CRYOGLOBULINEMIC VASCULITIS (CV)

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What is CV?

CV is a vasculitis that affects the small--sized blood vessels in the body. In CV, there are special proteins called **cryoglobulins** that circulate in the blood. They consist of antibodies (ie. immunoglobulins) and other proteins involved in immune responses. Normally, they stay dissolved in the blood at warm temperatures of 37°C and above without causing any problems. At lower temperatures, however, they clump together (or "**precipitate**") and deposit in blood vessel walls, leading to blockages and inflammation.

Why are cryoglobulins formed?

While it is not entirely understood why and how cryoglobulins are formed, doctors suspect they are the product of long-term immune system stimulation and abnormal clearance of immune proteins.

Cryoglobulins can be found in the blood of many individuals with chronic infections, especially with hepatitis C virus, or inflammatory diseases without causing actual disease. Only a small proportion go on to develop vasculitis.

What are the different types of cryoglobulins?

Type 1 cryoglobulins are associated with lymphoproliferative diseases such as lymphoma or myeloma.

Type 2 & 3 cryoglobulins are strongly associated with chronic infections (hepatitis C) and autoimmune diseases such as Sjogren Syndrome or rheumatoid arthritis.

What are possible symptoms?

- Raynaud's –discolouration (white to blue to red) with numbness and pain of the fingers and toes when exposed to the cold
- Skin rash resembling bleeding spots that appear on the feet and legs, and can progress to ulcers
- Shortness of breath & coughing up blood (if the lungs are affected)
- Joint pain & swelling
- Swollen lymph nodes
- Abdominal pain
- Weakness, tingling and/or burning sensation of the hands and feet
- Unusually bubbly / frothy / dark urine (if the kidneys are involved)
- Fevers, weight loss & unusually severe fatigue

How is CV diagnosed?

Diagnosis is made based on a combination of the following:

1. Compatible symptoms
2. Abnormal labs, including:
   a. High inflammatory markers (ESR and/or CRP)
   b. Elevated rheumatoid factor (RF)
   c. Low complement C4 level
   d. Positive cryoglobulins and elevated cryocrit in blood
   e. High creatinine and reduced kidney function
3. Supportive features on biopsy of affected organ(s). Common sites of biopsy include the skin and kidneys.
4. Imaging of the lungs
5. Electromyography (EMG) if there is suspected nerve involvement

When cryoglobulins are detected in the blood, we need to investigate for lymphoproliferative diseases, other autoimmune diseases, and chronic infections (hepatitis C in particular). This will include further blood tests and possibly a bone marrow biopsy.

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Treatment of CV may include:

- **Antiviral therapy** if the CV is related to hepatitis C. Treatment of the underlying hepatitis often controls the vasculitis.
- **Prednisone,** a steroid medication highly effective at reducing inflammation. You will typically start on a higher dose and slowly reduce the dose over time.
- Other **immune suppressing medications** such as rituximab, cyclophosphamide, methotrexate, hydroxychloroquine, azathioprine and mycophenolate mofetil.
- **Plasma exchange** (PLEX) is used in severe and life-threatening cases to filter out and remove the cryoglobulins from your blood. PLEX is usually used in conjunction with cyclophosphamide or rituximab.

Adjunctive therapies may include:

- **Stomach and bone protectants** to prevent certain complications related to long-term prednisone.
- **Pneumocystis pneumonia (PCP) protection** with an antibiotic if receiving cyclophosphamide or rituximab.

How is CV monitored?

Your rheumatologist often works with other specialists to treat your CV. Depending on what organs are affected and whether there is an underlying lymphoproliferative disorder or chronic infection, you may also see an **infectious disease doctor, hematologist** or a **nephrologist**.

Common tests used to monitor the vasculitis part of the disease include:

- Lab tests for blood counts, inflammatory markers, liver & kidney function, cryoglobulins, and C3, C4
- Urine studies for protein & blood

Is CV a fatal disease?

Fortunately, most patients have a non-severe form of the disease. The outcomes of CV are usually good when promptly and appropriately treated, however it also depends on whether there are organ- or life-threatening features, and whether there are treatment-related complications.

Markers of worse disease include gut involvement, rapidly progressive kidney disease (glomerulonephritis), or pulmonary hemorrhage (bleeding in the lungs).

Can keeping warm prevent CV?

While keeping your extremity and core temperatures warm can be helpful in preventing cryoglobulins from clumping and triggering the start of inflammation, it does not prevent cryoglobulin formation in the first place. Once inflammation has started, it still needs treatment with immunosuppressive medications.

What will happen to me? How long do I need to take medications for?

Since cryoglobulinemic vasculitis is often a secondary disease (to hepatitis C for example), treatment (and potential cure) of that underlying disease prevents cryoglobulin regeneration and should therefore prevent CV from recurring.

Long-term immune-suppressing medications are sometimes needed to suppress inflammation and prevent relapses.

Unfortunately, active vasculitis even when properly treated can result in permanent organ damage. In these cases, your physician may feel more strongly about keeping you on lifelong treatment to prevent further damage from occurring.

CRYOGLOBULINEMIC VASCULITIS DISEASE SUMMARY TOOL

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My symptoms included:

- ☐ Raynaud's phenomenon
- ☐ Skin rash
- ☐ Skin ulcers
- ☐ Livedo reticularis (lacy discolouration of the skin)
- ☐ Shortness of breath
- ☐ Coughing up blood
- ☐ Burning, tingling or numbness of the extremities
- ☐ Weakness of the arm or leg
- ☐ Joint pain or joint swelling
- ☐ Abdominal pain and nausea
- ☐ Enlarged lymph nodes
- ☐ Unusually frothy/bubbly or dark urine
- ☐ Fevers or drenching night sweats
- ☐ Weight loss
- ☐ Unusually severe fatigue
- ☐ Others: _____

Medications that have been prescribed:

	Date started	Date stopped
IV methylprednisolone _____ mg		
Prednisone (Starting dose _____ mg)		
Colchicine _____ mg		
Hydroxychloroquine _____ mg		
Methotrexate ____ mg		
Folic acid (only if taking methotrexate)		
Mycophenolate mofetil ____ mg		
Azathioprine ____ mg		
Leflunomide ____ mg		
Cyclophosphamide _____ mg		
Rituximab _____ mg (Number of infusions: _____)		
Septra/Bactrim/Sulfatrim		
Plasma exchange (PLEX) (Number of sessions: _____)		
Others:		

I have had the following tests done:

- ☐ Blood tests for inflammation markers, cryoglobulins, hepatitis & other infections, and hematological diseases
- ☐ Urine tests
- ☐ X-rays (circle all that apply): Chest | Abdomen | Joints | Head
- ☐ CT scans (circle all that apply): Chest | Abdomen | Head
- ☐ Ultrasound (circle all that apply): Abdomen & pelvis | Head & neck
- ☐ Biopsy (circle all that apply): Skin | Kidney | Nerve | Bone marrow
- ☐ Bronchoscopy
- ☐ Electromyography (EMG)

What do I need to do?

- ✓ Attend **regular** follow-up visits with my rheumatologist and other specialists
- ✓ **Do regular** blood and urine tests for disease and medication monitoring
- ✓ Ensure my medical team is monitoring me for diabetes, high blood pressure and high cholesterol.
- ✓ Seek urgent medical attention if you are having daily fevers, coughing up blood or experiencing other concerning symptoms.