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A rare case of Cryoglobulinemic Vasculitis

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Cryoglobulinemia is a rare medical condition characterized by the presence of abnormal proteins called cryoglobulins in the blood, which precipitate or clump together at low temperatures.

These cryoglobulins, composed of immunoglobulins and sometimes complement components, deposit in small- to medium-sized blood vessels throughout the body, causing endothelial injury and end-organ damage.

Cryoglobulins can cause a range of symptoms, including joint pain, skin rashes, and kidney problems, due to their tendency to obstruct blood vessels and trigger inflammatory reactions.

Often associated with underlying diseases such as hepatitis C, autoimmune disorders, or certain cancers, cryoglobulinemia poses a diagnostic and therapeutic challenge due to its varied clinical manifestations.

Treatment targets both the cryoglobulins and the underlying conditions, with options including pharmacotherapy, plasmapheresis, and management of associated diseases.

Diagnosis involves measuring cryoglobulin levels along with low C4 complement levels.

Treatment varies based on the severity and nature of the underlying disorder, with mixed cryoglobulinemia typically treated with steroids and Rituximab.

I. CASE REPORT

68 years old male, with no known comorbidities, hailing from coastal belt of Karnataka, presented with high grade fever since 1 week, associated with on and off loose stools since 1 week. In view of myalgia, he was advised injection Diclofenac from a nearby clinic, subsequent to which he developed bilateral lower limb pupuric rashes. On evaluation at an outside hospital, vitals recorded were stable. Cardiac evaluation was normal. Blood investigations revealed elevated serum creatinine, and thrombocytopenia (43,000). After 5 days, on arrival at our set up, BP recorded was slightly on higher side. Platelet count had improved to 2,00,000. Creatinine was 2.13. Hypoalbuminemia was present (2.5). Hemoglobin and total counts were within normal limits. Fever work up was negative as well. Blood culture showed no growth. He was HBV and HCV non reactive. USG abdomen pelvis revealed mild bilateral pleural effusion, minimal ascites and bilateral grade 1 medical renal disease.

Urine routine showed 20-25 RBC's/HPF and 24hrs urine protein was 450mg/day. No casts seen. As a part of further work up, ANA and ANCA profile was sent which were negative as well, however both C3 and C4 levels were low. Throughout the hospital stay, patient had elevated BP recording. As a part of renal work up, renal biopsy was performed which showed – glomerular tufts show diffuse and global coarse granular deposits along the capillary walls and mesangium and hyaline globules with IgG+1, IgM3+, and Lamba 3+

Immunohistochemistry showed global CD68 mononuclear deposits.

Giving an impression of immune complex mediated glomerulonephritis, monoclonal type. Pattern being diffuse endocapillary proliferative glomerulonephritis. As the pattern wasn't typical of amyloidosis, further diagnostic tests for amyloidosis wasn't performed.

Monoclonal deposits required further bone marrow biopsy and aspiration which were also normal.

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NATURE OF SPECIMEN: Kidney Biopsy.

GROSS MORPHOLOGY: Received 1 vials.
1] Received a linear core measuring 1.1 cm length for LM in formalin, All embed.

MICROSCOPIC DESCRIPTION:
Multiple step serial sections (32) from renal core stained with H & E, PAS, MT and PASM show SIXTEEN glomeruli. FIVE of them are obsolescent.
Glomeruli (viable glomeruli) : Majority of them appear solid and proliferative tufts. There is obliteration of capillary lumen secondary to proliferation of endothelial cells, mesangial cells admixed with mononuclear cells possessing moderate amount of cytoplasm. Upto two glomeruli show segmental hyaline globules in the lumen. Basement membrane is single contoured (Jones stain). There is no lobular accentuation. Necrotizing lesion or fibrinoid change is not seen. There is no crescent.
Tubules / Interstitium : Tubules show foci of RBC's in the lumen along with attenuated lining epithleium. Interstitium show patchy edematous appearance with scattered lymphocytes. There is no focus of tubular atrophy / interstitial fibrosis. Granuloma or eosinophilic infiltrates are not seen.

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HISTOPATHOLOGY
Vessels : Artery and arterioles show mild hyperplasia of tunica media. There is no focus of vasculitis.

IMMUNOFLUORESCENCE (Pronase-digested Paraffin sections, SALVAGE technique) : TEN viable glomeruli are seen. Glomerular tufts show diffuse and global, coarse granular deposits along the capillary walls and mesangium and hyaline globules with IgG (1+), IgM (3+), and Lambda (3+). Others including IgA, C3, C1q and Kappa are negative. No extra-glomerular deposits are seen.

IMMUNOHISTOCHEMISTRY (on paraffin block):
CD68 - Mononuclear cell infiltrates are positively stained deistributed diffusely and globally. External control is satisfactory.

IMPRESSION:
Kidney biopsy, native :
- Primary diagnosis: Immune-complex mediated glomerulonephritis, monoclonal type (SEE NOTE).
- Pattern of injury: Diffuse endocapillary proliferative glomerulonephritis.
- Additional features: Acute tubular injury.

Thus, this case of cryoglobulinemic vasculitis was confirmed and was started on steroids and Rituximab, after which the patient has been on routine follow up and has symptomatically improved with the same.

II. DISCUSSION

Cryoglobulins are proteins that precipitate from an individual's serum or plasma at temperatures lower than 37 °C. These cryoglobulins can be a mixture of immunoglobulins (Igs) and complement components or immunoglobulins alone.[1]

They deposit in small- to medium-sized blood vessels throughout the body, causing endothelial injury and end-organ damage known as cryoglobulinemia. Diagnosis of this entity should be suspected in patients presenting with skin ulcers, arthralgia, glomerulonephritis, neuropathy, and purpura.

Cryoglobulinemia predominantly affects adults, with a higher incidence observed in females than males. Based on the currently available case series, patients with type 1 cryoglobulin account for 5% to 25% of the cases. Geographic variations in prevalence are noted, correlating with the distribution of HCV infection and other associated diseases. Due to its association with various underlying conditions, the epidemiology of cryoglobulinemia reflects a complex interplay

between genetic, environmental, and infectious factors.

The Brouet criteria classify cryoglobulinemia into 3 subgroups based on their immunoglobulin composition.[2]

Type I: Type I cryoglobulinemia has monoclonal immunoglobulins, typically IgG or IgM, and develops in the setting of lymphoproliferative or hematologic disorders of B-cell lineage, such as multiple myeloma, Waldenströmmacroglobulinemia, chronic lymphocytic leukemia, or protein-secreting monoclonal gammopathies such as monoclonal gammopathy of undetermined significance (MGUS).[3]

Type II: Types II and III constitute mixed cryoglobulinemia, characterized by polyclonal immunoglobulins associated with autoimmune diseases, malignancy, or infections, notably hepatitis C virus (HCV) infection.[4] Their constituent immunoglobulin is not a single monoclonal immunoglobulin.

In type II cryoglobulinemia, cryoglobulins are composed of a mixture of monoclonal IgM (or IgG or IgA) with rheumatoid factor (RF) activity, along with polyclonal immunoglobulin.

Type II cryoglobulinemia is often associated with the following conditions:

- HCV infection, which is the most common causative factor of cryoglobulinemic vasculitis and mixed cryoglobulinemia.[5]
- Vaccines.
- Hepatitis B virus (HBV) infection.
- HIV.
- Autoimmune diseases, mainly systemic lupus erythematosus (SLE), Sjögren syndrome, and adult-onset Still disease.[6]
- Lymphoproliferative disorders.

About 10% of cases have no identifiable disease association; hence, cryoglobulinemia is termed "essential mixed cryoglobulinemia."

Type III: Cryoglobulins in type III cryoglobulinemia are a mixture of polyclonal IgG (all isotypes) and polyclonal IgM. These cases are often secondary to autoimmune disorders and occasionally associated with infections, most commonly HCV.

Chronic immune stimulation and lymphoproliferation lead to increased production of higher levels of mono-, oligo-, or polyclonal immunoglobulins, which subsequently form cryoglobulins.

These cryoglobulins circulate in the blood and can precipitate, forming immune complexes that deposit in small- to medium-sized blood vessels, leading to vascular occlusion and inflammation. The deposition triggers an inflammatory response, causing endothelial cell injury and attracting immune cells such as lymphocytes and macrophages to the site.

In addition, the immune complexes activate the complement system, further contributing to inflammation and tissue damage. Organs commonly affected include the skin, kidneys, and peripheral nerves, with clinical manifestations such as purpura, glomerulonephritis, and neuropathy.

For mixed cryoglobulinemia there is a role of genetic factors like the presence of BAFF (B-lymphocyte activating factor) and Fc receptor variants, especially in Hepatitis C infected individuals. It is hypothesized that Hepatitis C envelope protein E2 can bind with the B lymphocyte CD81 receptor, thereby acting as an antigenic stimulus. This leads to the formation of antibodies and the resulting antigen-antibody complexes that get deposited in vessel walls.

The treatment of cryoglobulinemia depends on the underlying primary disorder, severity, and nature of organ involvement.

In presentations of mixed cryoglobulinemia with symptoms, the treatment is directed at the underlying autoimmune or infectious disorders.

In the case of essential mixed cryoglobulinemia, the clinical course is more severe, and the recommended treatment is steroids combined with rituximab, with the steroids to be tapered.

In addition, the treatment for cryoglobulinemia focuses on each individual case and includes plasmapheresis and immunosuppression (such as glucocorticoids and rituximab) for patients with rapidly progressing or life-threatening outcomes. The treatment is directed toward the underlying infection or autoimmune disorder. Generally, the treatment is tailored to address the underlying (causal) disease, the presence of hyperviscosity, and any co-occurring organ involvement or damage.

HCV infections most commonly cause mixed cryoglobulinemia. The connection between infection and autoimmune or lymphoproliferative disorders is common. The general onset of this disease is slow-paced, but in some situations, rapid progression can occur. In recent years, with the advent of direct antiviral therapy, there has been a change in the treatment approach.[5] HCV-positive patients with cryoglobulinemia are now recommended to receive initial therapy with pan-

genotypic antiviral regimens (such as sofosbuvir or velpatasvir and glecaprevir or pibrentasvir). HCV genotyping and subtyping should continue, but initial treatment is still important.

Studies have demonstrated a response rate with minimal viral counts in almost 100% of patients, although about 13% experience a relapse. The administration of antivirals in HCV-B-cell clonalities is necessary to eliminate the viral threat, especially considering the immunosuppressives used to obliterate the clone. Direct antiviral agents have a better tolerability and safety profile than interferon (IFN), with the latter exhibiting a superior anti-lymphoma effect.[5] There were no significant differences in overall survival or progression-free survival between the 2 treatments.

Cyclophosphamide has been utilized alongside apheresis to address high cryocrit levels and prevent a post-apheresis rebound in cryoglobulin synthesis. However, its usage has diminished due to the rise of B-cell–depleting monoclonal antibodies such as rituximab. When using rituximab, close monitoring of patients with latent HBV infection is essential, and appropriate prophylaxis should be provided. Monitoring HBV DNA or hepatitis B surface antigen (HBsAg) is also recommended. Low-dose monoclonal antibodies or concurrent administration of an antiviral regimen may offer additional benefits.

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