

CRYOGLOBULINEMIC VASCULITIS/MIXED CRYOGLOBULINEMIA SYNDROME (MCS)

BOTTOM LINE

Mixed cryoglobulinemia syndrome is caused by the precipitation of serum immunoglobulins at temperatures $<37^{\circ}\text{C}$ and manifests as immune complex-mediated small-medium vessel vasculitis commonly associated with chronic hepatitis C, systemic rheumatic diseases (especially Sjogren's) and lymphoproliferative diseases. Patients present with small vessel vasculitis symptoms including petechiae/purpura, neuropathy, and renal failure; arthralgias and fatigue are common. Treatment starts with treating any underlying etiology for cryoglobulin production. In addition, treatment for mild disease (ex: petechiae, arthralgias) is supportive though may include agents like colchicine or methotrexate. Severe organ threatening disease (ex: glomerulonephritis, progressive neuropathy, gastrointestinal or pulmonary vasculitis) requires steroids and possibly rituximab and/or plasma exchange.

TERMINOLOGY

Cryoglobulin	Immunoglobulins that precipitate from blood in vitro $<37^{\circ}\text{C}$ and dissolve on rewarming		
Cryoglobulinemia	Cryoglobulins circulating in patient's serum, <i>not necessarily causing systemic vasculitis</i>		
Cryoglobulinemic Vasculitis	Clinical syndrome of systemic small-medium vessel vasculitis caused by cryoglobulin-containing immune complexes. This term is sometimes used interchangeably with Mixed Cryoglobulinemia Syndrome		
Mixed Cryoglobulinemia syndrome (MCS)	Clinical syndrome of systemic small-medium vessel vasculitis caused by cryoglobulin-containing immune complexes. Caused by either Type II and/or III cryoglobulins (see below). Can be primary/idiopathic or secondary to associated autoimmune disease, malignancy, or infection.		
Hyperviscosity syndrome	Syndrome of neurologic complaints (ex: blurry/lost vision, headache, vertigo, nystagmus, tinnitus/deafness, diplopia, or ataxia) due to increased circulating blood protein. Associated with Type I cryoglobulin (below)		
Meltzer's Triad	Triad of palpable purpura, arthralgia, & subjective weakness; seen early in 80% of patients with MCS		
Classification of Cryoglobulinemia	Type	Immunoglobulins	Disease associations
	Type I (10%)	Monoclonal IgM, Rarer monoclonal IgG, IgA	Protein-secreting monoclonal gammopathies: MGUS, myeloma, Waldenstrom's CLL, non-Hodgkin lymphoma, hairy cell leukemia. Vaso-occlusive manifestations
	Type II (65%)	Monoclonal IgM, RF+ (or monoclonal IgG, IgA), Polyclonal IgG,	Persistent infections, especially hepatitis C (80-90%), systemic rheumatic diseases (SRD. especially SLE and Sjogren's), lymphoproliferative disorders. Can cause MCS
	Type II-III	Oligoclonal IgM Polyclonal IgG	Persistent infections, especially hepatitis C, systemic rheumatic diseases lymphoproliferative disorders. Can cause MCS
	Type III (25%)	Polyclonal IgM Polyclonal IgG	Persistent infections, especially hepatitis C, systemic rheumatic diseases. Can cause MCS
Etiology of circulating cryoglobulins	- Idiopathic - Infection: Hepatitis C (HCV), Hepatitis B (HBV), HIV, EBV, CMV, bacteria that cause endocarditis, Lyme, syphilis - Systemic rheumatic disease (SRD): Sjogren's, SLE, Rheumatoid arthritis - Lymphoproliferative disorders: myeloma, Waldenstrom's macroglobulinemia, CLL, B-cell lymphomas		

EPIDEMIOLOGY

- Incidence and prevalence of MCS in the general population unclear - Prevalence $<5/10,000$ in Europe and North America; possibly higher in Mediterranean basin	
HCV-related MCS	80-90% of mixed cryoglobulinemia is caused by HCV - But, most HCV patients with circulating cryoglobulins do not develop MCS/cryoglobulinemic vasculitis - In HCV population: 40-60% of patients have circulating mixed cryoglobulins - In HCV population with mixed cryoglobulins: ~ 5-25% of patients develop MCS/cryoglobulinemic vasculitis - Longer duration HCV infection correlated to likelihood of cryoglobulinemia, cirrhosis, fibrosis
Non-HCV related MCS	10-20% of mixed cryoglobulinemia caused by other chronic infections, malignancies, or SRD (listed above) - SLE and RA: ~10% have circulating mixed cryoglobulins - Sjogren's: 5-20% may have Type II cryoglobulins, associated with worse prognosis in Sjogren's
Hematological disorders	- Risk of non-Hodgkin Lymphoma 35X higher in patients with cryoglobulinemia than in general population - Non-Hodgkin lymphomas includes: marginal zone lymphoma, de novo or transformed diffuse large B cell lymphoma, and follicular lymphoma - Type I cryoglobulinemia always associated with B-cell proliferative disorder (see above)

CLINICAL MANIFESTATIONS		
Most common features of MCS: fatigue, palpable purpura, arthralgias/arthritis, nephropathy, neuropathy, low C3, low C4		
Skin	• Erythematous macules and purpuric papules in lower extremities lasting 3-10 days: >90% • Post-inflammatory hyperpigmentation, scarring: 11-40% • Infarction, hemorrhagic crusts, skin ulcers (usually around malleolus): 10-25% • Exacerbation of symptoms by cold: 10% • Cold urticaria • Raynaud’s phenomenon (25%), livedo reticularis	
MSK	• Arthralgias (70%) involving bilateral hands, knees; less often elbows and ankles • True inflammatory arthritis is rare	
Neurological	Peripheral	• Peripheral neuropathy: 17-60% on EMG, clinically symptomatic neuropathy ~20% • Mononeuritis multiplex, sensorimotor disease uncommon
	Central	• Visual changes, headache, encephalopathy, transverse myelitis, medullary ischemia • Rarely involves cranial nerves
Renal	• Renal involvement in 30-60% of MCS • Microscopic hematuria and sub-nephrotic proteinuria +/- CKD: 41% • Nephrotic syndrome +/- CKD: 22% • Acute glomerulonephritis: 14% • Chronic kidney disease with normal urinalysis: 13% • Acute kidney injury: 9% • Hypertension 65%	
Respiratory	• Minor cough, dyspnea <5% • Uncommonly: Organizing pneumonia, alveolar hemorrhage, pulmonary vasculitis, pleural effusions	
Other	• Lymphadenopathy, splenomegaly, hepatomegaly, abdominal pain	
INVESTIGATIONS		
CBC	• Possible pseudo-leukocytosis, pseudo-thrombocytosis from interference of precipitated cryoglobulins on CBC	
Cr, U/A	• Baseline in all patients, may show decreased renal function and active urinary sediment	
ALT	• Baseline in all patients, may be elevated if Hep C or Hep B infection	
ESR, CRP	• ESR elevated due to increased circulating cryoglobulins (thus increasing erythrocyte sedimentation) • CRP: may be elevated, non-specific	
Viral serologies	• Baseline Hepatitis C, Hepatitis B, and HIV in all patients to screen for underlying etiology	
RF	• Often positive (recall an RF is simply IgM directed against the FC portion of IgG)	
Complement	• C4 low, consistently and often significantly • C3, CH50: decreased, less so than C4	
Antibodies	• Screen ANA and if positive, dsDNA and ENA panel in case of underlying etiology • Screen ANCA for differential diagnosis	
SPEP	• SPEP with immunofixation and serum free light chain assay, in case of underlying etiology	
Pathology	Diagnosis usually made with clinical/laboratory data; biopsy of affected organs can help if diagnostic uncertainty	
	Skin	Leukocytoclastic vasculitis; immunofluorescence shows IgM, IgG, C3 deposition
	Peripheral nerve	Vasculitis of epineural vessels, axonal degeneration; may show necrosis and demyelination; immunofluorescence may show IgM, IgG and complement deposition
	Renal	• Histology: most commonly membranoproliferative GN with endocapillary proliferation of infiltrating monocytes/macrophages, subendothelial deposits. • Immunofluorescence: deposition of immunoglobulins and C3 • Electron microscopy: characteristic subendothelial “comma like” or “fingerprint” pattern of cryoprecipitate

Cryoglobulins Challenging to detect	Collection	- Blood must be kept warm to prevent false-negative result caused by premature cryoprecipitation - Blood sample collected in prewarmed tubes not lined with anticoagulants at 37°C - Sample allowed to clot at 37°C for minimum 1h - Sample is centrifuged at 37°C to separate serum
	Cryocrit determination	- Sample is cooled to +4°C for 7 days to precipitate cryoglobulins - Cryocrit determination: % (packed cryoglobulins/total serum volume) after centrifugation at +4°C - Cryoglobulins characterized by immunofixation
	Rewarming	Aliquot of serum rewarmed to 37°C for 24h to test for reversibility, ruling out false-positive
		Cryoglobulins can be negative in 30-40% mixed cryoglobulinemia patients at presentation due to technical lab factors or variability in concentration of circulating cryoglobulins Cryoglobulins can be positive in patients <u>without</u> mixed cryoglobulinemia syndrome due to chronic infection, inflammation, lymphoproliferative disorder creating cryoglobulins without clinical signs or diagnosis of mixed cryoglobulinemia/cryoglobulinemic vasculitis

DIAGNOSIS

Suspect MCS in any patient presenting with characteristic purpura/skin ulcers, arthralgias, neuropathy, and/or renal involvement with low circulating complement and positive RF. Screen all suspected patients for hepatitis B/C, HIV, SPEP, ANA, and ANCA. Attempt to measure circulating cryoglobulins, though may be negative at presentation and require serial retesting. May seek supportive skin, nerve, or renal biopsy if possible, which should show features of immune-complex mediated small vessel vasculitis with deposition of immunoglobulins and C3 on immunofluorescence.

DIFFERENTIAL DIAGNOSIS

Vasculitis	- Immune-complex mediated: IgAV, Urticarial vasculitis, vasculitis secondary to RA or other SRD - Pauci-immune vasculitis: GPA, EGPA, MPA - Other vasculitis: Behcets; vasculitis secondary to malignancy, infection, IBD
Other SRD	- Sjogren's may also cause arthralgias, purpura, RF, circulating cryoglobulins, and lymphoma - Mixed cryoglobulinemia unlikely to be anti-Ro/SSA or anti-la/SSB positive - Sjogren's unlikely to be Hep C positive and less likely to have low C4 - Rheumatoid arthritis can cause arthralgias, positive RF; can also have overlap RA/MCS - Mixed cryoglobulinemia rarely has frank joint swelling and is anti-CCP negative
Vasculitis mimickers	- Hemorrhage: ITP, benign purpura - Thrombosis: anti-phospholipid antibody syndrome, TTP - Emboli: Cholesterol emboli, Bacterial endocarditis with septic emboli

TREATMENT

Underlying disease	All patients should receive therapy for any underlying etiology of their mixed cryoglobulinemia. Ex: Hepatitis C, non-Hodgkin B-cell lymphoma, systemic lupus erythematosus	
Assess severity	Mild	- Mild manifestations without organ threatening disease (ex: GN, digital ischemia) - Ex: petechial rash without necrotic lesions, mild sensory neuropathy, arthritis
	Mod-severe	- Organ/life threatening disease - Ex: GN, digital ischemia, GI-vasculitis with ischemia/bleed, progressive neuropathy, CNS symptoms (stroke, acute cognitive impairment), pulmonary vasculitis
Mild disease:		
Skin	- Treat similarly to idiopathic isolated cutaneous leukocytoclastic small vessel vasculitis - Ex: steroids, colchicine, methotrexate, dapsone	
Nerve	- Supportive symptomatic treatment - Ex: Amitriptyline, duloxetine, gabapentin, pregabalin	
Arthritis	- Inflammatory arthritis can be treated like RA (ex: steroids, methotrexate) - Arthralgias can be treated with NSAIDs	

TREATMENT (continued)

Moderate-Severe Disease: start with steroids plus rituximab; plasma exchange in some, and treat any underlying etiology

Timing	• HCV: can delay antiviral therapy for 1-4 months if severe disease requiring immunosuppression • HBV, HIV: start antiviral therapy alongside immunosuppression given higher risk of enhanced viral replication
Steroids	• Methylprednisolone 1g IV daily x 3 (if life-threatening disease), then • Prednisone 1mg/kg/day (maximum 60-80mg/day) x 2-4 weeks • Tapered quickly to 40mg/d for 2 weeks, 20mg/d for 2-4 weeks, then 5mg weekly until off (example taper) • Consider tapering quickly to reduce infectious complications related to prednisone if underlying infection
Rituximab (RTX)	• RTX 1g IV day 0 and Day 14 • Alternatively: RTX 375mg/m² weekly x 4, then 375mg/m² monthly x 2 • Avoid if active HBV or HCV flare due to risk of reported fatal fulminant hepatitis
Cyclophosphamide (CYC)	• Second choice after rituximab; Cyclophosphamide may enhance viral replication of HCV or HBV • CYC 1.5-2mg/kg/day oral x 3 months (until remission), then 1.5mg/kg/day oral x 3 months (max 200mg); or • CYC 15mg/kg/day q2 weeks x 3, then q3 weeks x 3-6 months • Lifetime cumulative dose should not exceed 25g of CYC • Remember to renally dose Cyclophosphamide (See GPA/MPA chapter)
Plasma exchange (PLEX)	• PLEX ~3L daily x10-14 sessions or 3x/week for 2-3 weeks; avoid PLEX 2-3 days before RTX infusion • Does not stop production of cryoglobulins, but may be needed for severe manifestations, including: • Hyperviscosity syndrome (seen more in Type I cryoglobulinemia) • Life-threatening (respiratory failure, acute severe renal failure, GI vasculitis with GI bleed) • Severe refractory skin ulcers • Cryocrit very high (i.e.: >10%)
Adjunctive	• PJP prophylaxis: consider if rituximab or prednisone >20mg/d + 1 other immunosuppressant • GI ulcer: Prophylaxis with PPI when on high dose steroids • Osteoporosis: BMD, Vitamin D; consider empiric bisphosphonate depending on osteoporotic risk factors

PROGNOSIS

- 5-year mortality 75%, 10-year mortality 63%.
- Cause of death:
 - Most-common: infection, HCV-related end-stage liver disease, cardiovascular disease
 - More rarely: vasculitis, lymphoma, neoplasia.
- Poor prognostic factors:
 - Severe liver fibrosis associated with HCV infection
 - Nervous system involvement
 - Renal involvement
 - Age >60

REFERENCES

- Cohen, S. J., Pittelkow, M. R., & Su, W. P. (1991). Cutaneous manifestations of cryoglobulinemia: clinical and histopathologic study of seventy-two patients. *Journal of the American Academy of Dermatology*, 25(1 Pt 1), 21–27. [https://doi.org/10.1016/0190-9622\(91\)70168-2](https://doi.org/10.1016/0190-9622(91)70168-2)
- Ferri, C., Sebastiani, M., Giuggioli, D., Cazzato, M., Longombardo, G., Antonelli, A., Puccini, R., Michelassi, C., & Zignego, A. L. (2004). Mixed cryoglobulinemia: demographic, clinical, and serologic features and survival in 231 patients. *Seminars in arthritis and rheumatism*, 33(6), 355–374. <https://doi.org/10.1016/j.semarthrit.2003.10.001>
- Johnson, R. J., Willson, R., Yamabe, H., Couser, W., Alpers, C. E., Wener, M. H., Davis, C., & Gretch, D. R. (1994). Renal manifestations of hepatitis C virus infection. *Kidney international*, 46(5), 1255–1263. <https://doi.org/10.1038/ki.1994.393>
- Kolopp-Sarda, M. N., & Miossec, P. (2021). Cryoglobulinemic vasculitis: pathophysiological mechanisms and diagnosis. *Current opinion in rheumatology*, 33(1), 1–7. <https://doi.org/10.1097/BOR.0000000000000757>
- Moretti, M., Ferro, F., Baldini, C., Mosca, M., & Talarico, R. (2024). Cryoglobulinemic vasculitis: a 2023 update. *Current opinion in rheumatology*, 36(1), 27–34. <https://doi.org/10.1097/BOR.0000000000000989>
- Roccatello, D., Fornasieri, A., Giachino, O., Rossi, D., Beltrame, A., Banfi, G., Confalonieri, R., Tarantino, A., Pasquali, S., Amoroso, A., Savoldi, S., Colombo, V., Manno, C., Ponzetto, A., Moriconi, L., Pani, A., Rustichelli, R., Di Belgiojoso, G. B., Comotti, C., & Quarenghi, M. I. (2007). Multicenter study on hepatitis C virus-related cryoglobulinemic glomerulonephritis. *American journal of kidney diseases : the official journal of the National Kidney Foundation*, 49(1), 69–82. <https://doi.org/10.1053/j.ajkd.2006.09.015>
- Roccatello, D., Saadoun, D., Ramos-Casals, M., Tzioufas, A. G., Fervenza, F. C., Cacoub, P., Zignego, A. L., & Ferri, C. (2018). Cryoglobulinaemia. *Nature reviews. Disease primers*, 4(1), 11. <https://doi.org/10.1038/s41572-018-0009-4>
- Silva, F., Pinto, C., Barbosa, A., Borges, T., Dias, C., & Almeida, J. (2019). New insights in cryoglobulinemic vasculitis. *Journal of autoimmunity*, 105, 102313. <https://doi.org/10.1016/j.jaut.2019.102313>