3-1973

Purpura Arthralgia Weakness Mixed Cryoglobulinemia Syndrome Treated with Splenectomy: A Case Report

Carl R. Haeger

Follow this and additional works at: https://scholarlycommons.henryford.com/hfhmedjournal

Part of the Life Sciences Commons, Medical Specialties Commons, and the Public Health Commons

Recommended Citation
Available at: https://scholarlycommons.henryford.com/hfhmedjournal/vol21/iss1/3

This Article is brought to you for free and open access by Henry Ford Health System Scholarly Commons. It has been accepted for inclusion in Henry Ford Hospital Medical Journal by an authorized editor of Henry Ford Health System Scholarly Commons.
Purpura Arthralgia Weakness Mixed Cryoglobulinemia Syndrome Treated with Splenectomy

A Case Report

Carl R. Haeger, MD*

Weakness purpura mixed arthralgia cryoglobulinemia (IgG - IgM) syndrome was first described by Meltzer in 1966. Such a case was recently reported after treatment with Cyclophosphamide and subsequent splenectomy for pancytopenia with beneficial effects on the cryocrit. The patient reported here underwent splenectomy without Cyclophosphamide and had subsequent amelioration of the clinical symptoms. Abnormal plasma cells found in the spleen presumably were responsible (at least in part) for the patient’s symptomatology.

The arthralgia, purpura weakness mixed cryoglobulinemia syndrome with rheumatoid factor activity has been reported by Meltzer and others. Mathison has reported the beneficial effects of Cyclophosphamide and incidental splenectomy in one patient with this syndrome. Our report is of a patient with this syndrome treated with splenectomy without Cyclophosphamide. Subsequently, our patient had amelioration of symptoms without fall in cryocrit. The spleen was enlarged weighing 247 gms and filled with abnormal cells presumably manufacturing the IgM component of the cryoglobulin.

Case Summary

This 39-year-old beautician was first referred to Henry Ford Hospital in January, 1970 with a three-year history of purpuric lesions appearing intermittently on her legs (Figure 1). These were associated also with urticaria. The purpuric lesions were heralded by a burning, stinging pain. They began as small red lesions with a surrounding halo and over a period of days gradually became brownish and macular. The patient had also experienced several months of foot drop with paresthesia in her right leg. This cleared spontaneously. She also complained of generalized intermittent joint pain although joint swelling was never clearly evident. Past history included a total hysterectomy with bilateral salpingo-oophorectomy in 1952 because of excessive vaginal hemorrhage. Postoperative diagnosis was periuterine pel-
Figure 1
Patient's leg showing typical purpuric lesions.

Figure 2
Section of kidney showing interstitial infiltration with mononuclear cells. (High power, 300 x H&E)
vic adhesions, fibro-cystic cervicitis, bilateral salpingitis with ovarian cysts. For a period of time she received thyroid medication. When it and estrogen therapy were discontinued in 1969, there were no untoward results. The patient also complained of severe retroorbital headaches. The main physical findings were purpuric lesions of the legs and hyperpigmentary changes of the legs.

Initial evaluation revealed mixed cryoglobulins of the IgG-IgM variety and a titer 5 volumes %. Rheumatoid factor activity was elevated at 1 to 620. The differential rheumatoid agglutination test of 40 at time of examination rose to 1240 in the next two years.

When she was admitted to Henry Ford Hospital in 1972, diagnostic gastrointestinal tests and IVP were negative except for a finding of a 5 mm polyp in the cecal tip. IgG was elevated at 1674 mg/ml and IgA was elevated at 390. White blood count was 6.2x10^3, hemoglobin 14.8, hematocrit 42.1 and mean corpuscle volume 93. Cryoglobulins at that time were 5 volumes percent. Kidney biopsy showed chronic focal interstitial nephritis

Figure 3
Kidney biopsy of patient showing prominent glomerular hyalinization. Mesangial thickening is also present.
(Figure 2). However, glomerular hyalinization was prominent (Figure 3). Electron microscopy showed evidence of basement membrane thickening of capillaries (Figures 4 and 5). Serum complement was 63 GH50/ml. Creatinine clearance was 94 ml/min. There was no evidence of hematuria. The patient obtained partial relief with Benadryl, Atarax and support stockings; but she was virtually incapacitated by disabling pain and swelling in her legs.

Elective splenectomy was done in March of 1972. The postoperative course was uneventful. One month later the patient reported that her purpuric lesions were much less noticeable and new lesions were few and less apt to be associated with pain or swelling. The headaches had disappeared and joint symptoms were minimal.

In late summer, symptoms began to increase but were less than before splenectomy. Anticoagulant therapy was initiated, again with a noticeable decrease in symptoms.

Discussion

Proteins that reversibly precipitate from blood on cooling were first described by Wintrobe and Buell11 in 1933 and first named cryoglobulins by Lerner and Watson in 1947.12 They are most commonly encountered in multiple myeloma, macroglobulinemia, and malignant lymphomas but occur rarely in cirrhosis, sarcoidosis, subacute bacterial endocarditis, leprosy, syphilis, infectious mononucleosis, cytomegalovirus disease, various connective tissue disorders, and in so-called “essential cryoglobulinemia.” Most of these proteins are immunoglobulins although

Figure 4

cryofibrinogens have also been found. In most instances, these cold precipitating proteins are an incidental finding, but they can give rise to symptoms of severe vascular insufficiency usually involving the extremities. The pathophysiology of the vasculitis is not well understood but is thought to be an autoimmune phenomenon. In 1966, Meltzer and Franklin reviewed 29 patients with cryoglobulinemia and found they could divide the patients into three groups. The first group had IgG (7S) gammaglobulins. These patients clinically had multiple myeloma, cancer, essential cryoglobulinemia and cirrhosis and had negative rheumatoid factors. One half were symptomatic and most were monoclonal with either K or L chains. Group II patients had IgM (19S) gammaglobulins. Clinically, these patients had leukemia and lymphosarcoma and a negative rheumatoid factor. This group tended to be monoclonal with either K or L chains and asymptomatic.

As in our case, their group III patients had mixed IgG-IgM gammaglobulins and were predominantly female. All the serums contained rheumatoid factors, usually IgG-IgM in type although one was a polymer of IgG. The cryoprecipitate tended to be polyclonal with both K and L chains, although this may be due to the fact that there are two immunoglobulins (IgM acting as antibody and altered IgG as antigen). All these patients were symptomatic and most had an unusual but easily recog-
nized clinical picture composed of weakness, purpura, arthralgia and elevated rheumatoid factor activity.

The patients with purpura had burning, stinging pain which was relieved partially by antihistamines. Lymphadenopathy, hepatosplenomegaly, epistaxis, uveitis, parotid swelling, and neuritis have all been reported in the mixed type of cryoglobulinemia. Furthermore, underlying malignancy or other disease were not found. It is noteworthy that the arthralgias were unaccompanied by swelling and redness. Two of the patients had Sjogren's syndrome, and one had thyroiditis, presumably of the
autoimmune type. The occurrence of nephritis rapidly progressed to acute renal failure, which has been reported in other series also.\(^\text{10}\)

Hemolytic anemia, renal tubular acidosis, and thrombocytopenic purpura have been reported.\(^\text{2,4,7}\) The rheumatoid factor seems to have different physical properties than classic rheumatoid factor. Serum complement was low, especially in patients with glomerular lesions. They had either a normal serum protein electrophoresis or a diffuse hypergammaglobulinemia rather than a monoclonal spike. Rheumatoid factor was generally quite elevated. Three patients studied at autopsy had findings of diffuse glomerulonephritis, arteritis and endocarditis.

Small vessels in the dermis showed infiltration of the walls and surrounding tissue with neutrophils and a smaller number of mononuclear cells. No
intraluminal precipitate or necrosis were seen. The lesions were similar to those seen in Henoch-Schönlein purpura. Figure 1 is a photograph showing the skin of our patient. Figures 6 and 7 are photomicrographs of the skin section showing infiltration with occlusion of the lumen in some small vessels.

The glomerular lesions were characterized by swelling and proliferation of endothelial and axial cells, mild to moderate neutrophil infiltration and slight increase in basement membrane-like material generally seen in axial regions. Immune deposits in glomeruli and electron dense glomerular endothelial deposits have been reported by means of electron microscopy and immunofluorescence. A section of our patient's kidney (Figure 2) shows capsular thickening and hyalinazation and mild proliferative changes (Figure 3). Endocarditis was found in one patient with a focus of necrosis and leukocyte infiltration. Inflammation could be seen in the small vessels at the base of the mitral valve. The valvular lesion did not have the appearance of atypical verrucous endocarditis.

It is supposed that for the kidney — the circulating complexes fix complement and cause glomerular basement membrane damage similar to the glomerulonephritis or systemic lupus erythematosis. In the skin — the complexes may precipitate in the cooler surface areas and cause intravascular coagulation and vasculitis damage in some way.

The red blood cells adsorb complexes and with the fixation of complement, hemolysis occurs. The red blood cell is the "innocent bystander." There must be other factors present however, because this type of vascular damage was not seen with patients with rheumatoid arthritis and high circulating rheumatoid factor. Also, patients with multiple myeloma and lymphoma do not have this type of vasculitis in spite of higher levels of circulating cryoglobulins. In fact, the IgG-IgM complexes may be a by-product rather than a cause of the disease.

Other possible clinical expressions of immune complex disorders include synovitis, serositis, hyperviscosity syndromes, Raynaud's phenomenon, leukopenia and thrombocytopenia.

Many therapies have been tried for this disease. Elastic stockings, elevation of legs and avoidance of cold reduce but do not eliminate the patient's symptoms. Salicylates may be helpful for the control of arthralgias.

The burning, stinging pain of the purpura which may reflect the initial advent of vasculitis is helped by antihistamines, especially Atarax. Anticoagulant therapy has been used with dramatic benefit in two patients with leg ulcers. Although the use of steroids seems logical because of their anti-inflammatory effects, they are usually of no benefit. Likewise, sympathectomy has not been of benefit. Penicillamine has been of benefit in some patients working perhaps by causing disruption of disulfide linkages of macroglobulins or by acting as a cytotoxic agent. Chlorambucil and steroids have also been used without much benefit. Cyclophosphamide, however, appears to lower the cryocrit and ameliorate the clinical symptoms. In one patient who developed pancytopenia while taking Cyclophosphamide, splenectomy was done in the hopes that Cyclophosphamide could be restarted since hypersplenism was suspected. After splenectomy, the cryocrit fell and hematuria and skin lesions abated. Our patient underwent splenectomy without previous Cyclophosphamide and had good relief of symptoms. Slight exacer-
Figure 8
Low power view of our patient’s spleen. 115x. H & E stain.

Figure 9
High power view showing atypical plasmacytoid lymphocytes. 300x. Wright's imprint.
bation was noted six months post-
splenectomy and anticoagulants were
begun again, with relief of symptoms.
We feel splenectomy should be consid­
ered in patients with this disease.

Figures 8 and 9 show photomicro­
graphs of our patient's spleen. Although
the low power view is relatively normal,
the high power view shows atypical
plasmacytoid lymphocytes. Presumably
these cells are manufacturing the IgM
antibody versus the altered IgG. We
cannot explain why the cryocrit seemed
to rise as the patient improved, but
since the pathophysiology of this dis­
ease is not clearly understood, we feel
the latter effect is more important.

Acknowledgements

We thank Quinton C. Callies, MD, for
his help with immunologic studies;
John Rebuck, MD; Pedro Cortes, MD;
and Paul Bartlett, PhD, for their help
with pathologic specimens.

References

1. Meltzer, M, and Franklin, EC: Cryo-
globulins, rheumatoid factors and con­
nective tissue disorders. *Arthritis
Rheum* 10:489-92, Oct 1967

study of twenty-nine patients. *Amer J
Med* 40:828-56, June 1966

3. Mathison, DA, et al: Purpura, arthralgia,
and IgM-IgG cryoglobulinemia with
rheumatoid factor activity, *Ann Intern
Med* 74:383-90, 1971

4. Barnett, EV, et al: Cryoglobulinemia and
disease, *Ann Intern Med* 73:95-107,
1970

5. Zinneman, HH, et al: On the nature of
cryoglobulins. *J Immun* 100:594-603,
1968

6. Franklin, EC: Medical grand rounds -
cryoglobulinemia. *Amer J Med Sci*
262:50-7, Jul 1971

weakness-cryoglobulinemia. *Arch Intern
Med* 126:287-9, Aug 1970

8. Whitsed, HM, et al: IGA/IgG cryo-
lobulinemia with vasculitis. *Clin Exp

9. Cream, JJ: Immunofluorescent studies of
the skin in cryoglobulinemic vasculitis.
*Brit J Derm* 84:48-53, 1971

cryoglobulinemia associated with atypical
glomerulonephritis and the
nephrotic syndrome, *Amer J Med*
47:957-66, Dec 1969

11. Wintrobe, MM, and Buell, MV: Hyper-
proteinemia associated with multiple
myeloma. *Bull Johns Hopkins Hospital*
52:156, 1933

12. Lerner, AB, and Watson, CJ: Studies of
cryoglobulins. 1. Unusual purpura
associated with the presence of a high
concentration of cryoglobulin (cold
precipitable serum globulin). *Amer J

13. Foley, JF, Karlen, M, and Watson, CJ:
Anticoagulant therapy of cryoglobu-
linemic ulcers in a case of Sjorgen's
syndrome. *Jama* 176:149-52, 1961

14. Domz, LA, and Feigin EU: Cryo-
globulinemia. Rationale and results of
dishydiodoxycoumarin (Dicumeral)
therapy. *Arch Intern Med* 100:471-3,
1957

15. Meltzer, M, Franklin EC, Elias K et al:
Cryoglobulinemia. A clinical and
laboratory study II. Cryoglobulins
with rheumatoid factor activity. *Amer

16. Golde, D and Epstein, W: Mixed cryo-
globulins and glomerulonephritis. *Ann