MIXED ESSENTIAL CRYOGLOBULINEMIA AND HEPATITIS C: A MODEL OF VIRAL INDUCED AUTOIMMUNITY?

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Medical Grand Rounds

October 8, 1992

INTRODUCTION

Case presentation. This 54 year old white male was well until the fall of 1983 when he presented to an outside hospital with a purpuric rash over his lower extremities. A physical exam revealed hypertension and initial laboratory workup revealed anemia, hypocomplementemia and renal insufficiency. A percutaneous renal biopsy was unsuccessful but a skin biopsy revealed leukocytoclastic vasculitis and a testicular biopsy revealed IgA in the vessel walls. A diagnosis of Henoch-Schonlein purpura was made and the patient was treated with prednisone.

In January of 1984 the patient presented to Parkland Memorial Hospital complaining of persistent abdominal pain and constipation. Physical exam revealed hypertension, splenomegaly, a purpuric rash over the lower extremities, right arm and buttocks. Laboratory exam revealed worsening renal insufficiency, a cryocrit of 125 mg% with IgG and IgM present. Kidney biopsy revealed glomerulonephritis with glomerulocapillary IgM and IgG. A diagnosis of essential cryoglobulinemia was made and the patient was treated with plasmapheresis and prednisone. His creatinine returned to normal by the sixth treatment with plasmapheresis. By late February of 1984 he returned with fatigue, rash, abdominal pain, persistently guiaic positive stools and renal insufficiency. The patient was started on cytoxan and returned to clinic in march with an improvement in his rash. The patient was found dead in his van in April of 1984. Autopsy revealed chronic inflammation in the liver with periportal fibrosis, splenomegaly, diffuse glomerulonephritis, pulmonary congestion, concentric left ventricular hypertrophy and submucosal hemorrhage throughout the duodenum, small bowel and colon. The cause of death was thought to be secondary to hypertensive cardiomyopathy with an associated arrhythmia.

This case illustrates a number of features of essential mixed cryoglobulinemia (EMC). The syndrome is characterized by purpura, chronic liver disease, weakness, renal disease, neurologic involvement and cryoglobulins that consist of IgM and IgG or IgA. Plasmapheresis is frequently successful as a initial step in the management, but patients frequently relapse and require cytotoxic agents. Recently a number of insights have been made into the pathogenesis and treatment of this disorder. The current review will review the epidemiologic and clinical aspects of this disease and then focus on the new insights into the pathogenesis and treatment.

In 1933 Wintrobe and Buell first described a cold-precipitable globulin in the blood of a patient with multiple myeloma. The term cryoglobulin was coined by Lerner and Watson to

describe these proteins. In 1962 Lopalluto and Ziff described a patient with a cryoglobulin made up of IgM and IgG in which the IgM component had rheumatoid factor activity. This was later termed a mixed cryoglobulin. The association between cryoglobulins, vasculitis and renal disease was described by Meltzer in 1966.

Cryoglobulinemia is a pathological condition in which the blood contains immunoglobulins that precipitate reversibly in the cold. According to the most widely used classification there are three types of cryoglobulinemia. In type I cryoglobulinemia, the cryoprecipitable immunoglobulin is a single monoclonal immunoglobulin, usually a myeloma protein or a macroglobulin. Type II and III cryoglobulinemia are both mixed cryoglobulinemias, composed of at least two immunoglobulins. In both, a polyclonal IgG is bound to another immunoglobulin. In type II cryoglobulinemia, the second component is a monoclonal IgM rheumatoid factor. In type III cryoglobulinemia the second component is a polyclonal rheumatoid factor. The current review will focus on type II and III cryoglobulinemia or "mixed cryoglobulinemia".

Since their description, cryoglobulinemia has been found in association with a variety of diseases. Type I cryoglobulins are usually found in myelomas and Waldenstrom's macroglobulinemias. The majority of mixed cryoglobulinemias, which are 60 to 75% of all cryoglobulinemias, are found in connective tissue diseases, infectious or lymphoproliferative disorders, or in immunologically-mediated glomerular diseases, and are considered "secondary mixed cryoglobulinemias". In 30% of mixed cryoglobulinemias, however, the etiology is not clear and the cryoglobulinemia is referred to as "essential".

One important concept to remember when considering this disorder is that cryoglobulins

occur in a number of clinical settings with or without the syndrome of purpura, arthralgias, liver involvement or renal disease discussed in this review. Thus, either cryoglobulins have nothing to do with the pathogenesis of these disorders or their are important differences between cryoglobulins that cause disease and others that do not.

EPIDEMIOLOGIC FEATURES

The incidence of EMC varies in different geographical areas, the majority of cases having been reported in the Mediterranean countries, namely Italy, France, Spain and Israel. Type II EMC manifests itself usually from the fourth to fifth decade of life, although the first presentation has been reported for younger patients. Women outnumber men in non-selected populations.

CLINICAL FEATURES OF MIXED CRYOGLOBULINEMIA

Cutaneous symptoms

Purpura. This is the most common symptom of MC and was present in our case. Its incidence varies from 59 to 100% in different series (Table I). Almost invariably it occurs on the lower extremities. Recurrent involvement over time may lead to hyperpigmentation and ulceration. Skin biopsies reveal leukocytoclastic vasculitis with perivascular infiltration by pycnotic PMNs. Intravascular deposits similar to those seen in the kidney can occasionally be seen in the skin. Rash has been reported to be accompanied by pain and pruritus in some cases.

Necrosis Incidence of 11% to 30% (Table II). It is much more common in type I than in type II or III MC. Usually on the lower limb in the submalleolar region, but necrosis secondary to

vasculitis has been reported over the nose, fingers, toes and ears.

Table I

EPIDEMIOLOGIC AND CLINICAL FINDINGS IN PATIENTS

WITH MIXED ESSENTIAL CRYOGLOBULINEMIA

Parameter	Ferri et al.	Gorevic et al.
Age	59 ± 8	52
Sex	33F:9M	24F:11M
Purpura	95%	100%
Arthralgias	90%	72%
Raynaud's	32%	25%
Peripheral neuropathy	65%	20%
Renal involvement	32%	55%
Liver involvement	55%[1]	70%

[1]On the basis of histologic and/or liver function tests.

Raynaud's Present in 50% of patients with MC. It is equally distributed over patients with type I, II and II MC. It is less common, however, when you remove patients with connective tissue

diseases from the population and study just those patient with EMC (incidence of 7-34%).

Table II

INCIDENCE OF SYMPTOMS OBSERVED IN 86 PATIENTS WITH CRYOGLOBULINEMIA

Symptoms	General Incidence (%)	Incidence (%) according to cryoglobulin type		
		I	II	III
Purpura	55	15	60	70
Distal necrosis	14	40	20	0
Raynaud's phenomenon	50	40	40	60
Articular symptoms	35	5	20	58
Renal symptoms	21	25	35	12
Neurologic symptoms	17	15	5	25

From Brouet et al.

Arthritis/arthralgia

50%-90% of patients with EMC complain of arthralgias (Tables I and II). PIP, MCP and knees are most commonly effected. Evolution to arthritis unusual and deformity uncommon. A smaller group of patient develop frank arthritis with an incidence of less than 30%. Erosion and

deformity is not common even within these patients. The joints most frequently involved are depicted in Table III.

Table III

JOINT MANIFESTATION OF 16 PATIENTS WITH

ESSENTIAL CRYOGLOBULINEMIA

Arthralgias	Arthritis	Joint Involvement
25%	25%	Knees, Ankles>Shoulder>MCP

From Weinberger et al.

Neurologic involvement

Table IV

NEUROLOGIC ABNORMALITIES REPORTED IN

ASSOCIATION WITH EMC

Symmetrical/Asymmetrical polyneuropathy
Foot drop
Paresthesias
Cerebral vascular accidents
Seizures
Coma (diffuse cerebral thrombotic vasculitis)

The incidence of neurologic involvement in EMC varies from 7% to 43% depending in part on the method used to assess involvement. In one study using electromyography 43% of patients had evidence of involvement whereas other studies using clinical criteria have reported lower percentages. Neurologic involvement (Table IV) generally manifests itself as a distal subacute sensory motor neuropathy, although acute presentations have been reported. In a few cases pure sensory neuropathies have been reported. It may be either symmetrical or asymmetric. Sural nerve biopsies reveal vasculitis of the vasa vasorum and demyelinization or axonic degeneration. CNS involvement is rare.

Hepatic and splenic involvement

The incidence of liver involvement in EMC varies between series with frequencies ranging from 16 to 80% (Table I). Although subclinical, it was present in the autopsy report of our patient. Liver biopsies tend to show chronic active or persistent hepatitis or cirrhosis. Liver involvement was the third leading cause of death in one series after cardiovascular accidents and infection.

Patients with liver disease without the clinical syndrome of purpura, weakness, arthralgia and renal disease have also been found to produce both rheumatoid factor and cryoglobulins at levels that are greater than normal individuals. For example, rheumatoid factor is found in 60% in patients with acute hepatitis, and 40% of patients with chronic hepatitis. Only 0-5% of patients with PBC produce rheumatoid factor. The incidence of cryoglobulins in patients with chronic hepatitis secondary to hepatitis C is more than twice that of patients with hepatitis from other causes. This latter finding suggests a relationship between hepatitis C and cryoglobulinemia. This

association has recently been confirmed in a number of studies. These studies have reported the presence of antibodies to hepatitis C in 30-90% of the patients with EMC. Moreover, a group of investigators has now demonstrated that 84-90% of patients with EMC have hepatitis C virus in their serum using PCR (Table V).

Table V

PREVALENCE OF HCV IN MIXED CRYOGLOBULINEMIA PATIENTS

HCV-RNA	HCV-Ab		
PCR	Chiron ELISA	Chiron ELISA	Wellcome ELISA
86%	90%	90%	90%
36/42	38/42	38/42	38/42

Population consisted of 46% type II and 54% type III.

From Ferri et al.

Most of these investigators have not been able to demonstrate that these antibodies are selectively concentrated in the cryocrit. However, Agnello et al have recently demonstrated a 1000 fold concentration of the virus in the cryocrit using quantitative PCR. Two groups have now reported

that a number of patients with hepatitis C and cryoglobulinemia have false negative tests for hepatitis C. For example, in one study of 19 patients with EMC, 54% had antibodies to hepatitis C whereas 84% had hepatitis C RNA in their serum. Thus, there may be something unusual about the immune response of patients with EMC to infection with hepatitis C. These studies suggest that the virus may be playing an important role in the pathogenesis of cryoglobulin formation.

The association of hepatitis B and EMC is controversial. Two studies have reported high frequencies of antibodies to hepatitis B in patients with EMC, but a number of more recent studies have found only modest increases or no increases in the frequency of antibodies to hepatitis B in these patients. The relationship between hepatitis B and EMC may be the result of a relationship between hepatitis C and hepatitis B. In several series the incidence of antibodies to hepatitis B appears to be higher in patients with hepatitis C than in normal individuals. In fact, prior to the discovery of the hepatitis C virus, antibodies to hepatitis C core antigen were used as method to screen blood for the agent that causes non-A, non-B hepatitis. This screening strategy was found to remove 30% of the donors with blood contaminated by hepatitis C.

Gastrointestinal involvement

Abdominal pain is found in 13% of patients with EMC and was present in the case discussed in the introduction. Colonic biopsies have shown diffuse colitis characterized by depletion of mucin, slight increase in lamina propria inflammatory cells and focal hemorrhages. Superficial ulceration of the cecal mucosa has been observed.

Pulmonary involvement

Dyspnea and pleurisy have been reported in 18% to 40% of patients with EMC. The symptoms are usually mild although death from pulmonary complication have been reported. Test

of small airways disease are frequently abnormal as are test of gas exchange (abnormal in 40%). Biopsies reveal infiltration of arteriolar walls and alveolar septum by lymphocytes, granulocytes and plasmacytes along with IgM and IgG deposition on the small vessel walls.

Miscellaneous

Parotid biopsies reveal changes consistent with Sjögrens syndrome in a high percentage of patients. Moreover, sicca symptoms are present in 15% of patients (Table IV).

Table VI

ASSOCIATION OF SJOGRENS SYNDROME IN PATIENTS WITH CRYOGLOBULINEMIA

	Investigators			
	Gorevic[1]	Brouet	Invernizzi	Vitali
N	50	86	166	21
Percent with Sjogrens	14%	9.3%	4%	41%

[1] 50% type II and 50% type III.

Lymphadenopathy is present in 2-17% of patients.

Renal involvement

The incidence of renal involvement varies from 20-50% (Table I). One review of 102 cases available from the literature in which detailed information is available about the onset, clinical features and outcome of the renal disease, the presenting renal involvement was

hematuria and/or proteinuria in more than half the patients. Nephrotic syndrome was the presenting syndrome in about 20% of the patients, while in another 20%, the presenting picture was one of hypertension, hematuria and proteinuria ("Nephritic syndrome"). The nephritic syndrome evolved into acute oliguric renal failure in less than 5% of the cases. 50% of patients that present with evidence of renal disease experienced a complete remission. For another 30% no evolution was observed. In antoher review of the literature, out of 11 patients with EMC and renal disease treated with supportive measures alone, 4 died or showed progressive renal disease, two had stable renal insufficiency whereas five had a spontaneous improvement.

Table VI

DIFFERENCES BETWEEN THE PATHOLOGY OF GLOMERULONEPHRITIS ASSOCIATED WITH CRYOGLOBULINEMIA AND THAT ASSOCIATED WITH SLE

1.	Massive endocapillary proliferation due mainly to monocytes.
2.	Eosinophilic, PAS-positive, Congo red-negative deposits of variable size lying along the inner side of the capillary lumen (intraluminal thrombi).
3.	Thickening of the glomerular basement membrane with double contour. More exuberant then in SLE or idiopathic GN.
4.	Extracapillary proliferation uncommon.
5.	Small and medium size arteritis.
6.	Interstitial infiltration with CD8+ T cells.
7.	Immunohistology reveals C3, IgG and IgM.

Renal involvement is usually a late complication of EMC, but the concomitant appearance

of renal and systemic signs of the disease (purpura, arthralgias, systemic vasculitis) is not infrequent. In some patients, the renal involvement is the presenting manifestation of the disease and makes diagnosis possible even before the appearance of purpura. The incidence of renal disease is somewhat higher in patients with type III EMC then type II EMC.

Light microscopy findings. In the majority of patients, a particular type of membranoproliferative exudative glomerulonephritis is found. The most characteristic finding is the presence of a intraluminal deposits that frequently occlude the lumen. The differences that distinguish the glomerulonephritis caused by cryoglobulins from that caused by systemic lupus erythematosus are illustrated in Table VI. One group on investigators has found a correlation between intraluminal thrombi and a worse renal outcome (Table VII).

Table VII

SIGNIFICANCE OF CAPILLARY THROMBI ON RENAL BIOPSY OF PATIENTS WITH MIXED CRYOGLOBULINEMIA

	Outcome	
Endocapillary thrombi[1]	Death	CRF
Present (n=9)	56	45
Absent (n=37)	35	16

[1] All patients had membranoproliferative glomerulonephritis on biopsy.

From Tarantino et al.

Electron microscopic findings. Electron dense deposits can be found in the capillary lumen, usually in a subendothelial position, but sometimes also filling the capillary lumen. They are sometimes amorphous immune complex-like deposits, but often they have a peculiar fibrillar

or crystalloid structure. In IgG-IgM EMC the crystalloid structure, which is identical to that seen in the *in vitro* cryoprecipitate of the same patients, consists of cylinders 100 or 1000 nm long which have a hollow axis. In cross sections they look like annular bodies with a light center, a dense ring and lighter peripheral protein coat. The crystalloid deposits, which present, are often surrounded by areas of amorphous, weakly osmiophilic and translucent material, attributed to deposit degradation. Both types of deposits are infrequently seen in the mesangial area and subepithelial ones are quite exceptional. Circulating aggregates or structured material can sometimes be found in peritubular capillaries and arterioles.

Immunohistological features. Three patterns of glomerular deposition can be seen by immunofluorescence: a) Intense massive staining of huge deposits that fill the capillary lumen (intraluminal thrombi), usually associated with faint irregular segmental parietal staining of some peripheral loops, in a subendothelial position; b) The same pattern of faint irregular segmental parietal staining of some peripheral loops, in a subendothelial position, but without any intraluminal staining; c) Intense granular diffuse staining of peripheral loops, with a subendothelial pattern.

PATHOGENESIS

The precise mechanisms underlying the pathogenesis of essential cryoglobulinemia are unclear. There are at least two important questions raised by the available data. The first is what is the role of cryoglobulins in the vasculitis? It remains possible that the cryoglobulins have no role in the pathogenesis of EMC. This might explain why cryoglobulins are present in a number

Table VIII

DO CRYOGLOBULINS PLAY A ROLE IN THE PATHOGENESIS OF EMC?

1. Cryoglobulins are found in patients with chronic inflammatory disorders including hepatitis, but most of these patients do not develop vasculitis.
2. The clinical course of EMC does not correlate with the levels of cryoglobulin.
3. The ultrastructure of renal deposits in EMC is nearly identical to that of the cryocrit.
4. Clinical improvement following plasmapheresis correlates well with disappearance of the cryoglobulin.

of patients without vasculitis. Moreover, it might explain why there is a poor correlation between the amount of cryoglobulin and the extent of the cutaneous vasculitis in any given patient. Arguing against this interpretation, however, is the finding that the ultrastructure of the precipitates present in the kidney resemble the ultrastructure of the cryoglobulin. In addition, removal of the cryoprecipitate with plasmapheresis frequently ameliorates the symptoms. Thus, while it is still quite possible that they play no role in the pathogenesis of the vasculitis, is seems somewhat more likely that the cryoglobulins are pathogenic. If cryoglobulins are pathogenic in patients with EMC, then they must differ from those in patients without vasculitis. One potential explanation for the pathogenicity of cryoglobulins from patients with EMC to cause vasculitis might relate to the presence of antigen in the complex. Simple complexes involving IgM and IgG

might be relatively innocuous, while those containing antibody bound to antigen might result in vasculitis. The presence of antigen might facilitate complement activation and increase the pathogenicity of the cryoglobulin. If this model is correct, then changes in the concentration of antigen might alter their pathogenicity within the same patient. In the case of hepatitis C, the presence of the virus in the precipitate may be responsible for the apparent pathogenicity of the cryoglobulins. Changes in the level of viremia might alter the clinical course without changing the concentration of the cryoglobulin.

The second question is what is the role of hepatitis C in EMC? The evidence pertaining to the role of hepatitis C in EMC is listed in Table IX. It remains possible that hepatitis C has

Table IX

WHAT IS THE ROLE OF HEPATITIS C OF HEPATITIS C

IN THE PATHOGENESIS OF EMC?

1. Association with hepatitis C viremia.
2. Presence of hepatitis C in the cryocrit.
3. Malignant and benign monoclonal and polyclonal rheumatoid factors present in patients with EMC are associated with hepatitis C.
4. Rapid improvement with α-interferon therapy.

no role in the pathogenesis of cryoglobulinemia. For example, it is possible that patients with hepatitis C are more susceptible to another agent that causes EMC. The tight association between hepatitis C viremia and EMC, however, suggests that it is likely that the virus plays a pathogenic role in EMC. The finding that hepatitis C is associated with both malignant and benign type II

cryoglobulinemia and type III cryoglobulinemia suggests a common pathogenesis for these disorders. The mechanism whereby a single stimulus leads to malignant monoclonal B cell growth in one setting while leading to polyclonal expansion in another is not yet clear. It is possible that rheumatoid factors themselves recognize viral antigens and that the repertoire of hepatitis C specific rheumatoid factors is rather limited leading to the expansion of a single rheumatoid factor component. If this is the case, then EMC would represent a case of molecular mimicry in which cross-reactivity between foreign and self antigen triggers an autoimmune response. The particular IgM molecules with specificity for both hepatitis C and IgG may have the peculiar property of precipitation upon exposure to cold. In some patients the production of monoclonal rheumatoid factor is accompanied by polyclonal rheumatoid factor production. The stimulus for the polyclonal rheumatoid factor production may be different from that which stimulates monoclonal rheumatoid factor production. For example, it is possible that the chronic liver disease caused by hepatitis C triggers polyclonal rheumatoid factor production in some patients. Acute hepatitis and chronic liver disease caused by alcohol abuse have been both associated with polyclonal rheumatoid factor production. The factors that might convert benign monoclonal B cell growth and differentiation into a malignant one are unknown.

NATURAL HISTORY AND PROGNOSIS.

The natural history of the renal disease is variable. For approximately 1/3 of patients, remission of renal symptoms has been described, despite the presence of acute nephritic syndrome or a severe nephrotic syndrome at the time of presentation. Another third of cases have a more indolent course in which urinalysis reveals persistent abnormalities for several years, but

they do not develop renal failure. In approximately one fifth of patients, reversible clinical exacerbations occur over time. There exacerbation are often associated with flare-ups of the systemic signs of the disease. Multiple exacerbations may occur in a patient, at variable intervals.

Many patients develop a moderate degree of renal insufficiency. The development of end-stage renal failure is uncommon. Chronic uremia developed in only 10% of the patients reported in the literature. After a mean follow-up of more than 10 years, only 6 of 108 patients with renal involvement studied in Milan required regular dialysis treatment, while 27 had died because of extrarenal complications. The most frequent causes of death in EMC are systemic vasculitis, infections, cardiovascular and cerebrovascular accidents. The two last of these are more common in arterial hypertension, which is an early and very common complicating sign in patients with EMC.

It has been stated in the past that the outcome for patients with EMC is worse if renal involvement occurs. Recent reports have suggested that this is no longer true. In one series of more than 100 patients with EMC and renal involvement, the mortality rate was 30% at 10 years after the beginning of the disease, similar to that previously reported for patients without renal disease.

Purpura, arthralgia, peripheral neuropathy, and hepatic involvement appear in the patients with renal involvement with the same frequency as in those who do not show signs of renal disease. The existence of multiple extrarenal symptoms, and in particular of those that suggest systemic vasculitis, is associated with more severe renal involvement and with a worse prognosis.

LABORATORY FINDINGS.

The amounts of circulating cryoglobulins may vary greatly within the same patient over

time and between patients. Serum titers of IgM rheumatoid factor are usually elevated. There is no correlation between these laboratory parameters and the degree of activity of the disease.

The serum complement pattern is rather specific in EMC nephritis. Early complement components (C_{1q}, C_4) and CH50 are usually very low. C_3 is only slightly depressed and may be normal. The later components (C_5 and C_9) tend to be higher than controls.

The complement pattern does not change very much with changes in clinical activities of the disease. In fact, early complement components tend to remain low, whatever the degree of activity of the systemic or renal disease.

TREATMENT

There is only one controlled trial of any therapy in the treatment of EMC. In general, most investigators reserve treatment for those individuals with visceral involvement (ie neuropathy or nephropathy). Thus, those patient receiving therapy are often critically ill making controlled trial more difficult. Uncontrolled studies have reported that patients improve following treatment with monthly pulse steroids, plasmapheresis alone, plasmapheresis with an immunosuppressive agent, and alpha interferon. Although plasmapheresis alone has been shown to be effective in some patients, a number of patients have relapsed despite therapy and most investigators give a cytotoxic agent in combination with plasmapheresis.

One group of investigators used plasma exchange to treat 15 patients with clinical flare ups characterized by acute exacerbation of extra-renal signs and rapid deterioration of renal function. This was associated with acute nephritic syndrome or acute renal failure in 10 cases, and with impressive increase in proteinuria in the other 5 (signs of systemic vasculitis were also present in 10 cases). All the patients were given cyclophosphamide and 14 of the 15 steroids as

well (i.v. pulses of methylprednisolone for 3 of them), together with a variable number of plasma exchanges (13 on the average). They obtained rapid significant decreases in cryocrit, serum creatinine and proteinuria in all cases, while mean C_3 and C_4 levels did not change significantly. The authors concluded that simultaneous use of steroids (starting with i.v. pulses), cytotoxic drugs such as cyclophosphamide, and plasma exchange is warranted to control the more severe renal exacerbations, especially if signs of systemic vasculitis are present.

Recent evidence suggesting that EMC is caused by hepatitis C has prompted a number of investigators to treat these patients with α interferon. In one series of 21 patients, α interferon induced a complete clinical remission in 16 patients and completely eliminated the cryoglobulin in 11 patients. Many of these patients required maintenance therapy with interferon, but some achieved long term remissions with a 1-2 year course of therapy. In another controlled trial reported by Ferri et al. α interferon reduced the number of purpura and the size of the cryocrit. While α interferon is expensive it is likely to be cheaper and less toxic than therapy with plasmapheresis and cytotoxic agents. The treatment of EMC is summarized in Table X. Moreover, the effectiveness of this form of therapy, which is also active at least temporarily in most patients with hepatitis C, supports the contention that the hepatitis C virus plays a role in the penesis of this disorder.

At least one controlled trial suggested that a "low-antigen-content" diet could ameliorate the symptoms of this disease. Finally one case report has reported improvement in symptoms and the size of the cryocrit following intravenous gamma globulin.

Table X

Treatment (summary)

Indolent course	**Severe course**
	Renal involvement
Cutaneous lesions and	Malig. Hypertension
arthralgias	Generalized Vasculitis
Conservative Therapy	Corticosteroids
	Immunosuppressive agents
	Plasmapheresis and
	immunosuppressive agents
	Interferon-α

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