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# Immunoglobulin and complement-mediated glomerular diseases with an MPGN pattern of injury: Unmasking the diagnosis of lupus in a patient with hepatitis A infection

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## Abstract

In cases with a broad differential or atypical features, it is important to continually review the original diagnosis. Diagnosing SLE can be challenging due to its multi-system presentations; a multidisciplinary approach is beneficial.

## KEYWORDS

cryoglobulinemia, glomerulonephritis, systemic lupus erythematosus

## 1 | INTRODUCTION

Cryoglobulinemia can occur secondary to infections, autoimmune diseases or be idiopathic. Making a confident overarching diagnosis can be challenging. We describe a case of cryoglobulinemia in a patient with recent hepatitis A infection and multisystem features and outline the clinical course that led us to diagnose systemic lupus erythematosus.

Cryoglobulins are immunoglobulins that precipitate at temperatures below 37°C and cause clinical manifestations through the creation of a hyperviscous state or immune complex-mediated disease. Type I cryoglobulins comprise monoclonal IgM or IgG, type II comprise monoclonal IgM with rheumatoid factor activity and polyclonal IgG, and type III are a mixture of polyclonal IgM and IgG. Type II and III cryoglobulinemia typically occur secondary to underlying infection, autoimmune conditions or malignancy. Around 10% of cases are idiopathic, termed essential cryoglobulinemia.<sup>1</sup> Knowledge of the wide range of primary causes is essential for workup and guiding treatment.<sup>1,2</sup>

While some primary causes of cryoglobulinemia are easily identified through serological tests, for example viral hepatitis, others are more challenging. Systemic lupus erythematosus is a complex autoimmune disease associated with a range of autoantibodies. It involves multiple organ systems and has wide variations in symptomatology. The average time between first symptoms and SLE diagnosis is 6 years, and nearly half of individuals receive an alternative initial diagnosis.<sup>3</sup> Diagnostic criteria require a positive ANA with at least one clinical criterion and a score of 10 or more on a domain-weighting system as demonstrated in Table 1.<sup>4</sup> Of note, criteria do not need to occur simultaneously or be persistently present.

We describe the clinical course that led to SLE being diagnosed in a patient with long-standing ANA positivity and multiple attendances to primary and secondary care, highlighting the importance of revisiting original diagnoses in individuals with atypical presentations.

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**TABLE 1** EULAR/ACR 2019 classification criteria for SLE

| <b>Clinical domains</b>     |   |           |
|-----------------------------|---|-----------|
| Constitutional              | Fever   | 2         |
| Hematological               | Leukopenia  | 3         |
|                             | <b>Thrombocytopenia</b>   | <b>4</b>  |
| Neuropsychiatric            | Autoimmune hemolysis  | 4         |
|                             | Delirium  | 2         |
|                             | Psychosis   | 3         |
|                             | Seizure   | 5         |
| Mucocutaneous               | Alopecia  | 2         |
|                             | Oral ulcers   | 2         |
|                             | Subacute cutaneous or discoid lupus erythematosus                     | 4         |
|                             | Acute cutaneous lupus erythematosus                                   | 6         |
| Musculoskeletal             | Joint involvement   | 6         |
| Serosal                     | Effusion  | 5         |
|                             | Acute pericarditis  | 6         |
| Renal                       | <b>Proteinuria &gt;0.5 g/24 hours</b>                                 | <b>4</b>  |
|                             | Class II/V lupus nephritis on renal biopsy                            | 8         |
|                             | <b>Class III/IV lupus nephritis on renal biopsy</b>                   | <b>10</b> |
| <b>Immunology domains</b>   |   |           |
| Antiphospholipid antibodies | Anticardiolipin, anti- $\beta$ 2GPI antibodies or lupus anticoagulant | 2         |
| Complement                  | <b>C3 or C4 low</b>   | <b>3</b>  |
|                             | C3 and C4 low   | 4         |
| SLE-specific antibodies     | Anti-Sm   | 6         |
|                             | Anti-dsDNA  | 6         |

Note: In people who have ever had a positive ANA test, a score  $\geq 10$  has a sensitivity of 96.1% and specificity of 93.4% for diagnosis. The domains relevant to our patient are shown in bold.

## 2 | CASE HISTORY AND EXAMINATION

A 70-year-old woman was admitted to the medical unit with a 5-day history of a nonblanching petechial rash on her buttocks and lower limbs, and 3 days of nausea and vomiting without abdominal pain. She had no fever, photophobia or neck stiffness, no cough or shortness of breath, and no chest pain. She described diarrhea without blood or mucous. Her urine appeared frothy but she had no dysuria or visible hematuria. She had developed swelling in her feet and ankles.

Three months earlier, she had been admitted to hospital with jaundice. Her husband was unwell with the same symptoms after they shared a take-away meal. She was found to have acute hepatitis A with a positive IgM and negative IgG antibody; her husband was diagnosed with the same infection.

Due to significant derangement in her liver function tests, slow clinical resolution and a positive antinuclear antibody (ANA), she underwent a liver biopsy to investigate for potential dual liver pathology. This showed multifocal hepatocellular necrotic lesions, hepato-canalicular cholestasis, and mild macrovesicular steatosis consistent with acute cholestatic hepatitis secondary to hepatitis A. At the time, her serum creatinine was  $93 \mu\text{mol/L}$  with an eGFR of  $43 \text{ mL/min/1.73 m}^2$ , stable from 3 years previously. She had been slowly recovering from this illness, only recently returning to her previous level of health.

Past medical history included a 30-year history of hypertension and preeclampsia in her two pregnancies. She had hyperthyroidism with a positive anti-thyroid peroxidase antibody, for which she had received radio-iodine treatment, and a long history of lethargy and myalgia diagnosed as chronic fatigue syndrome by her GP. She had prediabetes under surveillance. Two years previously a coincidental finding of deranged liver function tests had been detected on routine blood tests. An autoimmune liver screen detected positive ANA and smooth muscle antibodies. A liver ultrasound was normal, and no definitive diagnosis was made. Her liver function spontaneously improved, and she had been discharged from follow-up.

She had no recent foreign travel and no pets. She was a retired nurse with no history of alcohol excess, recreational drug use, tattoos, or blood transfusions. There was no significant family history.

On physical examination, she was hypertensive with a blood pressure of  $188/78 \text{ mm Hg}$ , oxygen saturations of 98% on room air and had no fever. Body mass index was  $32 \text{ kg/m}^2$ . There were no splinter hemorrhages or lymphadenopathy. She had a soft pan-systolic murmur, chest examination revealed good bilateral air entry, and the abdomen was soft with no palpable masses. There was a purpuric rash most prominent on her lower limbs and buttocks. She had pitting edema to her ankles and sacrum.

On admission, blood tests showed a raised serum creatinine at  $181 \mu\text{mol/L}$  with urea  $12.5 \text{ mmol/L}$ , a low sodium at  $130 \text{ mmol/L}$ , and normal potassium at  $4.7 \text{ mmol/L}$ . Baseline creatinine was  $95 \mu\text{mol/L}$ . Corrected calcium, phosphate, and glucose were normal. Liver function showed a normal bilirubin ( $8 \mu\text{mol/L}$ , peak  $297 \mu\text{mol/L}$  during hepatitis A), mildly elevated ALT at  $78 \text{ U/L}$  (peak  $970 \text{ U/L}$  during hepatitis A), and a normal ALP.

Full blood count showed a mild normocytic anemia with hemoglobin  $108 \text{ g/L}$ , normal white cell count at  $5.68 \times 10^9/\text{L}$ , and a thrombocytopenia with platelets  $88 \times 10^9/\text{L}$ . A blood clotting profile was normal. Haptoglobin was low at  $<0.03 \text{ g/L}$  but lactate dehydrogenase only slightly elevated at  $503 \text{ U/L}$ . C-reactive protein was mildly elevated at  $18 \text{ mg/L}$ .

Urinalysis was positive for blood and protein. Urine protein:creatinine ratio was elevated at  $461 \text{ mg/mmol}$  with low serum albumin at  $26 \text{ g/L}$ .

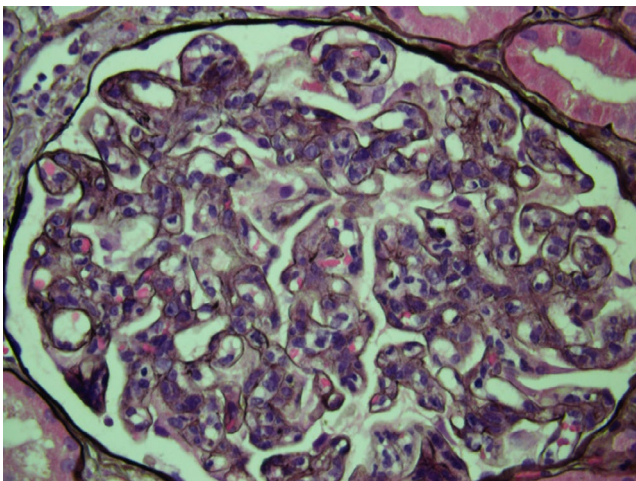
Immunology revealed a positive ANA but extranuclear antigens (SS-A, SS-B, Sm, RNP, Jo1, Scl70, and dsDNA)

were negative. Anticardiolipin antibody and rheumatoid factor were normal. C4 was low at 0.06 g/L and C3 normal at 1.18 g/L. Serum and urine electrophoresis were negative with a normal serum kappa:lambda light chain ratio. Immunoglobulins were normal (IgG 11.48 g/L, IgA 2.66 g/L, IgM 0.71 g/L). Type III cryoglobulins were detected.

Three sets of blood cultures and a urine culture showed no growth. Hepatitis A IgG was positive, and hepatitis A IgM was negative. Hepatitis B and C serology were negative. She had 3 equivocal HIV antibody tests, but HIV PCR was negative. Thiopurine methyltransferase level was low.

An abdominal ultrasound showed normal appearance of kidneys, liver, and spleen, and chest X-ray was normal. A transthoracic echocardiogram showed posterior mitral valve prolapse with mild mitral regurgitation and a small echogenic structure on the posterior leaflet. A transesophageal echocardiogram demonstrated thickening and echogenicity of the anterior and posterior leaflets of the mitral valve suggestive of a systemic inflammatory process, not typical for infective endocarditis. A skin biopsy was not performed as the rash spontaneously resolved.

A kidney biopsy was performed. This showed endocapillary and mesangial proliferation in 7 out of 9 glomeruli with focal double contours of the basement membrane, typical of a membranoproliferative glomerular injury (MPGN) (Figures 1 and 2). The remaining 2 glomeruli were globally sclerosed. On immunohistochemistry C3, IgG, IgM, and C1q showed strong mesangial and subendothelial positivity, and mild IgA positivity suggesting the “full-house” pattern of lupus nephritis. The arteries appeared normal. There was evidence of mild chronicity with 15% interstitial fibrosis and tubular atrophy. On electron microscopy, granular subendothelial electron-dense deposits were observed (Figure 3). There were no organized deposits, no tubuloreticular inclusions, and no subepithelial humps.



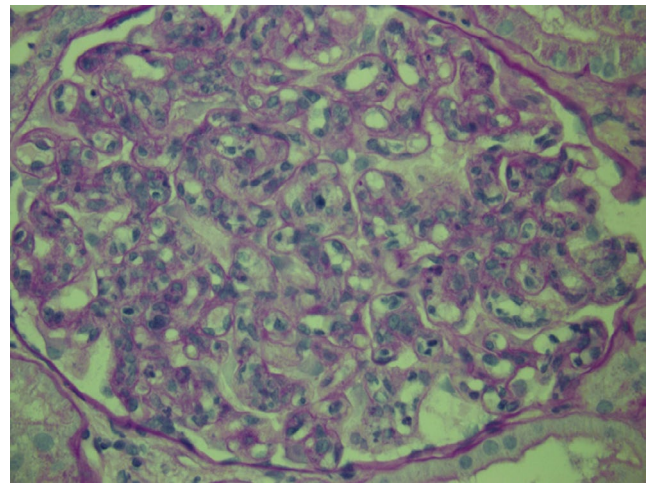
**FIGURE 1** Silver stain of kidney biopsy demonstrating mesangial and endocapillary proliferation

### 3 | DIFFERENTIAL DIAGNOSIS, INVESTIGATION, AND TREATMENT

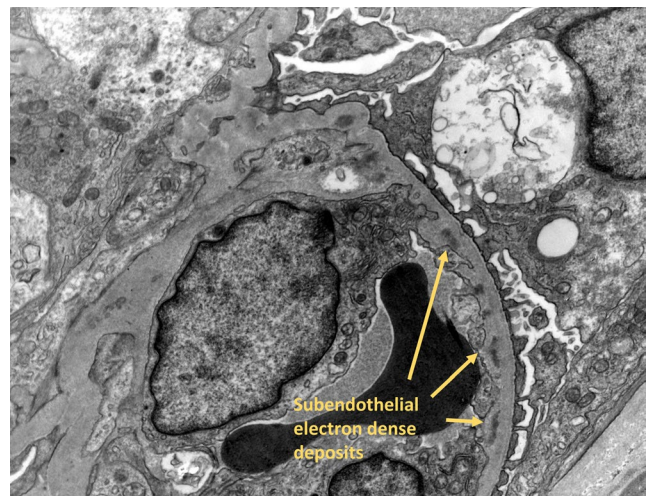
The differential diagnosis was between an infective, autoimmune, or idiopathic cause of cryoglobulinemia. The main differential within each category were as follows:

1. Cryoglobulinemia secondary to hepatitis A infection
2. Cryoglobulinemia secondary to SLE
3. Essential cryoglobulinemia

The recent hepatitis A infection and strong association between cryoglobulinemia and other viral hepatitis means an infective cause was initially considered the most likely diagnosis. ANA positivity has also been described in up to half of individuals in the recovery phase of hepatitis A infection and can persist for up to 3 months.<sup>5</sup> Further, as treatment of autoimmune



**FIGURE 2** Periodic acid-Schiff stain of kidney biopsy demonstrating mesangial and endocapillary proliferation



**FIGURE 3** Electron microscopy of kidney biopsy demonstrating subendothelial electron-dense deposits



or idiopathic cryoglobulinemia involves immunosuppression it was essential to investigate for underlying infection.

Hepatitis A induced cryoglobulinemia is encountered much less frequently than with other hepatitis viruses.<sup>6</sup> Cases have typically been described in the acute phase of infection, with late cases only occurring in the context of relapsing or recurrent disease.<sup>7</sup> Our patient had evidence of seroconversion with a positive hepatitis A IgG and negative hepatitis A IgM alongside normalization of her liver function tests and synthetic liver function. These findings led us to consider other causes of cryoglobulinemia.

Several features of our patient's history stood out when considering autoimmune etiologies. She had a long history of constitutional symptoms, ANA positivity that pre-dated her hepatitis A infection, and a history of preeclampsia (more prevalent in women with SLE<sup>8</sup>), autoimmune thyroid disease and serositis (with prior deranged liver function and mitral valve thickening). These features raised the possibility of a long-standing rheumatologic diagnosis.

The kidney biopsy did not show intraluminal hyaline thrombi typical of cryoglobulinemic vasculitis, and the sub-endothelial deposits on electron microscopy were granular rather than having the organized substructure typically seen with cryoglobulin deposition. No subepithelial humps were seen on electron microscopy, and so there was no convincing evidence of a postinfectious pathology.

Class III or class IV lupus nephritis can demonstrate an MPGN pattern as a result of endocapillary injury.<sup>9,10</sup> Alongside the full-house positivity on immunohistochemistry, the histological features were felt to most likely reflect lupus nephritis. The EULAR/ACR 2019 criteria (Table 1) were consulted, and a diagnosis of SLE was made given her ANA positivity alongside the presence of thrombocytopenia, hypocomplementemia, proteinuria, and kidney biopsy findings.

Initial management was symptomatic with antiemetics, intravenous loop diuretic with oral thiazide diuretic, and a salt and 1 liter/day fluid restriction to manage her edema.

The risks and benefits of commencing immunosuppression for SLE were considered, compounded by the fact her presentation was during the COVID-19 pandemic. Treatment options considered comprised oral corticosteroids with azathioprine or mycophenolate mofetil. Removal of cryoglobulins with plasma exchange or greater depletion of their production with rituximab was reserved in case of failure to respond to initial treatment.

Due to her low thiopurine methyltransferase level and recent deranged liver function tests, mycophenolate mofetil was favored and administered alongside 40 mg (0.5 mg/kg) oral prednisolone. Pulsed intravenous steroids and higher dose oral corticosteroids were avoided due to patient preference alongside her history of prediabetes and elevated BMI. Hydroxychloroquine was commenced to reduce the risk of SLE-related end-organ damage.

## 4 | OUTCOME AND FOLLOW-UP

Two weeks after commencing treatment, there were signs of clinical improvement. The patient noted an increase in urine output and reduction in edema, allowing a reduction in diuretic therapy. Six weeks after commencing treatment, her weight had dropped by 14 kg, her blood pressure had fallen, and antihypertensive agents were reduced. The patient reported improved energy levels and greater overall well-being.

Her urine protein:creatinine ratio fell to 133 mg/mmol, with a corresponding rise in serum albumin to 37 g/L. Her renal function improved with a creatinine of 118  $\mu$ mol/L and C4 rose to 0.24 g/L. A slow taper to her oral steroids was commenced. The patient remains clinically well at the time of writing. Of note, she remains ANA positive.

## 5 | DISCUSSION

Cryoglobulinemia can present in a variety of ways. Hyperviscosity syndromes typically occur with type I cryoglobulinemia in the context of hematological malignancy, presenting with headache, visual disturbance, and epistaxis. Cryoglobulinemic vasculitis is an immune complex-mediated disease. Constitutional symptoms such as malaise and low-grade fever are accompanied by a cutaneous purpuric rash in up to 80% of individuals. The kidneys are the next most frequently involved organ, and microscopic hematuria, proteinuria, renal impairment, and hypertension are present in up to 20% of individuals. Peripheral neuropathy, gastrointestinal, and respiratory symptoms can also occur.<sup>1</sup>

Hepatitis B and C infections are widely recognized causes of cryoglobulinemia.<sup>1</sup> Hepatitis A-associated cryoglobulinemia is rare but has been described in case reports.<sup>7,11</sup> While this seemed an attractive initial diagnosis, reports are of a type II cryoglobulinemia with positive rheumatoid factor occurring in the acute phase of the disease or in relapsing disease, contrary to what was observed here.<sup>7,11</sup> In animal studies, a proliferative glomerulonephritis has been reported up to 25 weeks after the initial infection, but again in the context of high antihepatitis A titres.<sup>12</sup>

An MPGN pattern of injury can be observed in a number of conditions. C3 dominance on immunofluorescence can associate with C3 glomerulopathy or dense deposit disease, while the presence of both immunoglobulin and complement staining can occur in infections, dysproteinemias and autoimmune diseases including SLE, Sjogren's, and rheumatoid arthritis. An MPGN pattern without immunoglobulin or complement staining can be seen in chronic thrombotic microangiopathy.<sup>13</sup> In the context of cryoglobulinemia, an MPGN pattern with deposition of immunoglobulins of the same type as those detected in serum is usually seen, with organized deposits in subendothelial and mesangial areas on electron microscopy.<sup>14</sup> This pattern was not

shown in the biopsy of our case; however, characterizing the nature of deposits on electron microscopy can be challenging and the absence of typical cryoglobulin deposits cannot fully exclude a cryoglobulinemic glomerulonephritis.<sup>14</sup>

In our patient, the features that led us to a diagnosis of SLE were based on her history of preeclampsia, long-standing fatigue diagnosed as “Myalgic Encephalomyelitis,” autoimmune thyroid disease and evidence of hepatitis and endocarditis in the absence of infection, alongside long-standing positive ANA with low C4, thrombocytopenia and “full-house” positivity on kidney biopsy immunohistochemistry.<sup>4</sup> While many of the biochemical and pathological features can overlap with an infection-driven phenomenon, the absence of subepithelial humps on the kidney biopsy led us away from this and we were satisfied that occult infection had been thoroughly investigated for. The patient’s response to immunosuppressive therapy, done with close supervision, was reassuring.

This case highlights several learning points. We discuss the broad categories within which cryoglobulinemia can occur and the potential causes of an MPGN pattern of injury on kidney biopsy. We demonstrate how the clinical presentations of SLE are wide-ranging and often nonspecific, making the diagnosis challenging, and emphasize the importance of continually reviewing the original diagnosis in cases with clinical uncertainty. The EULAR/ACR criteria assist in making the diagnosis. Multisystem presentations can relate to a single unifying diagnosis or separate concomitant disease processes, and a multidisciplinary approach to management is beneficial to avoid delays to diagnosis.

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## CONFLICT OF INTEREST

The authors have no conflicts of interest.

## AUTHOR CONTRIBUTIONS

AN, QZ, and PB: were part of the clinical team responsible for the patient’s care during the reported presentation and conceived and planned the report; AC: gave the pathology opinion; AN, QZ, and AC: collated the investigation results and biopsy images; all authors contributed to manuscript preparation.

## ETHICAL APPROVAL

The patient gave written informed consent to publish the case.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable as no new data were generated for this report.

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