

Essential mixed cryoglobulinemia type II

A.P. Rozin¹, M. Lewin²,
Y. Braun-Moscovici¹,
O.B. Itzhak³, R. Bergman⁴,
A. Balbir-Gurman¹

¹The B. Shine Department of Rheumatology; ²Department of Nephrology; ³Department of Pathology; ⁴Department of Dermatology, Rambam Medical Center and B. Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

Alexander Rozin, Mosche Lewin, Yolanda Braun-Moscovici, Ofer Ben Itzhak, Reuven Bergman, MD, Alexandra Balbir-Gurman.

Please address correspondence to: Alexander Rozin, Department of Rheumatology, Rambam Medical Center, POB 9602, Haifa 31096, Israel. E-mail: a_rozin@rambam.health.gov.il

Received on May 9, 2005; accepted in revised form on February 22, 2006.

© Copyright CLINICAL AND EXPERIMENTAL RHEUMATOLOGY 2006.

Key words: Essential mixed cryoglobulinemia type II, membranous proliferative glomerulonephritis type I, ramipril, colchicine, low antigen content diet, Coombs positive hemolytic anemia.

ABSTRACT

We report a rare case of essential mixed cryoglobulinemia type II with membrano-proliferative glomerulonephritis (MPGN) type I in which HCV was not found. Long-term history of palindromic rheumatism, skin leukocytoclastic vasculitis attacks and micro-normocytic anemia preceded the appearance of cryoglobulinemia. Cryoprecipitate consisted of monoclonal IgMk-RF and polyclonal IgG (essential mixed type II). The newly appreciated cryoglobulinemia was associated with Coombs positive hemolytic anemia. The MPGN in this case had a benign course and responded to complex simple therapies including prevention of exposure to cold, low antigen content diet, treatment of provoking factors such as UTI, and maximal dose of ACE inhibitor. Responsiveness of skin vasculitis to colchicine therapy was restored after a two-month colchicine withdrawal period and therefore corticosteroid and immunosuppressive therapy was postponed.

Introduction

Cryoglobulins (Cryo) are immunoglobulins (Ig) that precipitate in the cold and redissolve upon rewarming. Cryo are associated with a number of infections, autoimmune and neoplastic disorders. Three types of Cryo have been described. Type I Cryo is composed of monoclonal Ig, typically seen in myeloproliferative malignancy. Mixed cryoglobulines (MC) are composed of a polyclonal IgG bound to rheumatoid

factors (RF), either monoclonal, IgM k (type II) or polyclonal Ig (type III). The origin of MC is not clear in 5-30% of patients and this subset is therefore called "true essential" (1). The great majority (up to 95%) of patients with MC has been related to HCV infection. Type III or mixed polyclonal Cryo are often seen in autoimmune diseases such as lupus, Sjogren's syndrome and hematological malignant neoplasmas. We report a rare case of essential MC type II with membranous proliferative glomerulonephritis (MPGN) type I in which HCV was not found.

Case report

A 73 year old woman was admitted with severe purpura of the legs (Fig. 1A), painful and swollen ankles with limitation of joint movement. She was suffering from frequent (every 2-3 weeks) attacks of short duration (3-4 days) of mono-oligoarthritis (hot-red joint), accompanied by transient skin purpura. Palindromic rheumatism (PR) with leukocytoclastic vasculitis (LV) on skin biopsy was diagnosed and treated either with colchicine 1.5mg/day, or hydroxychloroquine (HCQ) 400 mg/day or a combination of both drugs at various stages of the disease. During therapy PR and LV attacks were rare and mild (once in 6 months), whereas the last attack, which began two months ago, was severe and persistent. Seroconversion to positive rheumatoid factor was observed three years ago. Since that time mild to moderate intermittent proteinuria was observed with

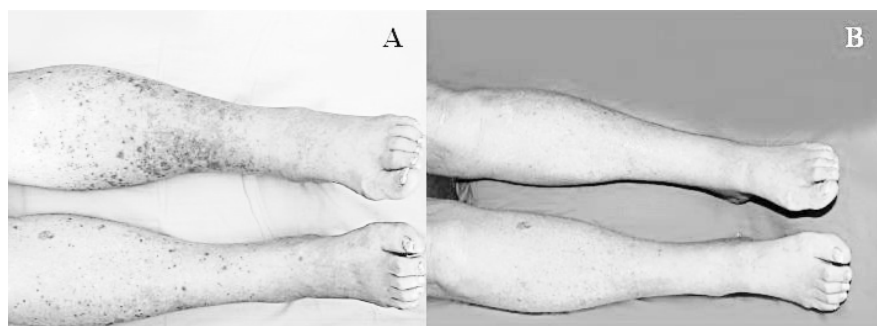


Fig. 1. A – leukocytoclastic vasculitis due to cryoglobulinemia on admission: eventual failure of long-term and successful hydroxychloroquine (HCQ) and colchicine therapy. The purpura stayed unchanged two months after discontinuation of HCQ and colchicine therapy and during low antigen diet and ACE inhibitor ramipril therapy. Ankles' swelling due to arthritis is seen.

B – complete disappearance of the rash 4 days after reinstitution of colchicine therapy in the same prior dose 1.5 mg/day (after two months of low antigen content diet and ACE inhibitor ramipril therapy).

Table I. Laboratory findings of the patient with essential cryoglobulinemia type II with MPGN type I.

Variable/Date	2001	2002	2003	3.2004 before admission	5.2004 on admission: Colchicine, Plaquenil therapy discontinuation	2 months after admission: 2 months of Ramipril therapy, Colchicine reinstitution	6 months after admission: 6 months of Ramipril, 4 months of Colchicine readministered
Creatinine (N < 1.2 mg/dl)	1.36 (N < 1.3)		1.1, 1.1, 1.16, 1.34, 1.12	1.20, 1.15	2.2	1.14	1.12
Creatinine clearance ml/min	63		52	50	24	48	63
Proteinuria mg/24 hours	253	550	920	503	3804	1289	969
Hb g/dl (Normal erythropoietin, ferritin)	9.5	10.5	9.2, 8.7, 9.0, 8.3, 9.6	8.9	8.2	11.1	11.2
LDH (N 230-460 U/L)	215 (N<225)	400	369	751	225 (N <225)		
Albumin (N3.5-5.2 g/dl)	3.6	3.8	3.1	3.02	3.4		4.21
Coombs-direct	negative			negative	positive	negative	negative
Cryoglobulines	negative	negative	negative		positiveX3		negative
IgG (N700-1600mg/dl)	734		630	699			
IgM (40-230mg/dl)	33		34	34			
IgA (70-400mg/dl)	201		217	212	281		
RF (N 0-14 IU/ml)	20		85	114			
C3 (N 90-180 mg/dl)	88 (N72-156)	100	84 (N 70-156)	107			
C4 (N 10-40 mg/dl)	8 (N13-37)	< 4	2.2	< 6			
ESR mm/hr CRP mg/dl				30/1.4			

reversible mild renal function impairment (Table I). No other internal involvement, neurological deficit or sustained joint damage was found. Cryo, HBSAg, HCV (antibodies and PCR), ANCA, ANA, Anti-DNA were negative during the entire course of the disease (16 years). C3 levels were normal while C4 and IgM were constantly low (Table I). An unusual finding was a decrease of hemoglobin (Hb) to 8-10 g/dl during the attacks (from a baseline Hb level of 10-11 g/dl) with low-normal MCV. Coombs test was negative. Extended work up of microcytic anemia was negative for thalassemia, gastro-intestinal disorder or malignancy. On admission, at the time of the flare-up, an increased blood pressure (BP180/110), deterioration in renal function (creatinine 2.2, proteinuria 3.8g/day) with nephritic sediment (hematic and granular casts), Cryo and Coombs positive anemia (8.2g/dl) were found. Analysis of cryoprecipitate for HCV antibodies as well as

HCV-RNA PCR was negative. The cryoprecipitate electrophoresis showed small monoclonal IgMk RF bound to polyclonal IgG (essential mixed cryoglobulinemia type II). Serum protein electrophoresis was negative for monoclonal gammopathy. Bone marrow, bone biopsy and urinary Bence-Jones protein showed no evidence of multiple myeloma or lymphoproliferative disorder. Urine analysis revealed proteinuria, microhematuria, and casts (hematic and granular), increased leukocytes and a positive culture for *E. coli*. Kidney needle biopsy results were consistent with membranous (double basement membrane) proliferative glomerulonephritis (MPGN) type I (immune complex deposits) with chronic vascular changes associated with Cryo. HCQ and colchicine were stopped at the time of admission. Low antigen content (LAC) diet was begun in hospital and continued after discharge according to LAC diet protocol (2). The patient was hemotransfused, and

treatment with ACE inhibitor ramipril in maximal dose of 10 mg/day was begun. Urinary tract infection was treated with cefuroxim for 2 weeks, in accordance with microbial sensitivity. The importance of a warm environment to prevent precipitation of Cryo was explained to the patient. Two months later the leg rash remained unchanged (Fig. 1A), blood creatinine decreased to 1.14, proteinuria to 1.29g/day, and Hb increased to 11.1; BP normalized. At this time colchicine therapy was reinstituted in prior dose of 1.5 mg/day. Four days later the rash disappeared completely (Fig. 1B). After 6 months of follow-up the patient remained asymptomatic with normal BP, clear skin, stable kidney function (creatinine 1.12, CCT 63 ml/min), and proteinuria (0.97 g/day), and Hb 11.2. Urine analysis, daily urinary protein and urinary culture were repeated once a month.

Discussion

We suggest that long-term history of

PR and LV were manifestations of MC type II with undetectable or transient serum level of the Cryo. The recent increase in Cry level may be the result of B-cell expansion (3) or possibly triggered by infection (UTI) or drugs. Low-moderate dose corticosteroids (CS) (0.05-0.3mg/kg/day) are usually recommended to control the purpura, arthralgia, arthritis and weakness, while larger doses (0.5-1.5mg/kg/day) are needed to treat the renal involvement, peripheral neuropathy and serositis (4). We think that before deciding to begin corticosteroid and immunosuppressive therapy for MPGN type I associated with Cryo, provoking factors should be removed (cold environment and drugs) and/or treated (infection). Good results have been obtained in the treatment of purpura, arthralgia, weakness and peripheral neuropathy utilizing LAC diet, a regimen designed to restore a saturated mononuclear phagocytic system (2). Furthermore, this dietary regimen may play a steroid sparing role. ACE inhibitors have an important role in decreasing glomerular filtration pressure and proteinuria and in preventing mesangial cellular expansion. These simple therapies proved to be effective in our case. We recommend a two-month withdrawal period of colchicine in order to restore the decreased susceptibility of skin vasculitis to this treatment (Fig.1 A-B). A distinguishing feature of our case was microcytic-normocytic anemia exacerbating during arthritis and skin vasculitis attacks with conversion to Coombs positive anemia during appearance of detectable Cryo. A relationship between anemia, Coombs positivity and Cryo expansion is suspected. We propose that a low undetectable level of Cryo was responsible for IgM-IgG-complement mediated hemolysis (high borderline LDH) during rash-arthritis attacks and might have induced antibodies to erythrocytes. Low-grade RF-mediated erythrocyte damage might be responsible for anemia in intercritical period and other rheumatic diseases associated with increased RF production. After having analyzed a report from Italy (5), which showed seroconversion

of MC to HCV positivity, we suggest the need to continue the search for HCV RNA in cryoprecipitate of our patients.

The deposition of circulating immune complexes induces renal damage. However, no correlation has been observed between the immune complex level and the severity of renal manifestations. The exact mechanism is not completely clarified. Intravenous injection of Cryo from patients with nephritis into mice induces MPGN (6) and IgM isolated from these Cryo when injected separately, deposits in the glomeruli (7). More specifically, the IgM isolated from sera of nephritis patients with MC binds to a 48kDa antigen abundant in the kidney (α -enolase) (8).

The intravascular precipitation of Cryo induced by exposure to cold temperature may account for some clinical signs of peripheral vasculitis, but fails to explain the precipitation of Cryo in regions where no significant temperature changes take place, such as in the kidneys. The activity *in vitro* of different ions on aggregation of Cryo was investigated and it was found that the concentration of Cl⁻ in solution is the most important variable controlling the size and the rate of formation of aggregates, both at low temperature and at 37 degrees C (9). Identification of a specific structural domain responsible for Cl⁻ binding may provide new targets for drugs selectively designed to interfere with cryoglobulin aggregation (9). According to this theory limited salt regimen may be expected to diminish Cryo aggregation.

The second line therapy (cyclophosphamide), plasmapheresis, interferon (INF) alpha, rituximab (anti-CD20) for selective B-cell blockade and fludarabine should be considered in case of deterioration of renal function and proteinuria (3). In the presence of acute Cryo glomerulonephritis, INF does not prevent progression of renal damage; combination therapy with cytotoxic and antiinflammatory drugs (corticosteroids), and sometimes plasma exchange, is recommended (1). Long-standing low C4 and IgM might be important markers of increased con-

sumption due to active Cryo, even when undetectable such as in our case. Rituximab therapy caused a decrease in serum RF and Cryo leading to increase in levels of C4 (10). This was associated with significant clinical improvement: disappearance of purpura, weakness, arthralgia and improvement of peripheral neuropathy.

In conclusion: 1) Palindromic rheumatism, leucocytoclastic vasculitis attacks and anemia are proposed to be early manifestations of essential cryoglobulinemia in spite of undetectable levels of Cryo in the early phase of the disease; 2) The second phase of the disease is suggested to be due to expansion in Cryo production associated with renal involvement, exacerbation of anemia and unremitted skin vasculitis and arthritis; 3) MPGN type I due to essential Cryo type II had a benign course and responded to simple therapies including: prevention of exposure to cold, low antigen content diet, treatment of provoking factors such as UTI, and the use of maximal dose of ACE inhibitor; 4) A withdrawal period of colchicine therapy may restore responsiveness of skin vasculitis to colchicine; 5) The above-mentioned basic therapy together with the removal of provoking factors might permit the successful reinstitution of colchicine treatment, allowing the postponement of CS and immunosuppressive therapy.

Acknowledgements

We are very grateful to Dr. Stuart Marsh for his help in editing this article.

References

1. FABRIZI F, COLUCCI P, PONTICELLI C, LOCATELLI F: Kidney and liver involvement in cryoglobulinemia. *Semin Nephrol* 2002; 22: 309-18.
2. FERRI C, PIETROGRANDE M, CECCHETTI R *et al.*: Low antigen content diet in the treatment of patients with mixed cryoglobulinemia. *Am J Med* 1989; 87: 519-24.
3. FERRI C, GIUGGIOLI D, CAZZATO M, SEBASTIANI M, MASCI MT, ZIGNEGO AL: HCV-related cryoglobulinemic vasculitis: An update on its etiopathogenesis and therapeutic strategies. *Clin Exp Rheumatol* 2003; 21 (Suppl. 31): S78-S84.
4. TAVONI A, MOSCA M, FERRI C *et al.*: Guidelines for the management of essential mixed cryoglobulinemia. *Clin Exp Rheumatol* 1995; 13S13: 191-5.
5. CASATO M, LILLI D, DONATO G *et al.*: Occult

- hepatitis C virus infection in type II mixed cryoglobulinaemia. *J Viral Hepat* 2003; 10: 455-9.
6. FORNASIERI A, LI M, ARMELLONI S *et al.*: Glomerulonephritis induced by human IgM K-IgG cryoglobulins in mice. *Lab Invest* 1993; 69: 531-40.
 7. DOLCHER MP, MARCHINI B, SABBATINI A *et al.*: Autoantibodies from mixed cryoglobulinemia patients bind glomerular antigens. *Clin Exp Immunol* 1994; 96: 317-22.
 8. MIGLIORINI P, PRATESI F, MOSCATO S *et al.*: Mechanisms of renal damage in mixed cryoglobulinemia nephritis. *Nephrol Dial Transplant* 2001; 16: 58-9.
 9. DI STASIO E, BIZZARRI P, CASATO M, GALTIERI A, FIORILLI M, PUCILLO LP: C1-regulates cryoglobulin structure: a new hypothesis for the physiopathological mechanism of temperature non-dependent cryoprecipitation. *Clin Chem Lab Med* 2004; 42: 614-20.
 10. ZAJAF, DE VITAS, MAZZARO C *et al.*: Efficacy and safety of rituximab in type II mixed cryoglobulinemia. *Blood* 2003; 101: 3827-34.