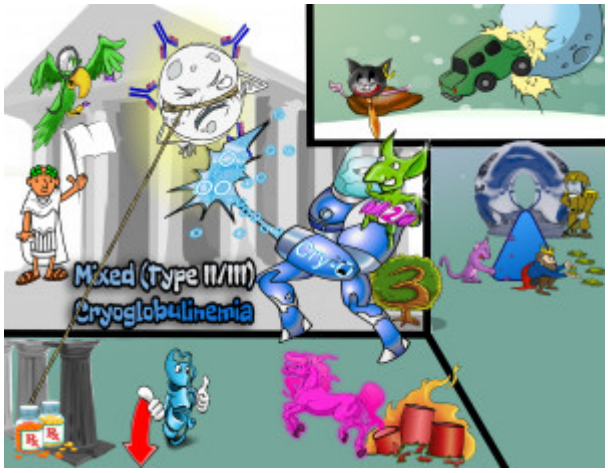
Mixed (Type II/III) Cryoglobulinemia

Mixed cryoglobulinemia is characterized by rheumatoid factor activity with a mixture of monoclonal or polyclonal immunoglobulins. It results from immune complex deposition in cold temperatures, which is commonly associated with hepatitis C and autoimmune diseases. Clinical manifestations may include Meltzer's triad, which is palpable purpura, arthralgias, and general malaise. Vasculitis and glomerulonephritis may also be seen. During diagnostic workup, decreased levels of complement proteins help to corroborate the clinical picture. Management consists of treating the underlying disorders and immunosuppressants.



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Characteristics

Rheumatoid Factor

Roman Flagger

Mixed cryoglobulinemia is detected by rheumatoid factor activity. This differs from type I cryoglobulinemia in which rheumatoid factor does not play a role. Rheumatoid factor is any antibody that targets the Fc portion of IgG. In this disease, rheumatoid factor antibodies form after infection with hepatitis C or as a result of an autoimmune disease. These rheumatoid factor antibodies then form immune complexes with hepatitis C antigens or autoantigens to result in inflammation and disease.

Monoclonal or Polyclonal

Monocle and Polly

Mixed cryoglobulinemia is a mixture of polyclonal IgG and monoclonal IgM (known as type II), or of polyclonal IgG and polyclonal IgM (known as type III). The monoclonal and polyclonal IgM antibodies are the autoantibodies with rheumatoid factor (RF) activity.

Immune Complex Deposition in Cold Temperatures

Moon Antibody Complex Freezing

Cryoglobulins are single or mixed immunoglobulins that can precipitate reversibly in cold temperatures, usually below 98.6^oF. Their presence in the blood is called cryoglobulinemia. Precipitation will result in clumping, which can restrict blood flow to organs. Cryoglobulinemia can be characterized as single (type I) or mixed (type II and type III). Mixed cryoglobulinemia is more common than single (80%).

Associations

Hepatitis C

Happy-tie Liver (C) Cat

Hepatitis C virus is the most common cause of mixed cryoglobulinemia, and the association is still not well understood. Viral antigens (e.g., NS3, NS4, NS5A, HCV core, envelop E2) may trigger a chronic stimulation of the immune system resulting in a 'benign' B-cell proliferation and autoantibody production, along with rheumatoid factor (RF) and immune complexes. The anti-HCV IgG antibody is found to increase 10-fold in most cases.

Autoimmune Diseases

Auto-in-moon

Other causes of mixed cryoglobulinemia include other infections (e.g., HIV), autoimmune disorders (e.g., systemic lupus erythematosus, Sjogren's syndrome), and lymphoproliferative disorders.

Clinical Features

Meltzer's Triad

Melting-zero Triad-triangle

Mixed cryoglobulinemia symptoms can be described by the Meltzer triad, which consists of palpable purpura (90-95% cases, particularly in lower extremities), weakness, and arthralgias This triad is present in 25-30% of cases.

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Palpable Purpura

Palpable-paw-print from Purple-cat

Purpuric lesions may be seen after standing or sitting for a long time This is known as orthostatic purpura. Ulceration and necrosis in the extremities can also develop.

Arthralgias

King Arthur-algae

Arthralgias can be present in up to 70% of cases. They often occur in the proximal interphalangeal and metacarpophalangeal joint of the hands, as well as in the knees and ankles.

General Malaise

General Malaise

Weakness is one of the most common symptoms of mixed cryoglobulinemia, and it is a part of Meltzer's triad. Other symptoms that can be seen include sicca syndrome (4-20%), abdominal pain (2-22%), acrocyanosis (9%), and arterial thrombosis (1%).

Vasculitis

Vessels-on-fire

The histopathological hallmark of mixed cryoglobulinemia is leukocytoclastic vasculitis. It is easily detected by skin biopsy and presents as an immune complex-mediated vasculitis of the dermal capillaries and venules. It may involve multiple organs, such as the skin, kidney, central nervous system, gastrointestinal tract, and lungs.

Glomerulonephritis

Glow-mare

Mixed cryoglobulinemia can affect the kidney, resulting in glomerulonephritis. Membranoproliferative glomerulonephritis is the most common histological finding in the kidneys of mixed cryoglobulinemia patients.

Diagnosis

Decreased Complement Proteins

Down-arrow Protein Complimenting

Decreased complement proteins may occur in mixed cryoglobulinemia. Low C4 is commonly seen in mixed cryoglobulinemia, which may occur due to activation of complement in the classical pathway. Other diagnostic indicators include serum chemistry, rheumatoid factor (positive in type II and III), and HCV testing.

Management

Treat Underlying Disorder

Treating Disorders Under the Pillars

The aim of treatment for mixed cryoglobulinemia is to treat the underlying disorder. For example, management of mixed cryoglobulinemia related to hepatitis C should begin with elimination of HCV through combined interferon-ribavirin treatment.

Immunosuppressants

Moon Suppressed

Immunosuppressants are used to reduce the immune activity that causes mixed cryoglobulinemia. Potential agents include corticosteroids, cyclophosphamide, azathioprine, or rituximab. Treatment should be monitored to avoid opportunistic infections. Supportive care should be included in management. This may consist of NSAIDs to treat pain and a low antigen complement (LAC) diet. Plasmapheresis is indicated in severe or life-threatening cases.

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