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دانشگاه علوم پزشکی اراک

CRYOGLOBULINEMIA

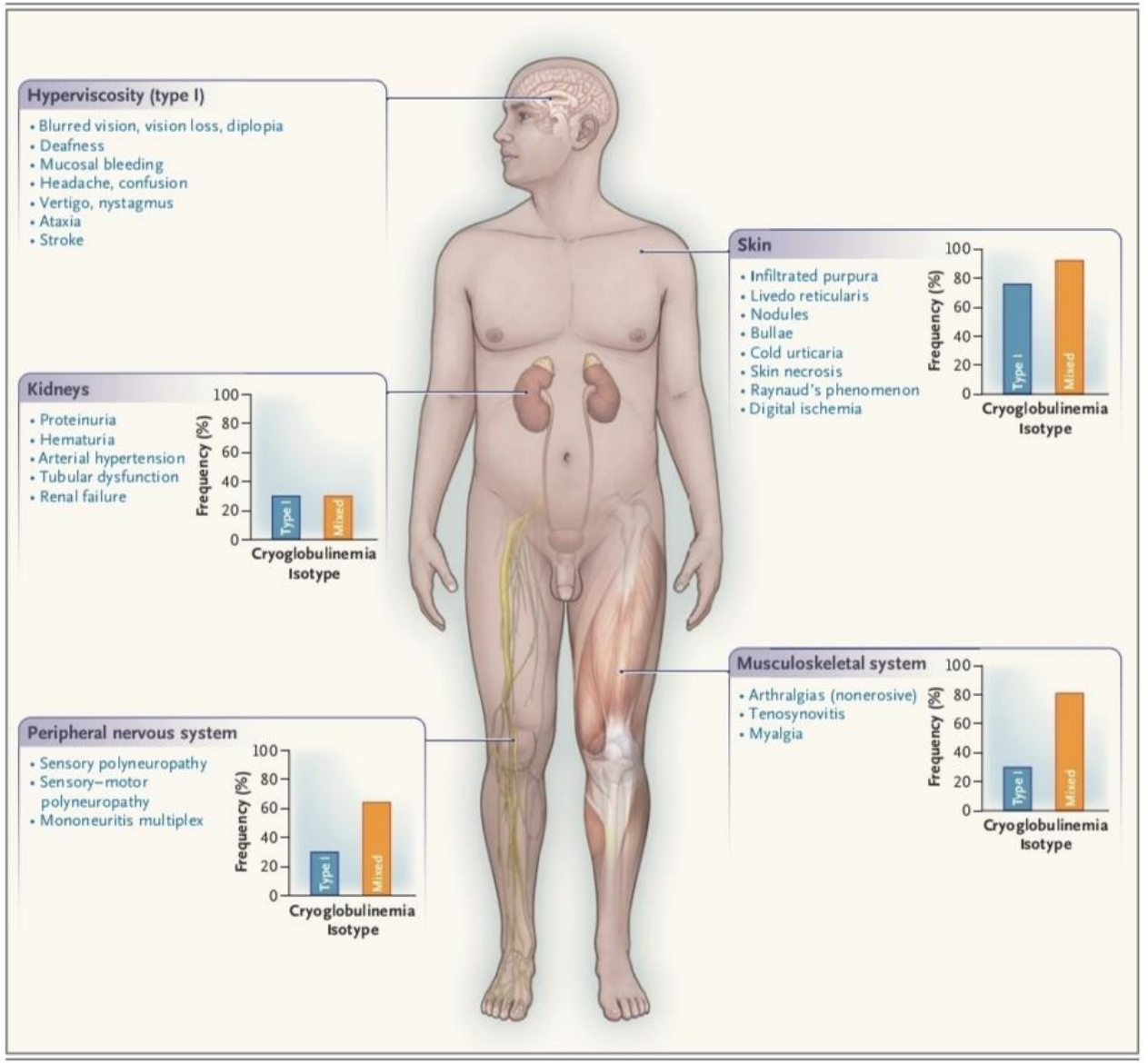
Terminology:

- Cryoglobulinemia…
- Mixed cryoglobulinemia…
- Mixed cryoglobulinemia syndrome…
- Essential Mixed Cryoglobulinemia…
- Type 1-2-3…

Table 1. Main Causes of Cryoglobulinemia.*

Cause	Disorders
Hematologic disorders	Waldenström's macroglobulinemia Multiple myeloma Non-Hodgkin's lymphoma Chronic lymphocytic leukemia Monoclonal gammopathy of clinical significance
Systemic autoimmune diseases	Sjögren's syndrome Systemic lupus erythematosus Rheumatoid arthritis
Chronic viral infections	Hepatitis C Hepatitis B Human immunodeficiency virus
Others (very rare)	Viral infections (e.g., adenovirus, herpes viruses, Epstein–Barr virus, varicella–zoster virus, human T-cell leukemia virus type 1, influenza virus, parvovirus B19, rubella virus) Bacterial infections (e.g., brucella, infective endocarditis, Lyme disease, rickettsia, syphilis) Fungal infections (e.g., coccidioidomycosis) Parasitic infections (e.g., echinococcosis, leishmaniasis, malaria, schistosomiasis, toxoplasmosis, trypanosomiasis)

* Additional tests should be performed systematically according to the cryoglobulinemia type, clinical manifestation, and suspected underlying diagnosis. Diagnostic testing generally prescribed for type I cryoglobulinemia includes a complete blood count, protein electrophoresis, serum protein immunofixation, thoracic and abdominal computed tomographic scans, a positron-emission tomographic scan, and bone marrow biopsy. For type II and III mixed cryoglobulinemias, initial testing should include viral serologic tests (anti–hepatitis C virus [HCV] antibody, HCV RNA, hepatitis B surface antigen, anti–hepatitis B surface antibody, anti–hepatitis B core antibody, and anti–human immunodeficiency virus antibody); tests for antinuclear antibodies, antibodies against extractable nuclear antigens, and anti–double-stranded DNA antibodies; and salivary-gland biopsy, if applicable. In addition, although hematologic cancers are commonly associated with type I cryoglobulinemia, they may also cause type II, so tests specific to type II cryoglobulinemia should be considered during diagnostic testing.


Hyperviscosity (type I)
• Blurred vision, vision loss, diplopia
• Deafness
• Mucosal bleeding
• Headache, confusion
• Vertigo, nystagmus
• Ataxia
• Stroke
Kidneys
• Proteinuria
• Hematuria
• Arterial hypertension
• Tubular dysfunction
• Renal failure
Frequency (%)
100
80
60
40
20
0
Type I
Mixed
Cryoglobulinemia Isotype
Peripheral nervous system
• Sensory polyneuropathy
• Sensory–motor polyneuropathy
• Mononeuritis multiplex
Frequency (%)
100
80
60
40
20
0
Type I
Mixed
Cryoglobulinemia Isotype
Skin
• Infiltrated purpura
• Livedo reticularis
• Nodules
• Bullae
• Cold urticaria
• Skin necrosis
• Raynaud's phenomenon
• Digital ischemia
Frequency (%)
100
80
60
40
20
0
Type I
Mixed
Cryoglobulinemia Isotype
Musculoskeletal system
• Arthralgias (nonerosive)
• Tenosynovitis
• Myalgia
Frequency (%)
100
80
60
40
20
0
Type I
Mixed
Cryoglobulinemia Isotype

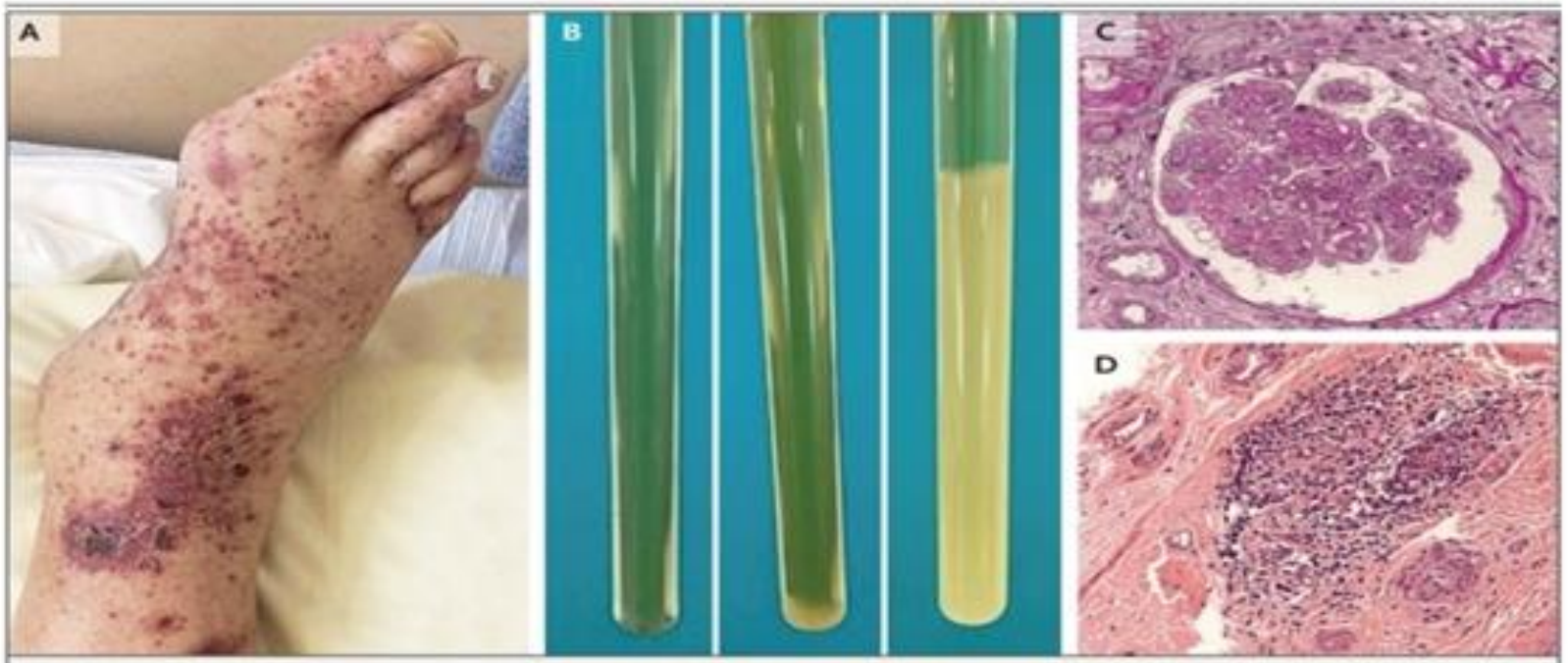
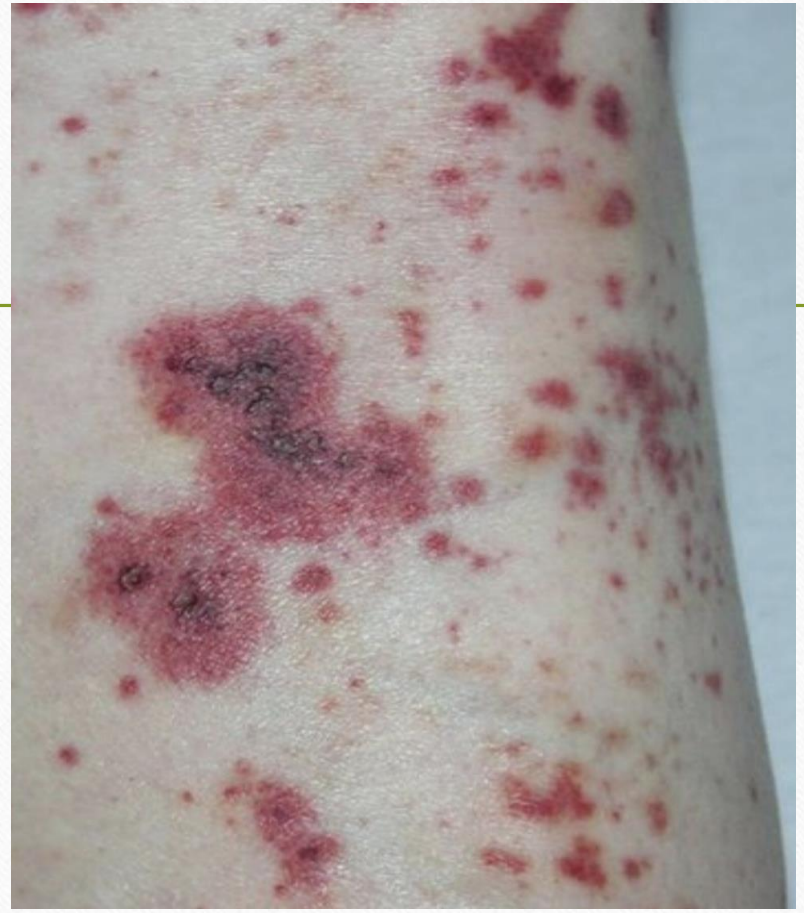
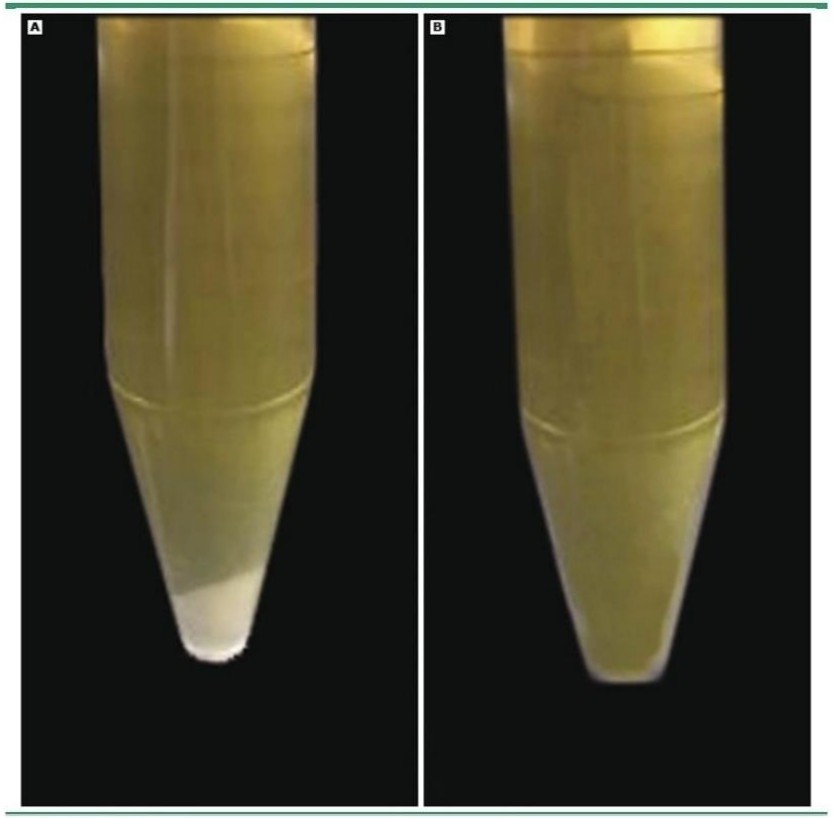


Figure 2. Diagnosis of Cryoglobulinemia.

The diagnosis of cryoglobulinemia is suspected on the basis of characteristic clinical features, such as vascular purpura of the lower limbs (Panel A). The diagnosis is confirmed through the detection of cold-induced precipitates on laboratory testing (Panel B). After centrifugation of blood at 37°C, serum is stored at 4°C for 7 days and then centrifuged at 4°C: tests might be negative (Panel B, left), positive with a low cryocrit (Panel B, middle), or positive with a very high cryocrit (cryoglobulin serum level) (Panel B, right). In cases in which a biologic diagnosis is not possible, targeted tissue biopsies may be helpful. Renal biopsy typically identifies lesions consistent with type I membranoproliferative glomerulonephritis, which is characterized by immunoglobulin deposition (the same isotype as cryoglobulinemia) and complement deposition (C3 and C1q) on immunofluorescence. Endocapillary proliferation, vasculitis, or small intrarenal artery thrombosis is common. Shown is a renal-biopsy specimen with an enlarged glomerulus with glomerular basement membrane duplication, mesangial hypercellularity, endocapillary hypercellularity, and positivity for pseudothrombi on periodic acid–Schiff staining (Panel C). Electron microscopy would show a double-contour pattern of the glomerular basement membrane. A peripheral-nerve biopsy may also be performed and would typically show a perivascular lymphocytic infiltrate adjacent to affected nerves (Panel D).



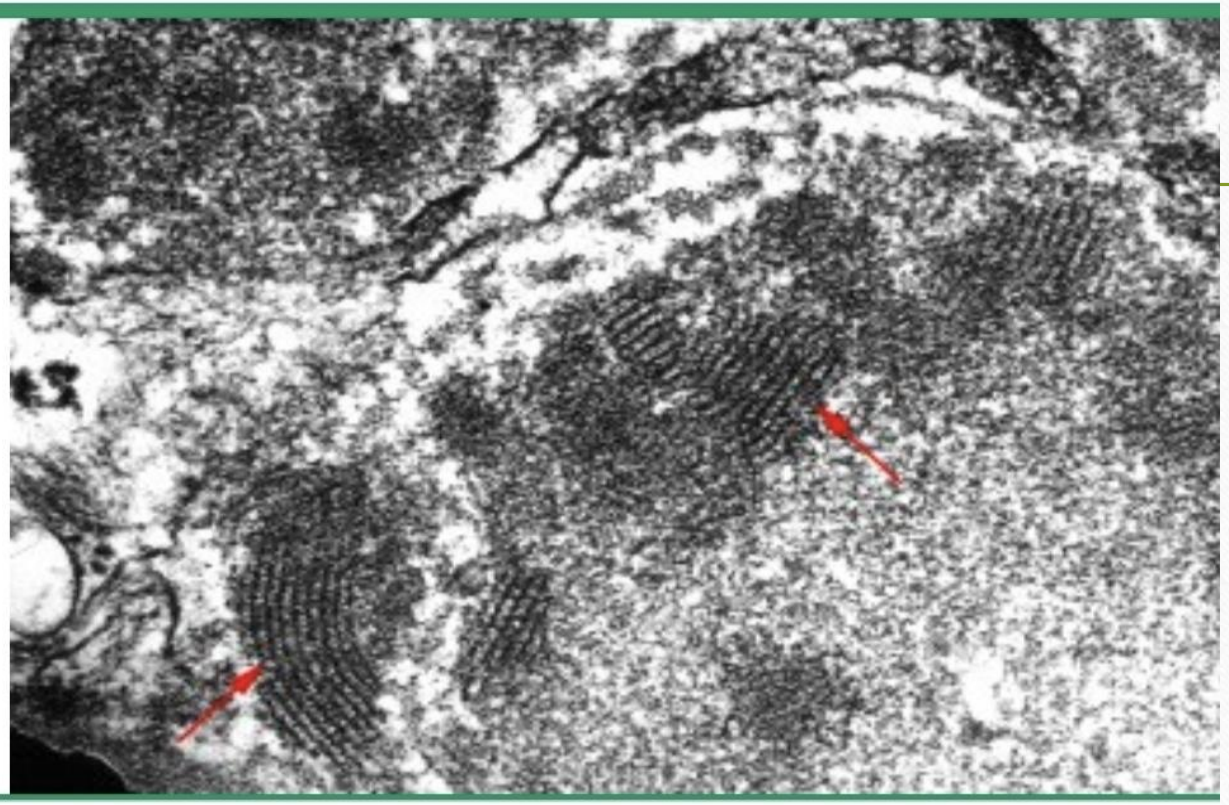
Serum cryoglobulin qualitative test



(A) Serum cryoprecipitates appeared after 7 days of incubation at 4°C.
(B) Serum cryoprecipitates redissolved after rewarming at 37°C.

Graphic 126400 Version 1.0

Fingerprint pattern in mixed cryoglobulinemia



High-power electron micrograph of a cryoprecipitate in the mesangium, showing the characteristic substructure which often h
appearance (arrows).

Table 2. Biologic and Pathologic Profile of Cryoglobulinemias.*

Characteristic	Type I Cryoglobulinemia	Type II Cryoglobulinemia	Type III Cryoglobulinemia
Range of cryoglobulin levels in serum — g/liter	1–30	0.5–2	0.05–0.5
Findings on serum protein electrophoresis	Monoclonal spike	Monoclonal spike and polyclonal elevation of gammaglobulins	Polyclonal elevation of gammaglobulins
Serum protein immunofixation	IgG (most frequent), IgM, IgA (least frequent)	Typically IgM kappa	None
Rheumatoid-factor activity	Very rare	Frequent	Variable
Low C4 level	Very rare	Frequent	Variable
Skin biopsy	Noninflammatory thrombotic lesions, with downstream infarction or hemorrhage	Leukocytoclastic vasculitis, hyaline thrombi	Leukocytoclastic vasculitis, hyaline thrombi
Peripheral-nerve biopsy	Pauci-inflammatory occlusive lesions with neuronal ischemia	Lymphocytic infiltrate around epineurial vessels, with axonal degeneration of affected nerves (vasa vasorum) Necrotizing vasculitis or demyelination might be present	Lymphocytic infiltrate around epineurial vessels, with axonal degeneration of affected nerves (vasa vasorum) Necrotizing vasculitis or demyelination might be present
Kidney biopsy	Thrombotic and hypocellular glomerular lesions Type I membranoproliferative glomerulonephritis may occur	Type I membranoproliferative glomerulonephritis, endocapillary proliferation, deposits of subendothelial or intraluminal immune complexes (or both) Electron microscopy: double-contour pattern of the glomerular basal membrane, microtubular immunoglobulin deposits Mesangial proliferative glomerulopathy, intraglomerular hyaline thrombi, and vasculitis with fibrinoid necrosis might be found	Type I membranoproliferative glomerulonephritis, endocapillary proliferation, deposits of subendothelial or intraluminal immune complexes (or both) Electron microscopy: double-contour pattern of the glomerular basal membrane, microtubular immunoglobulin deposits Mesangial proliferative glomerulopathy, intraglomerular hyaline thrombi, and vasculitis with fibrinoid necrosis might be found
Direct immunofluorescence	Monoclonal immunoglobulin, usually without complement deposition	Deposits of IgM, IgG, or C3 (or a combination of the three)	Deposits of IgM, IgG, or C3 (or a combination of the three)

* The cryocrit (i.e., the percentage of the total serum volume made up of cryoglobulins) is generally very high in type I, moderate in type II, and low in type III. Biopsy samples from patients with mixed cryoglobulinemia usually have lymphocytic infiltrates surrounding small vessels (arterioles, venules, or capillaries), with no infiltration of polymorphonuclear cells or macrophages and no true vascular wall destruction, which distinguishes mixed cryoglobulinemia from other systemic vasculitis conditions. Immunofluorescence may show arterial deposits of IgM, IgG, or C3 (or a combination of the three). Differentiating between type I and mixed cryoglobulinemia, and even differentiating between cryoglobulinemia and other conditions, can be challenging when interpreting renal biopsies because of potential overlap in the immunomorphologic characteristics of these diseases. Electron microscopy can be invaluable in this context. Tissues affected by type I cryoglobulinemia, rather than mixed cryoglobulinemia, have thrombotic vascular obstruction of small vessels with severe downstream ischemic findings and little-to-moderate cellular infiltrate.

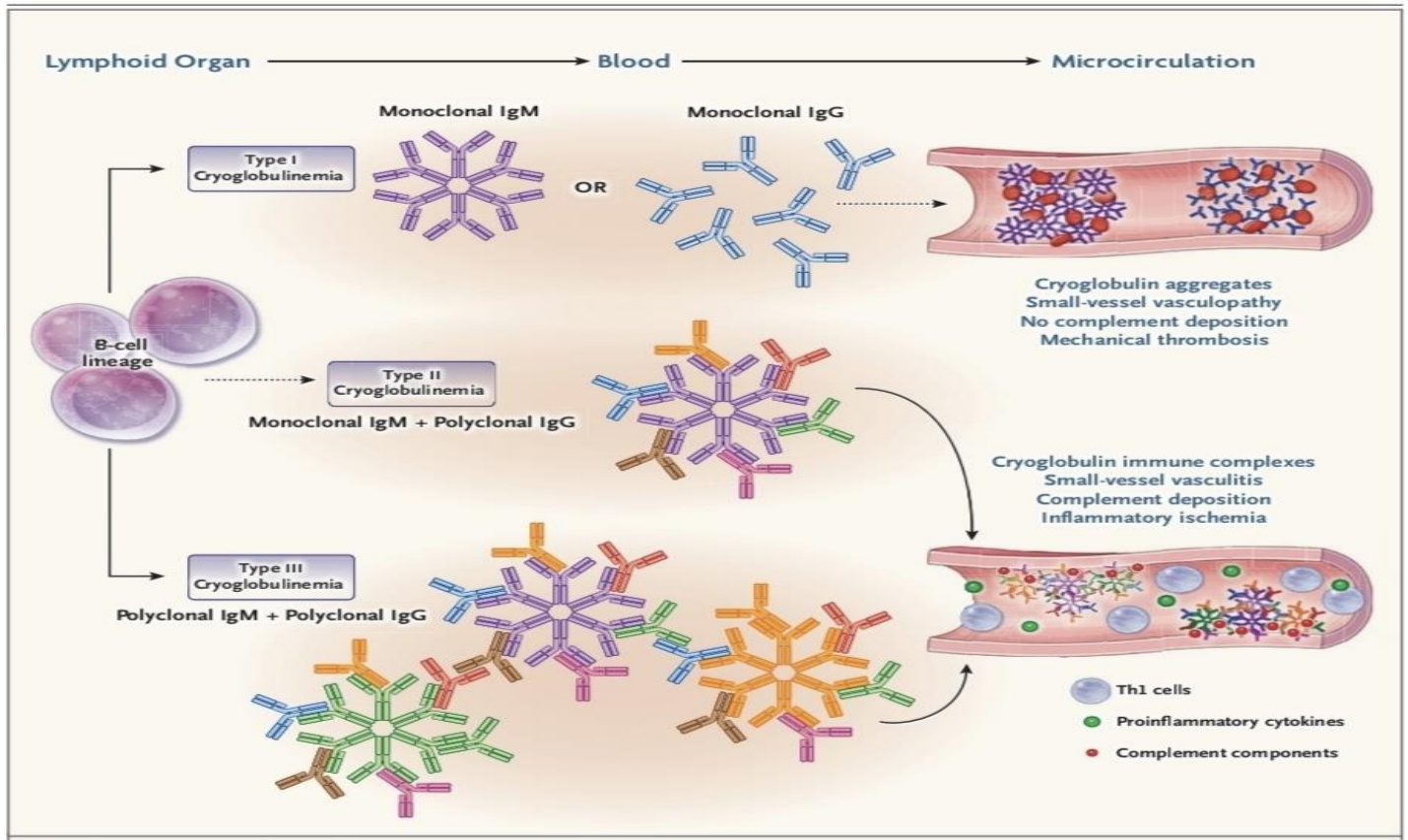


Figure 3. Mechanisms of Cryoglobulinemia.

Cryoglobulinemia has two distinct underlying mechanisms: type I cryoglobulinemia evolves as a vasculopathy affecting small and medium-sized arteries, whereas type II and III mixed cryoglobulinemias manifest as a true autoimmune vasculitis affecting small-to-medium-sized vessels. In both types, lymphocytes from the B-cell lineage (such as memory B cells or plasma cells) produce cryoglobulins in a monoclonal or polyclonal manner. Type I cryoglobulins are monoclonal IgM or IgG produced in large amounts by plasma cells, forming tightly compacted macromolecular nets that physically trap cells within blood vessels, a process known as *rouleaux* formation. Because type I cryoglobulins rarely have rheumatoid-factor activity, complement-mediated inflammatory vasculitis is infrequent. Instead, the primary mechanism in type I cryoglobulinemia involves mechanical vascular obstruction by cold-induced aggregates within the microcirculation, which leads to microthromboses of small vessels. Mixed cryoglobulins consist exclusively of polyclonal immunoglobulins (type III) or a combination of polyclonal immunoglobulins with monoclonal IgM (type II). This IgM typically has rheumatoid-factor activity, which activates complement within immune complexes, ultimately leading to tissue inflammation and injury. Another key mechanism in mixed cryoglobulinemia is the expansion and tissue infiltration of lymphocyte type 1 helper T cells (Th1) and effector T cells, which produce proinflammatory cytokines such as tumor necrosis factor α and interferon-γ, at the expense of regulatory T cells.

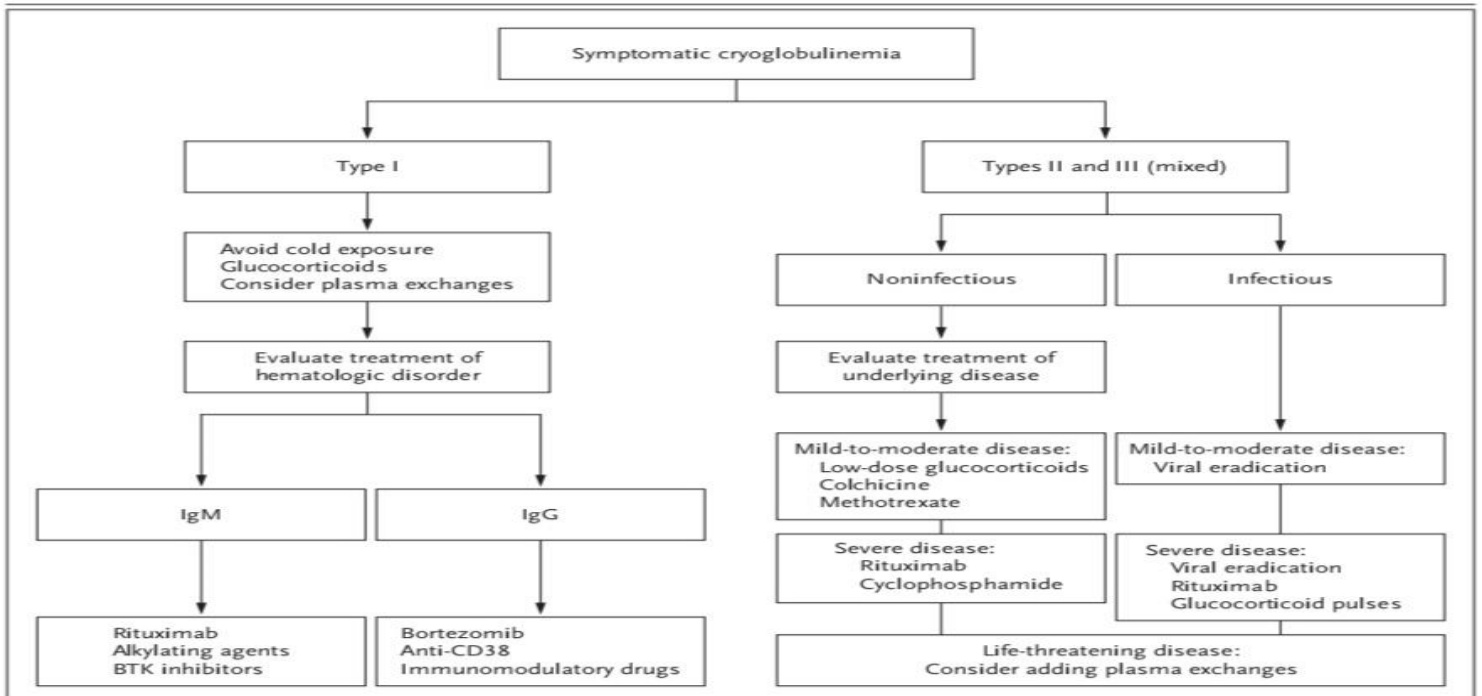


Figure 4. Treatment Algorithm for Cryoglobulinemias.

Patients presenting with symptomatic cryoglobulinemia should be assessed to determine treatment, with particular consideration given to the underlying causes. For every patient with type I cryoglobulinemia, avoiding cold exposure is an essential measure, and compression socks might be enough for patients presenting only with purpura. Glucocorticoids and plasma exchanges are usually considered among the first-line strategies for patients with a pharmacologic indication. Close collaboration with hematologists is imperative, and in the absence of an indication for treating the underlying hemotologic condition, the treatment for type I cryoglobulinemia should be determined on the basis of the disease isotype. Rituximab (a first-generation anti-CD20 agent), alkylating agents, and Bruton's tyrosine kinase (BTK) inhibitors are preferred in the management of IgM-mediated disease, whereas bortezomib (a proteasome inhibitor), anti-CD38 agents (e.g., isatuximab and daratumumab), and immunomodulatory drugs (e.g., lenalidomide and thalidomide) have been used for IgG-mediated disease. For type II and III mixed cryoglobulinemias, therapeutic regimens are chosen on the basis of the severity of vasculitis and involve eradication of the viral trigger when the cause is infectious. In hepatitis C virus–related mixed cryoglobulinemia, direct antiviral agents are usually sufficient to achieve a sustained virologic response and vasculitis remission in mild-to-moderate disease. Short-term, low-dose glucocortoid treatment (i.e., ≤0.5 mg per kilogram of body weight per day) might eventually be prescribed concomitantly, although most patients recover with a glucocorticoid-free regimen. For severe forms of disease, direct-acting antiviral agents should be combined with rituximab (375 mg per square meter of body-surface area on days 1, 8, 15, and 22). In life-threatening circumstances (e.g., glomerulonephritis with impaired renal function, motor deficit, multiple mononeuropathy, extensive skin necrosis, or digestive, cardiac, or pulmonary involvement), direct-acting antiviral agents should be combined with high-dose glucocorticoids (i.e., 0.5–1.0 g of methylprednisolone for 3 consecutive days, followed by tapering doses of oral glucocorticoids) and plasma exchanges. In rare forms complicated by a hematologic cancer, combinations of rituximab, fludarabine, and cyclophosphamide have been used successfully in expert centers. For patients who do not have a response to direct-acting antiviral agents or who have a contraindication to them, rituximab can be used alone for induction, followed by a 500-mg infusion every 6 to 9 months as maintenance treatment. Noninfectious mixed cryoglobulinemia can be managed further with the use of the arsenal of treatments available for the underlying cause (e.g., colchicine or methotrexate).

- Thanks
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