



HCSP FACT SHEET

• HCV EXTRAHEPATIC MANIFESTATION OF HCV •

Cryoglobulinemia

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FORWARD

A large study by the MULTIVIRC group reported that 74% of patients with hepatitis C had at least one extrahepatic (outside the liver) manifestation. The most common conditions included essential mixed cryoglobulinemia (40%), arthralgia or joint pain (23%), paresthesia (burning or pricking sensations) (17%), myalgia (muscle pain) (15%), pruritus (itching) (15%), and sicca syndrome (dry eyes/mouth) (11%). This factsheet will discuss one of the most common conditions associated with hepatitis C called essential mixed cryoglobulinemia (EMC).

Cryoglobulinemia 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 Cryoglobulinemia

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 the 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.

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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 about 3% of people with cryoglobulinemia show signs or symptoms of this condition. The other 97% 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 the 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 formations
- **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 cryoglobulinemia 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. Cryoglobulin disappearance, improvement in kidney function and complete or partial resolution of cryoglobulinemia syndrome occurs after successfully curing hepatitis C. Also, improvement or disappearance of cryoglobulin levels and kidney function also improved.

In addition to treating hepatitis C, there are other medications to control cryoglobulinemia and some of the consequences of the disease. Non-steroidal anti-

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inflammatory medications (NSAIDs) are used to control the muscle and joint pain. Plasmapheresis (removing blood and filtering out the cryoglobulins) and returning the blood to the body) to 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 is effective at controlling vasculitis, peripheral neuropathy, arthralgias, 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 40% of people with hepatitis C have blood markers for this condition. However, only a small fraction of persons with hepatitis C are asymptomatic. Also, consequences of hepatitis C-related cryoglobulinemia usually require an extended period of infection with hepatitis C virus before the severe damage occurs. Treatment of symptomatic HCV-related cryoglobulinemia usually consists of treating the underlying cause—hepatitis C. Talk with your medical provider or a specialist in cryoglobulinemia if you have any signs or symptoms of cryoglobulinemia or if you have questions about the condition.

Related publications:

- **Extrahepatic Manifestations Glossary**
<http://hcvadvocate.org/resources/glossaries/extrahepaticglossary/>
- **An Overview of the Liver**
http://hcvadvocate.org/hepatitis/factsheets_pdf/The_Liver.pdf
- **Monthly Drug Pipeline Report**
<http://hcvadvocate.org/treatment/drug-pipeline-monthly-report/>

For more information

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www.ada.gov • Centers for Disease Control and Prevention
www.cdc.gov | <ul style="list-style-type: none"> • National Cancer Institute:
www.cancer.gov/cancertopics/factsheet/Sites-Types/WM • Waldenstrom Macroglobulinemia at the Mayo Clinic
www.mayoclinic.org |
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