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by experts in the field of liver
disease

Extrahepatic Manifestations: Cryoglobulinemia

Alan Franciscus, Editor-in-Chief

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 (17%), myalgia (15%), pruritus (15%), and sicca syndrome (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 that is caused by abnormal proteins in the blood called cryoglobulins that precipitate or clump together when blood is chilled and then dissolve when rewarmed. These proteins can be deposited in small and medium-sized blood vessels which can lead to restricted blood flow to joints, muscles, and organs.

The cause of cryoglobulinemia is not completely understood, but it is thought to be an autoimmune disorder (caused by the body's immune system producing antibodies that attack healthy cells). 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 type 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 direct relationship between HCV and cryoglobulinemia has not been established but it is believed that the hepatitis C virus attaches itself to B lymphocyte cells, which causes the immune system to produce autoantibodies.

The high prevalence of HCV in people with cryoglobulinemia leads us to believe that there is a direct link between HCV and cryoglobulinemia. In fact, one study found that 95% of patients with cryoglobulinemia had evidence of the hepatitis C virus or HCV antibodies. Cryoglobulinemia is also associated with hepatitis B infection and other liver disorders, but to a much lesser extent. 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 10% of people with cryoglobulinemia show signs or symptoms of this condition. The other 90% of people with HCV and cryoglobulinemia have no symptoms or any of the blood or organ disorders associated with the condition.

Symptoms

The people with symptomatic hepatitis C-related cryoglobulinemia can have ongoing problems that can cause many symptoms and disorders. The most common symptoms and disorders associated with the condition 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 (especially on the lower extremities of the body), rashes, sores, and ulcers
- **Renal (kidney) disease:** caused by the deposition of proteins in the kidney. Symptoms include blood and proteins in the urine
- **Arthralgias and arthritis:** pain and/or inflammation in the joints
- **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 that is due to decreased blood and/or inflammation of the peripheral nerves.
- **Stomach pain**
- **Bleeding disorders:** internal bleeding and abnormal blood clot formations

Other conditions associated with cryoglobulinemia include 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), and multiple myeloma (cancer of the bone marrow). The more serious consequences of cryoglobulinemia are usually only seen after many years or decades of infection with HCV.

Diagnosis

Cryoglobulinemia is usually noticed in patients because of the blotchy skin rash seen on the lower extremities. A simple blood test is performed to diagnose cryoglobulinemia, but the blood sample has to be handled very 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. Prior to pegylated interferon and ribavirin therapy, interferon monotherapy was used with very little effectiveness. However, studies have found that the use of pegylated interferon plus ribavirin has produced better results especially in patients who achieve a sustained virological response. Cryoglobulin disappearance, improvement in kidney response and complete or partial cryoglobulinemia syndrome response has been found in some people successfully treated with pegylated interferon therapy. It should be noted that interferon may exacerbate some autoimmune disorders so monitoring for these potential problems during interferon/ribavirin treatment is needed.

Other treatment strategies include medication to reduce the inflammation and suppress the immune system with a combination of nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, corticosteroids) to reduce the inflammatory response, plasmapheresis (removing the plasma from the body, returning the blood cells to the body, and replacing the plasma with a saline solution to remove the cryoglobulins) and hypo-antigenic-content diet (LAC diet). Immunosuppressive therapy is not recommended for HCV-related cryoglobulinemia since immunosuppressant drugs can lead to increased hepatitis C viral replication. Rituximab is a drug currently used to treat non-Hodgkin's lymphoma and rheumatoid arthritis, and it is being studied to treat cryoglobulinemia. In the studies to date, rituximab has been found to be effective in most patients with cryoglobulinemia, but, since the drug can increase HCV viral replication, more studies are needed to further understand the implications of increased viral replication.

In conclusion, HCV-related cryoglobulinemia is one of the most common extrahepatic manifestations of HCV. Approximately 40% of people with hepatitis C have blood markers for this condition. However, only a small fraction (10%) of the people with hepatitis C who have these markers are symptomatic. In addition, severe consequences of hepatitis C-related cryoglobulinemia usually require a long 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—HCV. Talk to your medical provider or a specialist in cryoglobulinemia if you have any of the signs or symptoms of cryoglobulinemia.


Be sure to checkout these other publications on Extrahepatic Manifestations of HCV. They can be found on the Fact Sheet page of our website:

- *Extrahepatic Manifestations (overview)*
- *Lichen Planus*
- *Non-Hodgkin's Lymphoma (NHL)*
- *Porphyria Cutanea Tarda (PCT)*
- *Pruritus (Itching)*
- *Sjögren's (Show grins) Syndrome*

For more information about hepatitis C, hepatitis B and HCV coinfections, please visit www.hcvadvocate.org.

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<p>Executive Director Editor-in-Chief, HCSP Publications Alan Franciscus</p> <p>Design Paula Fener</p> <p>Production C.D. Mazoff, PhD</p> <p>Contact information: Hepatitis C Support Project PO Box 427037 San Francisco, CA 94142-7037 alanfranciscus@hcvadvocate.org</p>	<p>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.</p> <p>This information is provided by the Hepatitis C Support Project • a nonprofit organization for HCV education, support and advocacy • © 2008 Hepatitis C Support Project • Reprint permission is granted and encouraged with credit to the Hepatitis C Support Project.</p>
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