex vasculitis.[1,S11] Crystallization of a cryoglobulin may or may not occur. When crystallization occurs, it is referred to as crystal cryoglobulin, and typically on histology there is less glomerular hypercellularity with intraluminal thrombi (periodic acid–Schiff weak positive) predominating with a grid-like crystalline structure on electron microscopy.[S12,S13] The picture in this case was mixed, with a membranoproliferative pattern accompanied by glomerular thrombi. The differential diagnosis includes intracapillary monoclonal deposit disease, but in this instance deposits are usually composed of IgM monoclonal paraprotein, are periodic acid–Schiff positive, and have no substructure.

More recently, 4 studies have focused exclusively on type I cryoglobulinemia with patient cohorts between 36 in the smallest and 102 patients in the largest.[S7–S9,S14] Skin manifestations were most common (50%–86% of patients), and included purpura, acrocyanosis, Raynaud phenomena, skin necrosis, and ulcers. Extracutaneous manifestations included musculoskeletal (6%–28%), neurological (14%–47%), and renal (14%–30%) (Table 1). The underlying lymphoproliferative disorder was characterized in most of the cases. Hematological malignancy accounted for 56% to 64%, including MM, lymphoblastic lymphoma/Waldenström macroglobulinemia, chronic lymphocytic leukemia, and other. MGUS was described as the underlying hematological condition in 36% to 44% of the cases (the studies did not use the term MGRS). The isotype of the MIg was IgG in 30% to 60% of the cases.[S8,S9,S14] Two studies reported on the light chain as being kappa in 54% and 72%, respectively.[S8,S14]

Overall, renal involvement was reported in 14% to 30% of cases. One study reported renal involvement in 4 of 13 (30%) cases of MGUS, equal in comparison to 7

Table 2. Teaching points

- Cryoglobulins cause a wide spectrum of clinical manifestations from asymptomatic cryoglobulinemia to life-threatening systemic disease.
- Cryoglobulins type I are monoclonal immunoglobulins produced by plasma cell or B-cell clones in the context of lymphoproliferative diseases such as multiple myeloma (MM), Waldenström macroglobulinemia (WM), and other lymphomas. Symptomatic cryoglobulinemia has distinct clinicopathological characteristics, etiopathogenetic mechanisms, and differences in management compared with mixed cryoglobulinemias (type II and III).
- In a significant number of symptomatic cases, the underlying pathogenic clone does not fulfill the diagnostic CRAB-SLiM criteria for myeloma or symptomatic lymphoma. Monoclonal gammopathies that cause renal disease, including Type I cryoglobulinemic glomerulonephritis, but the tumor burden is too low to meet the criteria for hematological treatment are now termed monoclonal gammopathies of renal significance (MGRS).
- Consensus treatment recommendations exist for MM and WM, but the optimal treatment approach for type I cryoglobulinemia in MGRS remains unknown. Recent studies suggest that appropriate chemotherapy to induce a deep hematological response in MGRS improves renal outcomes, especially with the use of novel antimyeloma agents. Autologous stem cell transplantation may be considered in severe cryoglobulinemic-related manifestations.
- International multicenter studies and registries are needed to clarify the efficacy and safety of different treatment strategies.

CRAB-SLiM, Calcium elevation, Renal insufficiency, Anemia, Bone disease–Sixty percent clonal B cells, Serum-free Light chain ratio involved:uninvolved >100, MRI focal lesion >1; MRI, magnetic resonance imaging.

of 23 (30%) cases of hematological malignancies.[S14] Proteinuria was present in most of the cases, and was described as nephrotic or high-grade proteinuria. Ten percent to 30% had renal impairment at presentation and 50 patients had renal biopsies. The histopathological pattern of injury on light microscopy was described as membranoproliferative glomerulonephritis in 42 cases. Harel *et al.*[S8] described glomerular thrombi in 7 of 9 patients who had a renal biopsy.

The heterogeneity of treatment regimens used across and within the previous studies preclude conclusions on the efficacy of treatment. Moreover, studies included patients with a wide variation of disease severity and only 1 reported on treatment and outcomes separately for MGUS and MM. Presently, for MM and Waldenström macroglobulinemia there are published consensus recommendations for treatment, but for MGRS the optimal therapy is not yet known and is usually based on low-grade evidence and expert opinion. Terrier *et al.*[S7] described prednisolone alone as initial therapy in most of patients with MGUS, but approximately 65% of patients failed to respond or relapsed. They suggested rituximab- or bortezomib-based regimens for severe or refractory MGUS type I cryoglobulinemic disease.[S7] Neel *et al.*[S14] described similar prevalence of cryoglobulinemic manifestations between nonmalignant monoclonal gammopathy and hematologic malignancy with the recommendation that more potent chemotherapy should be used in patients with MGUS. Harrel *et al.*[S8] reported worsening of cryoglobulin symptoms in 7 of 28 patients (including 2 patients with renal manifestations) who had MGUS and mild symptoms at diagnosis and, by result, had not received treatment. Sidana *et al.*[S9] concluded that for non–IgM-MGUS and MM, novel antimyeloma agents should be considered, and that rituximab/alkylator treatment maybe more appropriate for IgM-MGUS and Waldenström macroglobulinemia. Plasma exchange was instituted based on the severity of cryoglobulin-related symptoms across studies. ASCT was used in only a few cases; Sidana *et al.*[S9] reported ASCT in 6 patients (3 with smoldering myeloma and 3 with MM) and Harel *et al.*[S8] reported 4 patients treated with ASCT with resolution of cryoglobulin-associated symptoms in 2 of 4 patients who achieved complete remission.

CONCLUSION

In conclusion, this case illustrates that effective hematological treatment leading to a complete response improves renal outcome and prevents relapse in a disease known to have high relapse rates (Table 2). ASCT may be considered in severe cryoglobulinemic-related manifestations irrespective of the tumor burden. Outcome of ASCT in amyloid light-chain amyloidosis, a condition with similar hematological background, suggests high complete response–rates and long event-free survival, supporting the same treatment paradigm for more rare clinical entities.[S15] However, to assess emerging novel chemotherapeutic agents and with the rarity of this disease, international multicenter studies and registries are needed to clarify the efficacy and safety of treatment strategies.

DISCLOSURE

FWKT is the chief investigator of an international clinical trial of spleen tyrosine kinase inhibitor in IgA nephropathy (funded by Rigel Pharmaceuticals, San Francisco, CA, USA); has received research project grants from Baxter Biosciences, Boehringer Ingelheim, and MedImmune; and has consultancy agreements with Rigel Pharmaceuticals and Novartis. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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