



HCSP FACT SHEET

• EXTRAHEPATIC MANIFESTATIONS OF HCV •

Mixed Cryoglobulinemias

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Forward

There is a strong association between hepatitis C and mixed cryoglobulinemias. Mixed cryoglobulinemias are a devastating disease but if hepatitis C can be identified early on, treated and cured people will not develop them.

Mixed Cryoglobulinemias

Mixed cryoglobulinemias is a blood disorder caused by abnormal proteins in the blood called cryoglobulins. The cryoglobulins precipitate or clump together when blood is chilled then dissolve when rewarmed. The proteins can be deposited in small and medium-sized blood vessels which can lead to restricted blood flow to joints, muscles, and organs. The term frequently used is essential mixed cryoglobulinemia because the exact cause is unknown. There are three types of cryoglobulinemia – type I, type II and type III. Type I does not have rheumatoid factor activity whereas types II and III have rheumatoid factor activity. Rheumatoid factor is an antibody found in the blood of people afflicted with rheumatoid arthritis (a chronic autoimmune disease characterized by inflammation of the joints).

HCV and Mixed Cryoglobulinemias

The relationship between HCV and cryoglobulinemia is believed to occur by way of the hepatitis C virus attaching itself to B lymphocyte cells, which causes the immune system to produce autoantibodies. The high prevalence of hepatitis C in people with cryoglobulinemia lends credence to the direct link between HCV and cryoglobulinemia. One study found that 90% of patients with type 2 or type 3 cryoglobulinemia had evidence of hepatitis C antibodies.

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A publication of the
Hepatitis C Support Project

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The information in this fact sheet is designed to help you understand and manage HCV and is not intended as medical advice. All persons with HCV should consult a medical practitioner for diagnosis and treatment of HCV.

This information is provided by the Hepatitis C Support Project a nonprofit organization for HCV education, support and advocacy

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Additionally, treating the underlying cause— hepatitis C—improves or resolves cryoglobulinemia further establishing the link. Also, cryoglobulinemia is associated with the hepatitis B virus and other liver disorders but to a much lesser extent. Additional factors that strongly correlate with an increased risk for HCV-related cryoglobulinemia include the presence of cirrhosis, HCV infection over many years or decades, and female gender. In people with hepatitis C only the minority of people with cryoglobulinemia show signs or symptoms of this condition. The majority of people with HCV and cryoglobulinemia have few symptoms or any of the blood or organ disorders associated with the more severe outcomes. It is important, however, to be monitored on a regular basis to make sure that the symptoms or disease progression does not worsen.

Symptoms

People with symptomatic hepatitis C-related cryoglobulinemia can have ongoing problems that can cause many symptoms and disorders. The most common symptoms and complications associated with cryoglobulinemia include:

- **Vasculitis:** inflammation of the small blood vessels of the skin, kidneys, gastrointestinal tract and other organs of the body. It can also cause red or purple blotching skin that usually appears on the lower extremities of the body. Rashes, sores, and ulcers can also occur
- **Renal (kidney) disease:** caused by deposits of the cryoglobulins in the kidneys. Symptoms include blood and proteins in the urine
- **Arthralgias and arthritis:** pain and/or inflammation in the joints

- **Pruritus (itching):** mild to severe
- **Fatigue:** mild to severe
- **Pain:** mild to severe
- **Lymph node enlargement:** swollen gland-like tissue in the lymphatic vessels containing cells that become lymphocytes (white blood cells)
- **Peripheral neuropathy:** numbness and tingling in the hands, legs and feet due to decreased blood and/ or inflammation of the peripheral nerves
- **Stomach pain**
- **Bleeding disorders:** internal bleeding and abnormal blood clot formation
- **Non-Hodgkin’s lymphoma:** cancers of the lymphoid system
- **Raynaud’s syndrome:** a disorder that causes the blood vessels in the fingers, toes, ears, and nose to constrict or narrow causing pain
- **Multiple myelomas:** cancer of the bone marrow and blood. The more serious consequences of mixed cryoglobulinemias usually occur after many years or decades of infection with the hepatitis C virus.

Diagnosis

A simple blood test is performed to diagnose cryoglobulinemia, but the blood sample has to be handled carefully – drawing the blood sample at room temperature then cooling it to see if the blood precipitates or clumps together.

Treatment

The approach to treating HCV-related cryoglobulinemia is to treat the underlying cause – hepatitis C. Successful treatment (cure) with direct-acting medications

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results in a complete or partial remission in up to 75% of cryoglobulinemia cases. In addition to treating hepatitis C, there are other medications to control cryoglobulinemia and some of the consequences of the disease. Non-steroidal anti-inflammatory medications (NSAIDs) are used to control the muscle and joint pain in people who do not have serious disease progression from cryoglobulinemia. Plasmapheresis (removing blood and filtering out the cryoglobulins and returning the blood to the body) is used to treat cryoglobulinemia.

Immunosuppressive drugs may also be prescribed. Corticosteroid and cytotoxic agents are prescribed for some patients. Rituximab is an anti-CD20 chimeric monoclonal antibody drug that is effective at controlling vasculitis, peripheral neuropathy, arthralgia's, low-grade B-cell lymphomas, kidney disease and fever—all possible consequences of cryoglobulinemia

Conclusion

HCV-related cryoglobulinemia is one of the most common extrahepatic manifestations of hepatitis C. Approximately 10-15% of people with hepatitis C have blood markers for this condition. However, only a small number of people with hepatitis C are symptomatic. Also, consequences of hepatitis C-related cryoglobulinemia usually require an extended period of infection with hepatitis C.

Related publications:

Extrahepatic Manifestations Glossary

<http://hcvadvocate.org/resources/glossaries/extrahep-glossary/>

Non-Hodgkin's lymphoma (NHL)

http://hcvadvocate.org/hepatitis/factsheets_pdf/NHL.pdf

Peripheral Neuropathy

http://hcvadvocate.org/hepatitis/factsheets_pdf/PN.pdf

For more information

- **Americans with Disabilities Act**
www.ada.gov
- **Centers for Disease Control and Prevention**
www.cdc.gov
- **Mayo Clinic**
www.mayoclinic.com
- **MedlinePlus**
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