

CASE OF THE WEEK 5

Clinical history:

A 58 year old male presented with pedal edema for last 10 days and feeling of lethargy and vague myalgias for about one and a half months. He was detected with hypertension 6 months back and was on treatment. There was no history of liver diseases, diabetes mellitus or any other major illness in the past.

Examination:

Pedal edema +, mild pallor +, few petechial rashes were noted over lower limbs, BP 148/94 mmHg . Rest of systemic examination: WNL

Investigations:

Haemoglobin 8.6 g%, TLC 13,600/mm³, P72 L24 E 3 M1, ESR 32 mm/1st hour, PS: normocytic normochromic

Urea 68 mg% (24.2 m mol/L), Creatinine 2.8 mg% (247.5 u mol/L)

Urine albumin 3+, RBC 15-20/hpf, spot protein creatinine ratio 6.2

Serology for ANA, anti dsDNA, p and c ANCA, anti GBM antibodies- negative

Serum C3 110 mg% (1.1 g/L), C4 8 mg% (0.08 g/L)

HBsAg/HIV- negative, anti HCV- positive

Lipid profile- WNL

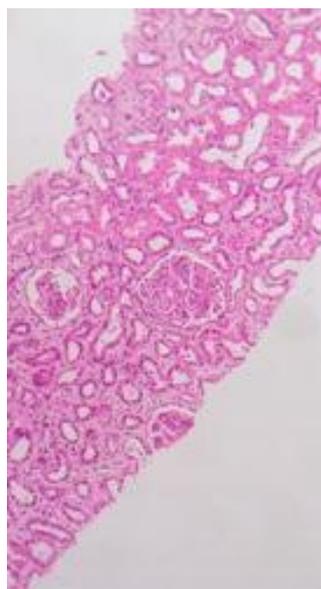
In view of nephritic- nephrotic presentation with renal dysfunction and HCV positivity, a renal biopsy was performed.

Light microscopic and DIF images can be viewed .In addition to the images shown there was 1+ staining for IgG and lambda light chains in DIF studies. Glomeruli were negative for IgM, C3 and C1q

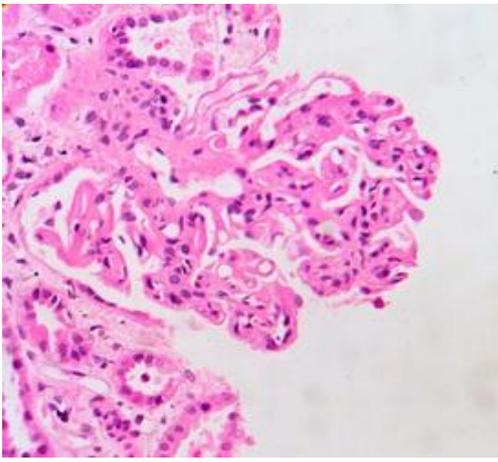
MICROSCOPY



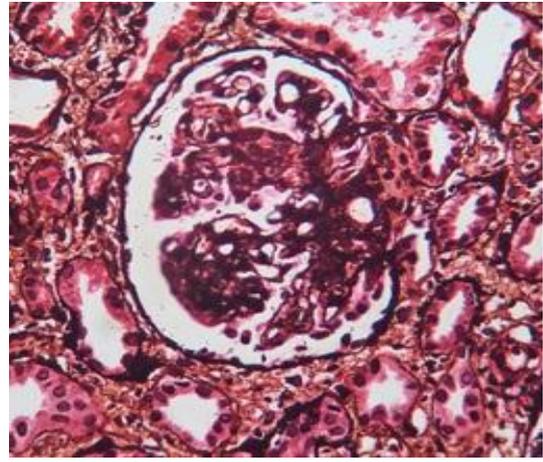
a



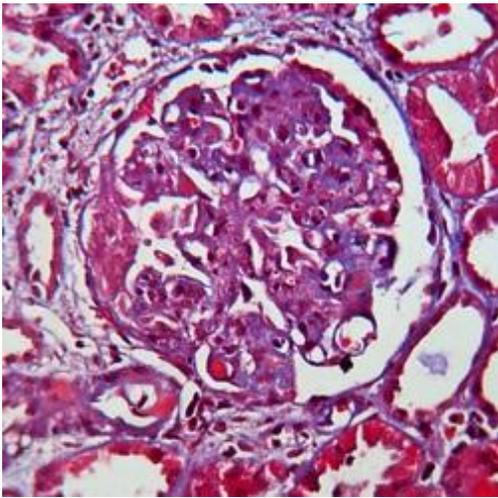
b



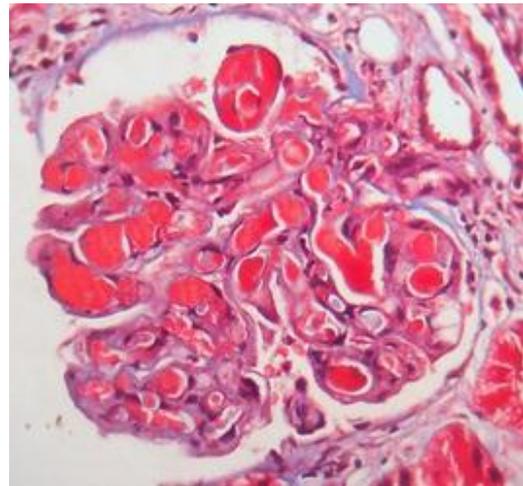
c



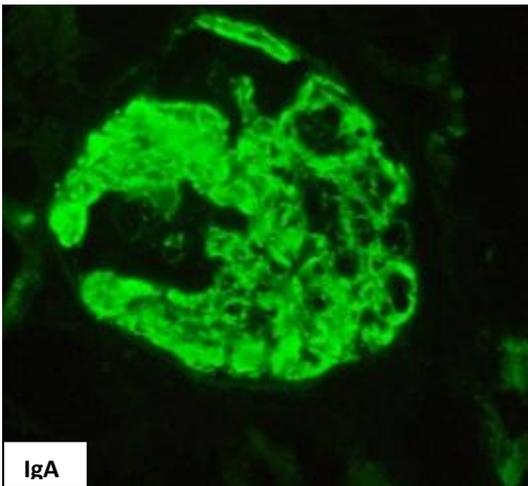
d



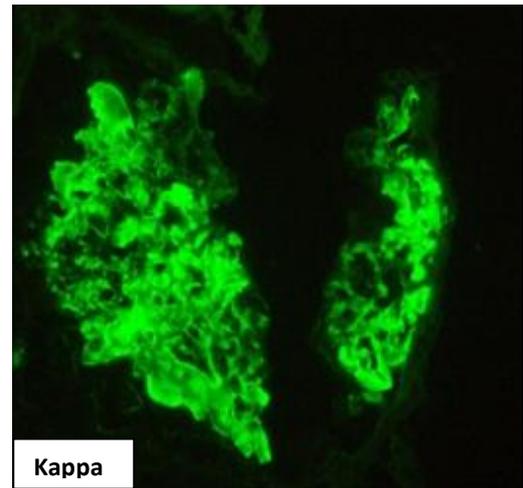
e



f



g



h

Microscopic examination showed features of a proliferative glomerulonephritis with a membranoproliferative or mesangiocapillary pattern. Silver methenamine stained sections revealed few capillary wall splits (Fig d) and occasional glomeruli revealed large intraluminal hyaline thrombi and subendothelial deposits (Fig e & f).

DIF studies showed intense staining for IgA along the mesangium and capillary wall including the intraluminal “thrombi” and similar intense positivity for kappa light chains. Less intense similar staining was seen for IgG and lambda light chains.

In view of the morphological features (membranoproliferative pattern, Hepatitis C positivity and prominent intraluminal thrombi/subendothelial deposits), serum cryoglobulins assay was performed which detected Type II cryoglobulins with monoclonal heavy chain alpha, with associated kappa light chain (IgA-kappa) and polyclonal immunoglobulin (IgG). Tissue for EM studies was not available in the present case.

FINAL DIAGNOSIS:

Renal involvement in Type II (mixed) cryoglobulinemia (IgA kappa - IgG)

DISCUSSION:

The term cryoglobulinemia refers to the presence in the serum of one (monoclonal cryoimmunoglobulinemia) or more immunoglobulins (mixed cryoglobulinemia), which precipitate at temperatures below 37° C and redissolve on re-warming. This is an *in vitro* phenomenon; the actual mechanisms of cryoprecipitation *in vivo* remain obscure. These could be secondary to intrinsic characteristics of both mono- and polyclonal immunoglobulin (Ig) components, or be the result of interaction among single components of the cryoprecipitate.

Cryoglobulinemia is usually classified into three subgroups according to Ig composition

Classification of Cryoglobulinemia

	Type I	Type II mixed CG	Type III mixed CG
Composition	Single monoclonal Ig mainly IgG, IgM, or IgA, or monoclonal free light chains	Presence of monoclonal component: usually IgM, IgG, or IgA and polyclonal Ig (mainly IgG)	Polyclonal mixed Ig
Biological characteristics	Self-aggregation through Fc fragment of Ig	RF activity of monoclonal component against Fc portion of polyclonal Ig predominant	RF activity of one polyclonal component (usually IgM)
Clinical associations	Lymphoproliferative disorders: multiple myeloma, Waldenstrom's macroglobulinaemia, chronic lymphocytic leukemia, B cell NHL	Viral, bacterial, parasitic infections (mainly HCV, less HBV, others), autoimmune diseases, lymphoproliferative disorders rare	Viral, bacterial, parasitic infections (mainly HCV, less HBV, others), autoimmune diseases, lymphoproliferative disorders rare

CG — cryoglobulinemia; Ig — immunoglobulin; RF — rheumatoid factor; NHL — non-Hodgkin's lymphoma; HBV — hepatitis B virus; HCV — hepatitis C virus

Type I cryoglobulinemia is composed of only one isotype or subclass of immunoglobulin. Both type II and type III mixed cryoglobulinemia (MC) are immune

complexes composed of polyclonal IgGs, the autoantigens, and mono- or polyclonal immunoglobulins, IgM in vast majority of cases.

Etiology of Mixed Cryoglobulinemia

Following the discovery of hepatitis C virus (HCV) as the major etiologic agent of non-A-non-B chronic hepatitis, a several clinico-epidemiological, histopathological, and virological studies (HCV RNA detection by polymerase chain reaction -PCR- and/or in situ hybridization -ISH) have established the important role for HCV in the pathogenesis of MC. The prevalence of serum anti-HCV antibodies and/or HCV RNA in MC patients ranges from 70% to almost 100% among different patient populations.

Diagnosis criteria / classification

In 1989 the Italian Group for the Study of Cryoglobulinaemias proposed preliminary criteria for MC classification. A revised version of these criteria is presented in Table 1.

Table 1: Proposed criteria for the classification of mixed cryoglobulinemia patients.

Criteria	serological	pathological	clinical
major	mixed cryoglobulins low C4	leukocytoclastic vasculitis	purpura
minor	rheumatoid factor + HCV + HBV +	clonal B-cell infiltrates (liver and/or bone marrow)	chronic hepatitis MPGN peripheral neuropathy skin ulcers
definite mixed cryoglobulinemia syndrome:			
a) serum mixed cryoglobulins (\pm low C4) + purpura + leukocytoclastic vasculitis			
b) serum mixed cryoglobulins (\pm low C4)+ 2 minor clinical symptoms			
+ 2 minor serological/pathological findings			
essential or secondary mixed cryoglobulinemia:			
absence or presence of well-known disorders (infectious, immunological or neoplastic)			

HCV+ or HBV+: markers of hepatitis C virus or hepatitis B virus infection (anti-HCV \pm HCV RNA; HBV DNA or HBsAg); *MPGN:* membranoproliferative glomerulonephritis

De Vita et al have recently published proposed criteria for diagnosis of cryoglobulinemic vasculitis, which need further validation studies

[Marzona M, et. al. Chemical analysis of cryoglobulins observed in a case of essential IgG-IgA cryoglobulinaemia. Boll Soc Ital Biol Sper. 1979 Jul 30;55\(14\):1388-90.](#)

[Ferri C; Cryoglobulinemia. Orphanet encyclopedia, October 2002:
http://orphanet.infobiogen.fr/data/patho/GB/uk-cryoglobul.html](#)