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INVITED REVIEWS

HCV-related cryoglobulinemic vasculitis/Cryoglobulinemic vasculitis: Definition based on Chapel Hill Conference Consensus 2012 and case report

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Definition: Cryoglobulins are immunoglobulins that form precipitate at low temperatures and causing turbidity in the tube, and solubilise when the temperature is raised again to 37°C [1]. Detection of cryoglobulins in serum is called cryoglobulinemia. The formation of cryoglobulins is usually associated with an underlying disease [2]. The structure of the synthesized cryoglobulin varies depending on the underlying disease.

Three different subtypes were first defined by Brout et al. in 1974 according to their structure [3]. Type I Cryoglobulins are characterised by a monoclonal increase of a single immunoglobulin type, usually immunoglobulin M (IgM), less frequently IgG and rarely IgA. Bence Jones proteinuria can be detected because of mild chain loss in the urine. 10-15% of all cryoglobulinemias are type I [2]. Type II Cryoglobulins (Mixed Cryoglobulinemia); polyclonal IgG increase, light chain kappa or lambda structure, and monoclonal IgM increase against them (rheumatoid factor (RF) activity). 50-60% of cryoglobulinemias are type II. Type III Cryoglobulins (Mixed Cryoglobulinemia); Polyclonal IgM and IgG structure. 25-30% of cryoglobulinemias are type III [3]. It is important to obtain blood sample under appropriate conditions for cryoglobulinemia. There are several points to consider when detecting cryoglobulins. 10-20 ml of blood should be collected in an anticoagulant-free collection tube or syringe preheated to 37 °C. The sample should be transferred at ≥ 37 °C. Allow to clot for 1 hour at 37 °C. Centrifuge the collected serum at 37 °C. After centrifugation, the clot is removed with a Pasteur pipette and the serum is divided into 3 tubes. The centrifuged serum should be refrigerated (4 °C). If there is a precipitate, it should be re-solubilised at 37°C. Wash 3 times with isotonic at 4°C and centrifuge again at 4°C and solubilise again at 37°C for qualitative and quantitative examinations. Immunofixation electrophoresis, immunoglobulin levels and light chain (κ and λ) analysis are performed to typify the immunoglobulins in the cryoprecipitate [4,5].

Cryoglobulinemic vasculitis: The clinical importance of cryoglobulins has been recognized with the discovery of their association with purpura, arthralgia, renal failure and asthenia [6]. Cryoglobulinemic vasculitis, a disease that occurs in the presence of symptoms associated with the presence of cryoglobulins in serum. It is classified as immune complex-associated small vessel vasculitis according to the Chapel Hill consensus criteria [7].

Epidemiology: The prevalence of cryoglobulinemic vasculitis is rare and is approximately 1/100.000. It is usually observed between 45-65 years of age. The geographical distribution is variable. It is more common in southern Europe, where the endemic prevalence of hepatitis C virus (HCV)is higher, than in northern Europe. The female-to-male ratio is approximately 2-3/1 [8].

Etiology:

Type I: monoclonal - B-cell lymphoproliferative disorders:

– MGUS (monoclonal gammopathy of unknown significance) (50%), Multiple Myeloma, Waldenström's Macroglobulinemia, Non-Hodgkin's Lymphoma, Chronic lymphocytic leukemia, Castelman's disease

Type 2-3 (Mixed): Infectious and Non-infectious mixed:

– Essential (idiopathic) mixed type (48%)
– Infectious causes: Hepatitis B virus (HBV), HCV, etc.
– Connective tissue diseases [9].

Classification Criteria for Cryoglobulinemic Vasculitis

1. Subjective symptoms: Have you ever had one or more small red rashes on the skin, especially on the legs, have you ever had a red rash on the lower extremities that healed with brown scars, have you ever been told by a doctor that you have viral hepatitis?
2. Objective symptoms: constitutional symptoms (fever, fatigue, myalgia), joint involvement (arthralgia, arthritis), vascular involvement (purpura, skin ulcers, necrotizing vasculitis, hyperviscosity syndrome, Raynaud's phenomenon), neurological involvement (peripheral neuropathy, cranial nerve involvement, CNS involvement)
3. Laboratory abnormalities: Low C4 level, RF positivity, positive serum M component.

Cryoglobulinemia is classified as cryoglobulinemia when at least two of the findings summarised under the three headings are positive in a patient who has been cryoglobulin positive at least twice within a 12-week interval.

Clinical features: The majority of patients with cryoglobulinemia are asymptomatic and 2-50% may become symptomatic. The triad of purpura, arthralgia and malaise is present in more than 90% of patients. Hyperviscosity syndrome may be seen rarely in mixed cryoglobulinemias with a rate of <3% [10]. Clinical findings that may be observed less frequentlyinclude leg hyperpigmentation, Raynaud's phenomenon, leg ulcers, arterial hypertension, glomerulonephritis, hemorrhagic alveolitis, interstitial lung fibrosis, gastointestinal vasculitis, peripheral neuropathy, heart failure [11]. Factors associated with poor prognosis: pulmonary involvement, glomerular filtration rate (GFR) <60 ml/min, gastrointestinal involvement, age > 65 years [12].

Diagnosis: The diagnosis of cryoglobulinemic vasculitis begins with a detailed history and physical examination[13].TheItalianCryoglobulinemiaStudy Group (GISC) established a validated classification system for clinical trials and epidemiological purposes in 2014. These classification criteria are important for epidemiological studies due to their high specificity, but are not used for diagnosis [14]. The history should include constitutional symptoms (fever, weight loss, weakness, fatigue), arthralgia, myalgia, arthritis, rash and history of infection.Physical examination, should look for petechiae, purpura, livedo reticularis, skin ulcers, arthritis, neuromuscular findings (sensory neuropathy, clubfoot, etc.). In addition to laboratory tests (high RF, low C4, high AFR, microscopic urinary hematuria, proteinuria, hepatitis serology), it is important to detect cryoglobulins in the serum [15]. Investigation of monoclonal proteins, autoantibodies, tissue biopsy in selected patients, EMG and imaging studies are also helpful in the diagnosis. The diagnosis is usually made by the presence of typical symptoms (rash, arthralgia, myalgia, fatigue) and the detection of cryoglobulins in serum [16]. It is important to exclude differential diagnoses and to investigate other underlying diseases.

Differential Diagnosis: In the differential diagnosis, other autoimmune diseases, neoplastic diseases and other vasculitides should be kept in mind. Clinical findings may be similar to other vasculitides affecting small or medium-sized vessels. Sjögren's syndrome also shares common laboratory and clinical findings [17]. Positive Hepatitis C serology, the presence of autoantibodies and a low C4 level may be useful in the differential diagnosis. Erosive, symmetrical polyarthritis may develop in HCV-associated cryoglobulinemia. Similar to rheumatoid arthritis, RF elevation may also be observed. Anti-CCP antibodies are helpful in differential diagnosis [18].

Treatment: In type II/III cryoglobulinemias, the goal is to remove existing cryoglobulins from the circulation, suppress new cryoglobulin production and treat the underlying disease (autoimmune or viral disease) that triggers it. In non-severe involvement in mixed cryoglobulinemias, treatment is in the form of treatment of the underlying disease. In essential mixed cryoglobulinemias, low dose corticosteroids may be the first treatment option. Immunosuppressive and biologic agents are used to suppress B cells, antivirals are used to treat underlying chronic viral diseases such as HCV/HBV, and plasma exchange is used to remove cryoglobulins in the circulation [13].

CASE PRESENTATION

A 54-year-old male patient with no previous history of any medical conditionpresented with a rash on his legs. His history included, rash on the legs, swelling in the ankles, pain, difficulty in walking for the last 3-4 days,. Rheumatologic system questioning revealed weakness, fatigue, arthralgia, myalgia and rash. On physical examination, fever was 38.1 °C, liver was 2-3 cm palpable below the costae. Bilateral ankles are swollen and tender. There were Petechial-purpuric rashes on the lower extremities. Blood tests revealed high RF (363 IU/l), sedimentation (33 mm/h) and CRP (15.4 mg/dl). Blood tests revealed leukocyte 5280/mm3, hemoglobin 10.6 gr/dl, ANA 1/100 granular, Anti ds DNA negative, ANCA profile negative, Brucella agglutination, CMV, parvovirus PCR negative. C3: 42.6 (79-152), C4: 3.3 (16-38), Anti HCV positive, HCV RNA 2773 copies /ml, Cryoglobulin positive. In radiographic findings, liver size was 170 mm and spleen size was 150 mm in abdominal USG. There was no valvular pathology or vegetation in Echocardiography. İmaging studies showed no findings suggestive of infection or malignancy in. Based on theerse findings, The patient was diagnosed as cryoglobulinemic vasculitis.Ribavirin, roferon-A, prednisolone 30mg/day were started. Significant improvement was observed in his complaints. At the 12th month of follow-up, he presented with difficulty in stepping on his right foot. Physical examination revealed dorsiflexion weakness in the right ankle and big toe. EMG revealed decreased right peroneal superficial nerve conduction velocity. Cranial MRI and lumbar MRI showed no pathology. The patient was treated with pulse (1 g/day methylprednisolone) and rituximab 1000 mg (on days 0 and 15. every 6 months) with the diagnosis of low foot. Rituximab treatment was continued for 2 years. At the end of 2 years, the low foot improved. In blood tests, HCV RNA was negative, acute phase reactant, C3, C4, RF levels were normal. There were no signs of disease activation during follow-up.

Key messages

- Cryoglobulins are immunoglobulins that can precipitate at low temperatures and are responsible for the clinical picture of cryoglobulinemic vasculitis.
- The underlying disease is usually responsible for the synthesis of cryoglobulins.
- It is classified as small vessel vasculitis and shares clinical findings with other small vessel vasculitides. The detection of cryoglobulins in the serum is important in the differential diagnosis.
- The basis of treatment is to remove the cryoglobulins from circulation and to eliminate the disease that cause their synthesis.

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