Peter Schlesinger, MD

Project ECHO, Hennepin Healthcare

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Cryoglobulinemia

Objectives

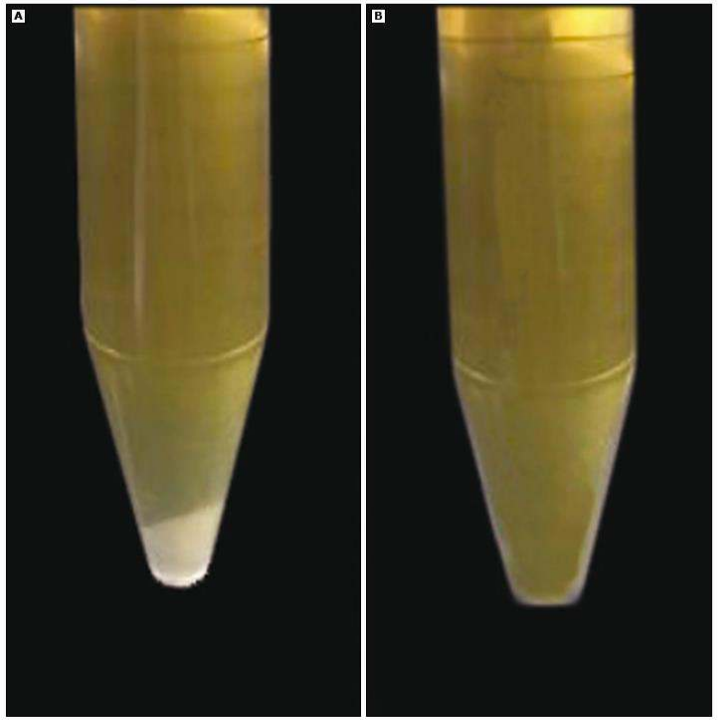
- Describe the physico-chemical properties of cryoglobulins, and their classification.
- Understand the associations between cryoglobulins and various medical conditions.
- Describe a general approach to treatment.

- I will mention off-label use of rituximab for HCV-associated cryoglobulinemic vasculitis
- I have no financial COI to disclose.

Cryoglobulins: definition

- Immunoglobulins that spontaneously precipitate from serum in the cold, after the specimen has been maintained at 37° C for clot formation and retraction, and centrifugation. They will redissolve upon rewarming.
- If large enough amount present, can be reported as cryocrit.

Serum cryoglobulin qualitative test



(A) Serum cryoprecipitates appeared after 7 days of incubation at 4°C.

(B) Serum cryoprecipitates redissolved after rewarming at 37°C.

Other cold-related conditions/lab phenomena

- Acrocyanosis
- Raynaud’s phenomenon
- Chilblains
- Livedo reticularis

- Cold agglutinins
- Cryoprecipitate
- Cryofibrinogen

Classification of cryoglobulins

- Type I: monoclonal immunoglobulin, usually IgM
- Type II: monoclonal immunoglobulin targeting polyclonal IgG
- Type III: polyclonal immunoglobulin targeting polyclonal IgG

Types II and III cryoglobulins are also immune complexes and RF

Relationship between cryos and RF

- Rheumatoid factors (RF) are autoantibodies that recognize the Fc region of IgG.
- Rheumatoid factors can be of multiple Ig classes, mainly IgM or IgG.
- Lab assays for RF measure only IgM-RF.
- IgG-RF can self-aggregate.

- Most RF do not have cryo activity, but essentially all type II or III cryos have RF activity.

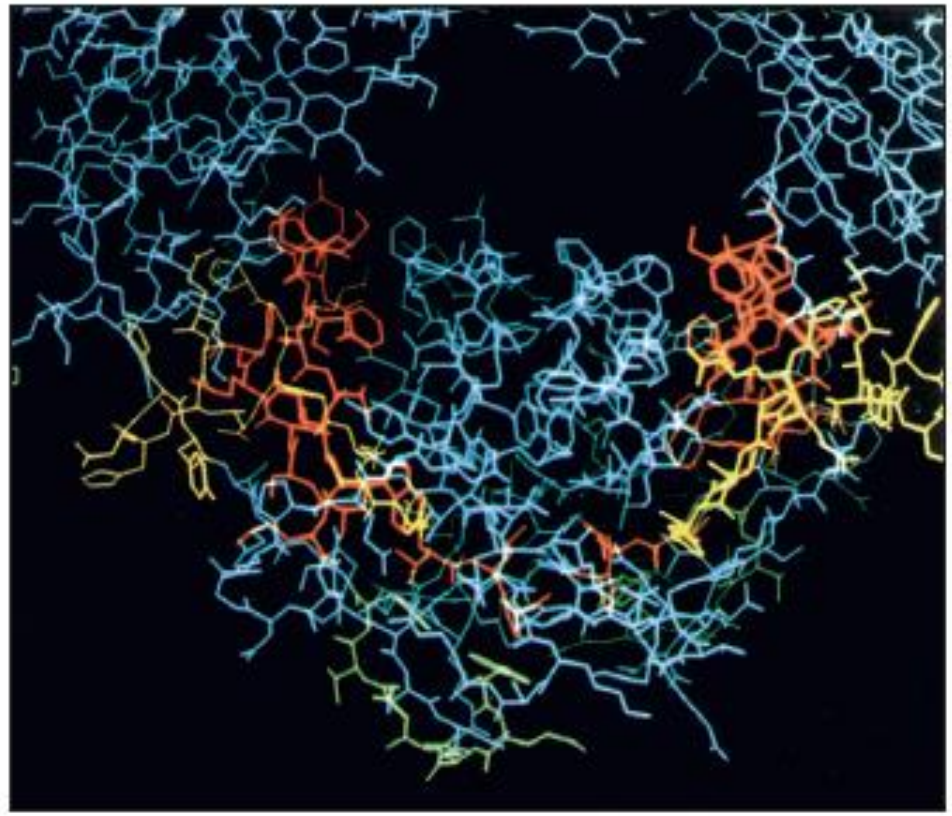


FIG. 96.1 Rheumatoid factor epitopes on IgG-Fc. A molecular model of the CH_2 and CH_3 domains of IgG show (in *yellow*) the antigenic sequence around His 435, which can be seen to protrude from the surface. Binding sites are scattered within the Cg2 and Cg3 regions of IgG-Fc. The presence of His 435 is an essential constituent of the Ga determinant and absent in IgG3. (With permission of Elsevier Science Ltd, reprinted from Peterson C, Malone CC, Williams RC Jr. Rheumatoid factor reactive sites on CH3 established by overlapping 7-mer peptide epitope analysis. Mol Immunol 1995;35:57–75.)

From Rheumatology, e-edition, 8th ed, Chapter 96.

- Cryoglobulins manifest clinically through either their sheer amount, including hyperviscosity (mainly type I); or through their ability to activate the complement system (types II and III).

- The most often involved organs are the skin, joints, kidneys, and peripheral nerves.

Table 31.1 Classification of the Cryoprecipitate According to the Brouet System.

	MEASUREMENT AS CRYOCRIT (%)	Ig CONCENTRATION (MG/ML)	Ig CONCENTRATION (MG/DL)	Ig CONCENTRATION (µG/ML)
Type I (monoclonal Ig)	>5	5–30	500–3000	5000–30,000
Type II (monoclonal Ig with RF activity against polyclonal Ig)	1–5	1–10	100–1000	1000–10,000
Type III (polyclonal Ig with RF activity against polyclonal Ig)	<1–2	0.1–1	10–100	100–1000
Normal	0	Up to 0.02	Up to 2	Up to 20

Ig, Immunoglobulin; *RF*, rheumatoid factor.

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CRYOGLOBULINEMIA

Duane Pearson, MD

Rheumatology Secrets, 4th ed.

Table 2
Differences according to cryoglobulin type.

	Type I cryoglobulin	Mixed (type II/III) cryoglobulin
Mechanism	Occlusion of the capillary lumen Vasculitis is uncommon.	Small-vessel vasculitis++ Occlusion of the capillary lumen is less common.
Clinical manifestations	Skin necrosis/ distal ischemia +++ Cold-induced symptoms	Purpura, arthralgia, glomerulonephritis
Laboratory tests	RF activity is rare. Hypocomplementemia is inconsistent.	RF activity C4 consumption
Type of monoclonal Ig	IgM> IgG> IgA	IgM+++ (Kappa » Lambda)

RF: rheumatoid factor; Ig: immunoglobulin; C4: complement component 4.

Table 1
Main clinical, laboratory, and associated manifestations according to the immunochemical type of cryoglobulinemia [16,18,20,27].

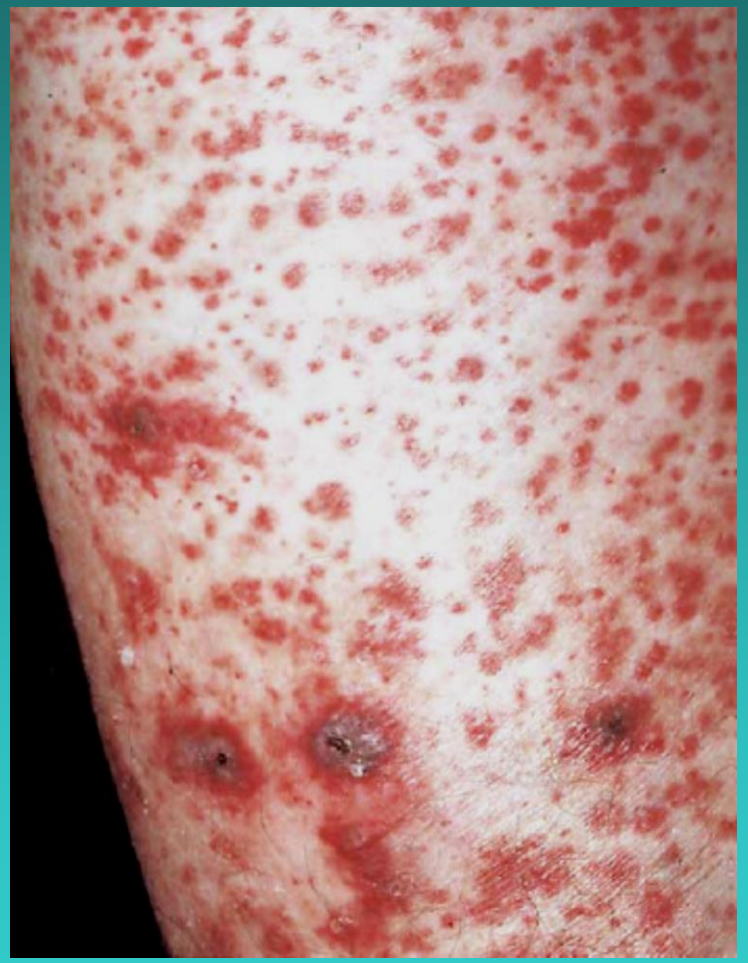
Immunochemical type	I[a]	II–III[b]
Skin		
Purpura	80%	75–90%
Raynaud's phenomenon	25–40%	20–30%
Distal ulcers/necrosis	30–35%	5–15%
Cold-induced symptoms/cold urticaria	90–100%	0–10%
Livedo	10–15%	5–10%
Arthralgia/arthurite	25–30%	50–80%
Neurological involvement		
Peripheral neuropathy	30–50%	50–75%
CNS involvement	exceedingly rare	5–10%
Renal involvement	15–30%	30–40%
Gastrointestinal involvement	exceedingly rare	rare
Cardiac involvement	exceedingly rare	rare
Pulmonary involvement	exceedingly rare	rare

CNS, central nervous system.

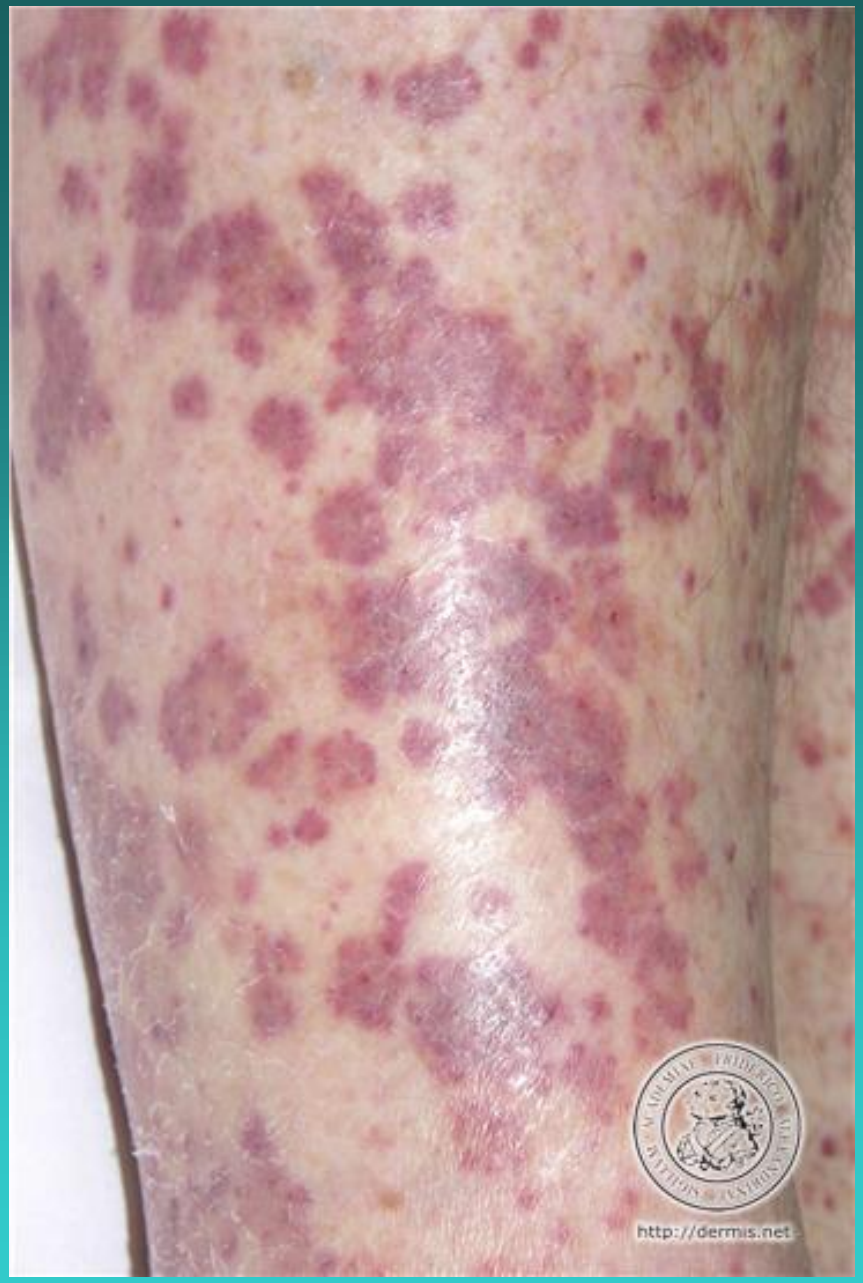
[a] simple cryoglobulin composed of a monoclonal immunoglobulin.

[b] mixed cryoglobulins; type II: monoclonal and polyclonal immunoglobulins; type III: polyclonal immunoglobulins only.

Small vessel vasculitis with palpable purpura



Jennette JC and Falk RJ, NEJM, 1997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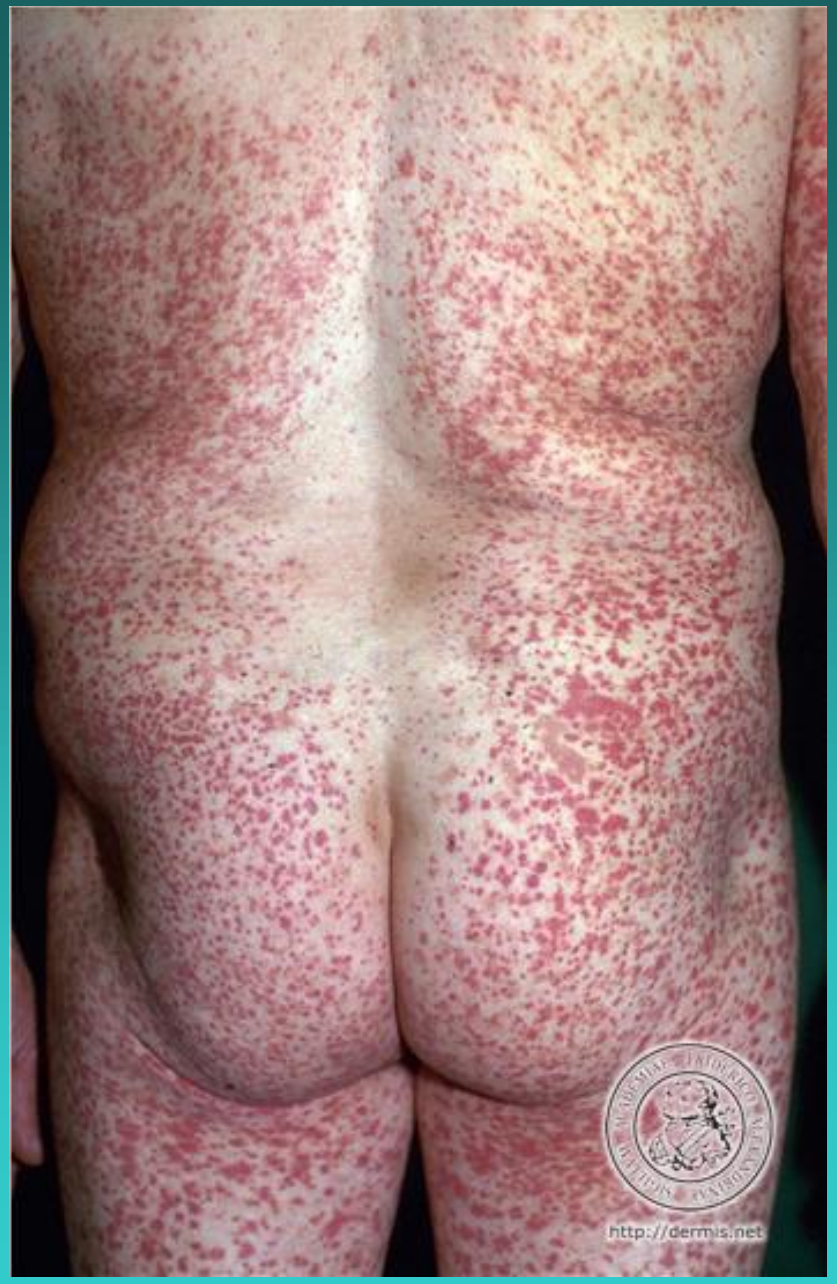
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Clinical manifestations of cryoglobulinemic vasculitis

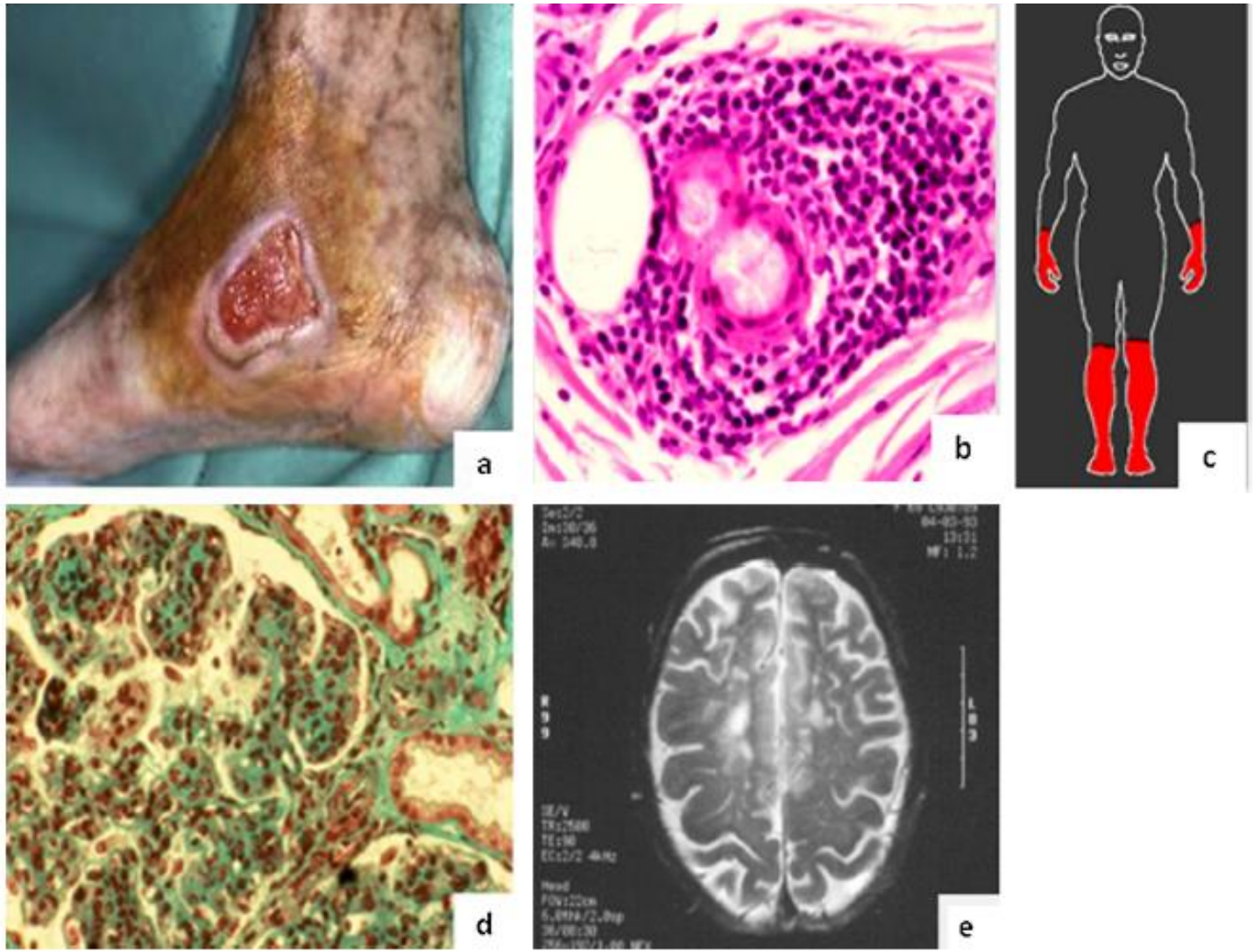
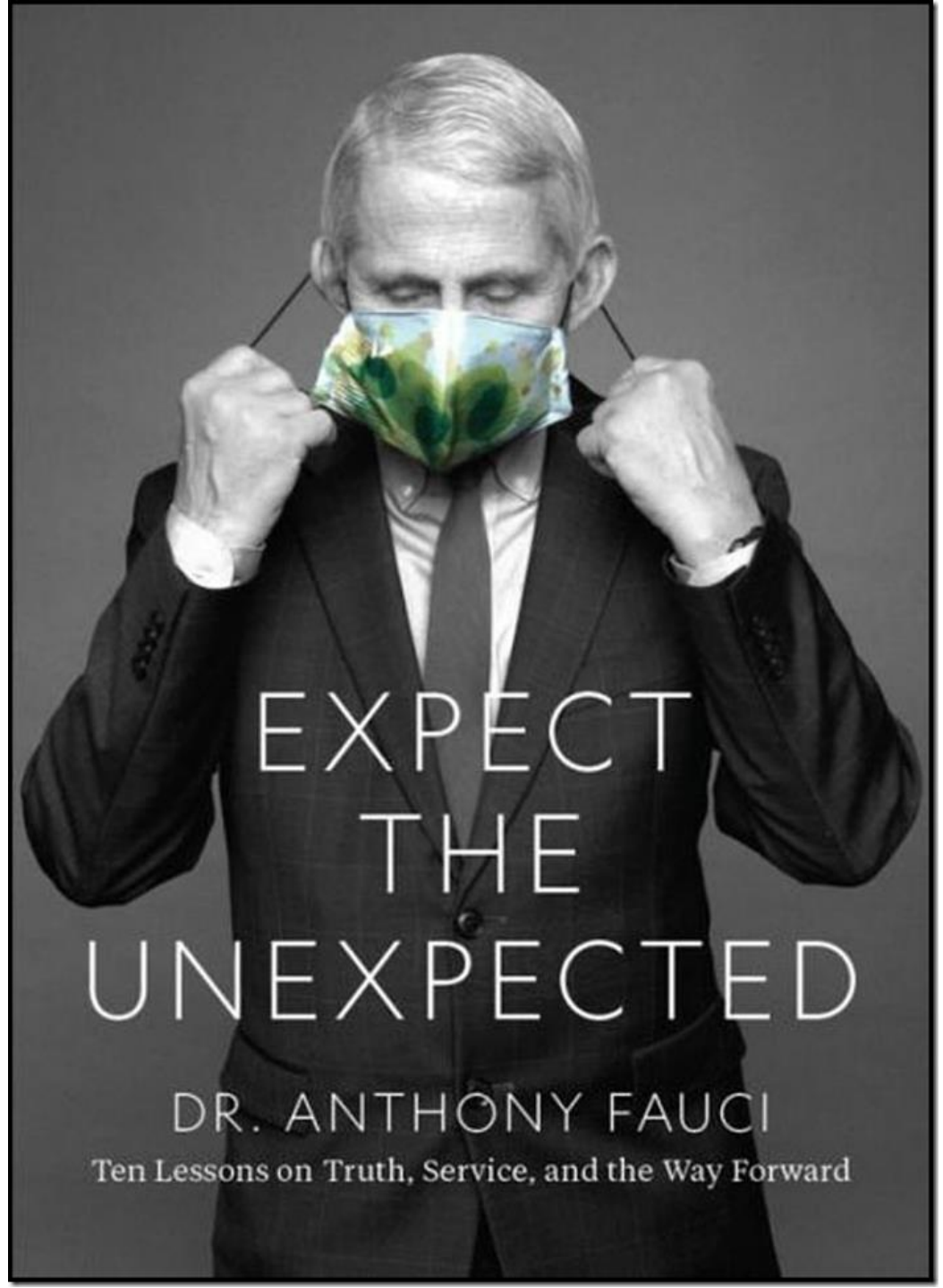


Fig. 1. Clinical manifestations of cryoglobulinemic vasculitis; a: severe skin ulcer; b: nerve biopsy specimen showing vasculitis with a perivascular inflammatory infiltrate; c: distribution of the peripheral neurological involvement indicating length dependency; d: renal biopsy showing membranoproliferative glomerulonephritis; e: magnetic resonance imaging of the brain showing vasculitis.

A.C. Desbois, P. Cacoub and D. Saadoun / Joint Bone Spine 86 (2019) 707–713

Cryoglobulinemia: disease associations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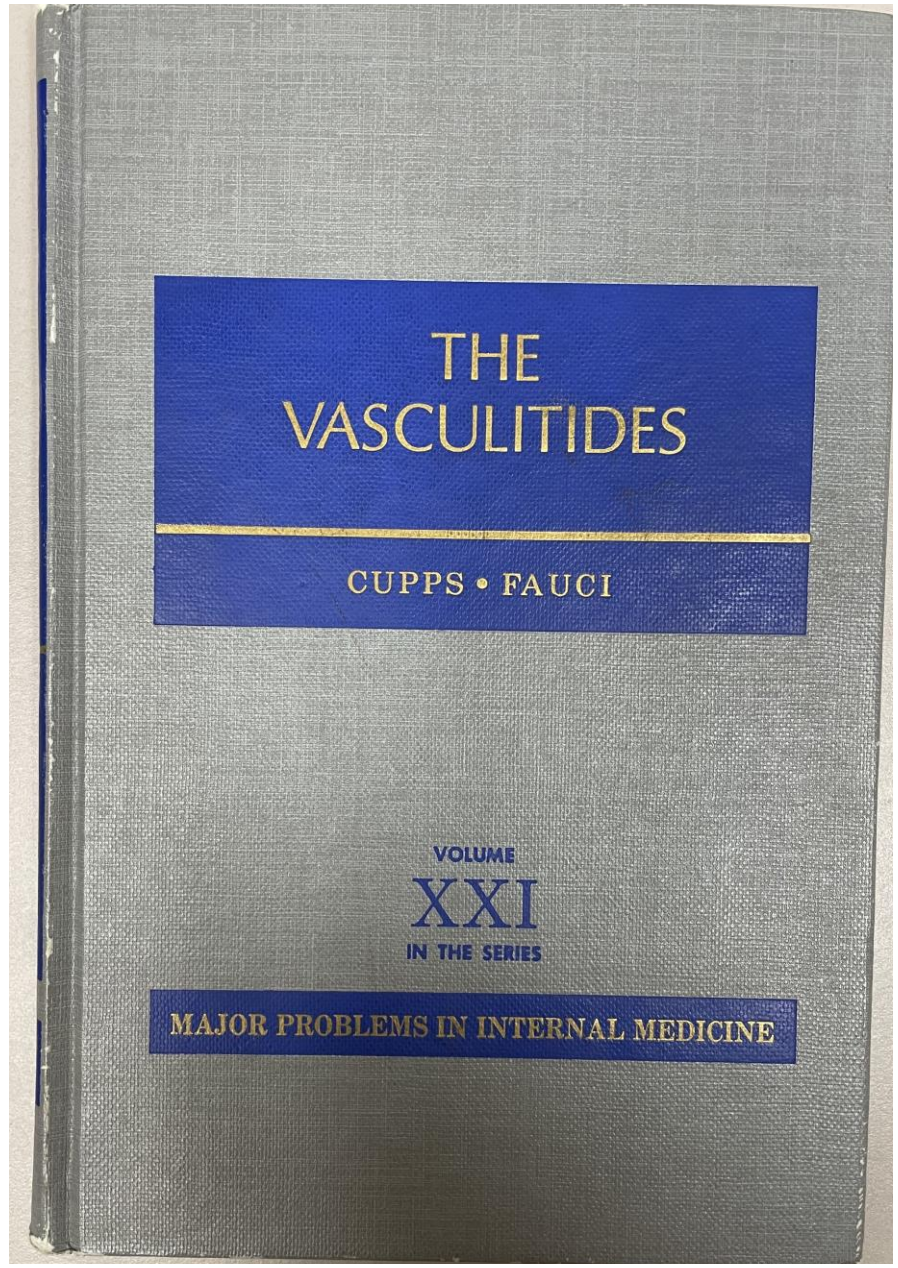
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spontaneously after one to several recurrent episodes, the prognosis even in an untreated patient is excellent.Therapy consists of supportive care and symptomatic relief. If an infectious agent is identified, an appropriate drug should be started. Any particular food implicated as a source of antigen should be eliminated from the diet. Corticosteroid therapy may be effective in reducing local edema and in suppressing gastrointestinal and joint symptoms.[248, 288] Aspirin is ineffective in suppressing symptoms and may increase the risk of bleeding. Bed rest has also been suggested, particularly if renal failure is present.[255] There is no good evidence to suggest that corticosteroids affect the outcome in patients with altered renal function,[289] and immunosuppressive therapy also seems to produce a variable response.[290, 291] However, in the rare case in which there is progressive deterioration in renal function despite corticosteroid therapy, a trial of cytotoxic therapy may be warranted.

"Vasculitis with Mixed Cryoglobulinemia"

Definition. The diseases in this group were originally referred to as essential mixed cryoglobulinemias.[104, 292, 293] However, with the demonstration of exogenous antigens (namely, hepatitis B antigen[66] and coccidioidin antigen[106] in the cryoprecipitate of certain patients with this disease), the descriptive term "essential" is no longer appropriate for all patients with mixed cryoglobulinemia and vasculitis. "Vasculitis with mixed cryoglobulinemia" is the preferred term to describe this subgroup of patients within the spectrum of hypersensi-

Box 1: Manifestations associated with cryoglobulin production; the most common are in bold type.

1. B-cell malignancies

Waldenström macroglobulinemia

Multiple myeloma (Plasmacytoma)

MGUS

B-cell non-Hodgkin's lymphoma

Chronic lymphocytic leukemia

Hairy-cell leukemia

2. Systemic and/or autoimmune diseases

Sjögren's syndrome

Systemic lupus erythematosus

Rheumatoid arthritis

Schönlein-Henoch purpura

Dermatopolymyositis

Scleroderma

Granulomatosis with polyangiitis (e.g., Wegener granulomatosis)

Periarteritis nodosa

Behçet's disease

Sarcoidosis

Autoimmune thyroiditis

Primary biliary cirrhosis

Celiac disease

Pemphigus vulgaris

Endomyocardial fibrosis

Idiopathic pulmonary fibrosis

3. Infections

a. Viral infections

Chronic hepatitis C

Chronic hepatitis B

Epstein-Barr virus infection

Cytomegalovirus infection

Acute hepatitis A

Human immunodeficiency virus infection

Human immunodeficiency virus infection

Adenovirus infection

Parvovirus B19 infection

Bacterial infections

Subacute endocarditis

Syphilis

Acute post-streptococcal glomerulonephritis

Lyme disease

Brucellosis

Coxiella infection

Mediterranean spotted fever

Atrioventricular shunt infection

Lepromatous leprosy

b. Parasitic infections

Paludism

Visceral leishmaniasis

Toxoplasmosis

Schistosomiasis

Echinococcosis

Tropical splenomegaly syndrome

c. Fungal infections

Coccidioidomycosis

4. Other

Extracapillary glomerulonephritis

Cancer: breast, nasopharynx, esophagus

Cryoglobulinemic vasculitis: differential dx

- The primary rheumatic condition most likely to mimic HCV-related cryoglobulinemic vasculitis is Sjogren's syndrome (SjS), and, to a lesser extent, systemic lupus erythematosus (SLE).
- Sjogren's causes mainly sicca symptoms (ocular, oral), but can produce extra-glandular involvement with a very similar clinical spectrum to HCV-CV.
- Excluding HCV infection is a critical step in diagnosing primary SjS.
- Both SjS and HCV infection increase the risk of lymphoma.
- SjS may progress from a "benign autoimmune exocrinopathy" to a malignant lymphoproliferative illness.

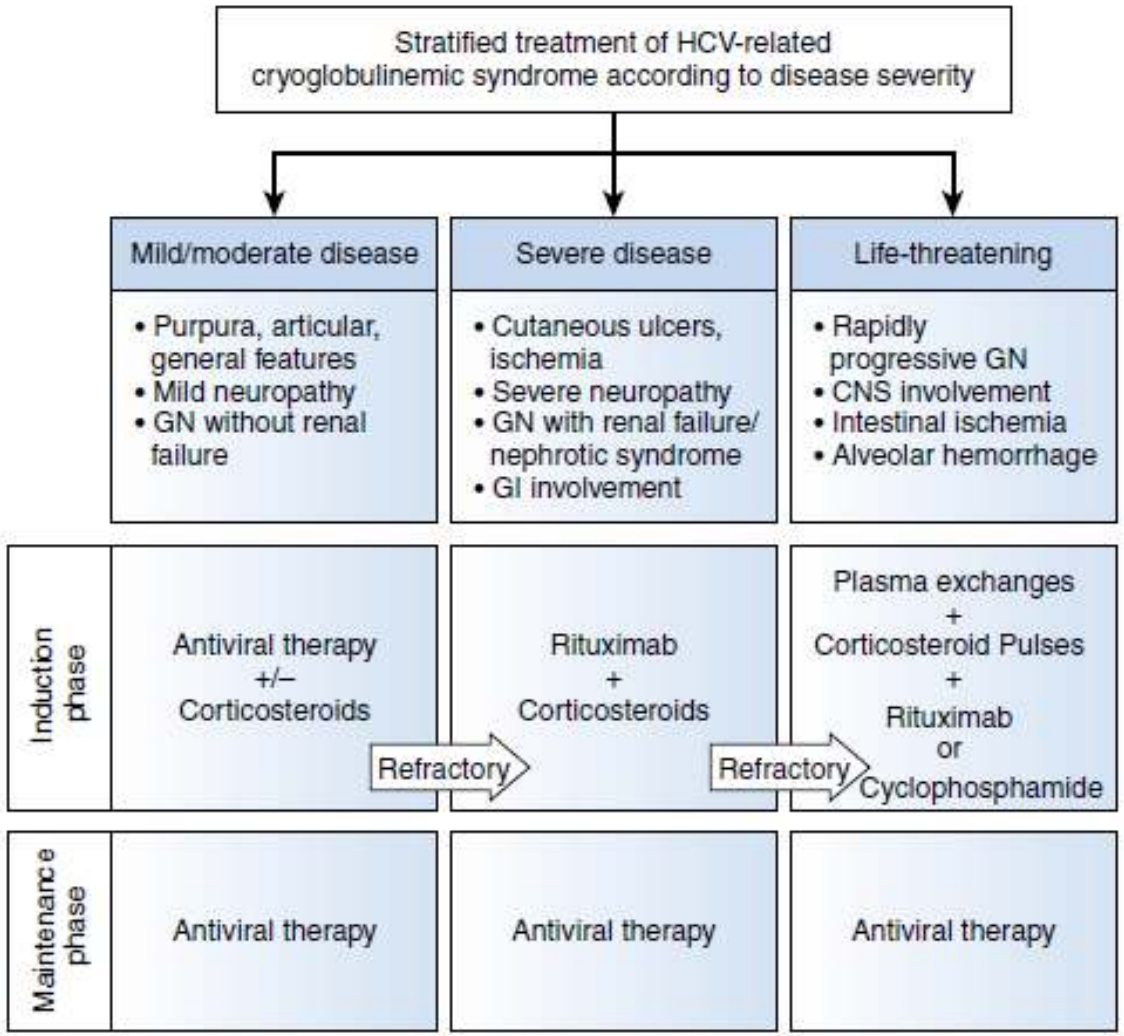

Fig. 31.2 The general treatment principles of hepatitis C virus-associated cryoglobulinemia. *CNS*, Central nervous system; *GI*, gastrointestinal; *GN*, glomerulonephritis.

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CURRENT OPINION

The dilemma of treating hepatitis C virus-associated cryoglobulinemia

Dario Roccatello, Roberta Fenoglio*, and Savino Sciascia*

Summary

Mixed cryoglobulinemia may present with multiorgan vasculitis involving kidneys, joints, skin, and peripheral nerves. Data on DAAs efficacy in HCV-associated cryoglobulinemic vasculitis are disappointing possibly because of the inability of these drugs to suppress the immune-mediated process once it has been triggered. Immunosuppression has often been employed in the past as a first-line therapy in cryoglobulinemic vasculitis despite the potential risk of the infection exacerbation. However, more manageable Rituximab-based therapeutic approaches have been more recently used without increase of viral load. Rituximab substantially changed the outcome of HCV-associated cryoglobulinemic vasculitis by providing long-term remission. A combination schedule of DAAs and Rituximab may result in eradication of both cryoglobulinemic vasculitis and HCV infection.

Curr Opin Rheumatol 2019, 31:499–504