

Case Report

C3 Glomerulopathy in a Patient with Chronic Hepatitis B Virus Infection, an Unknown Causal Relationship?

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Abstract

GC3 is an entity whose clinical, pathogenetic, and evolutionary characteristics have been outlined in recent years. GC3 is a rare, heterogeneous clinicopathological entity secondary to dysregulation of complement ATP, which ultimately manifests as glomerular disease. This hyperactivation of complement ATP results in the deposition of C3 and its cleavage products in the glomeruli, leading to inflammation and progressive kidney injury. The estimated incidence of the disease is 1-3 cases per million per year, and it is most frequently diagnosed in childhood and adolescence, although it can also be observed in adults and the elderly. This entity results from abnormal regulation of complement ATP and is now classified under the heading of GC3. The clinical presentation is variable, and the diagnosis is based on the presence of intense, isolated, or clearly predominant deposits of C3 on immunofluorescence. Although MPGN was initially considered the characteristic histological pattern (leading to a reclassification of this entity) (**Figure 3**), the emergence of other histological patterns (necrotizing GN, mesangial GN, SFGS) with predominantly C3 deposits in immunofluorescence and altered AV has recently led to a modification of its definition.

Keywords: C3 glomerulopathy, Immunofluorescence, Entecavir, Furosemide, Nephrotic syndrome

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Case report

A 74-year-old patient with a history of SEVERE obstructive sleep apnea/hypopnea syndrome (OSAS)-hiatal hernia, erosive gastritis, and inactive carrier status of hepatitis B. He is currently undergoing EC follow-up by the Gastroenterology Department. He has high blood pressure and is being treated with losartan 50 mg/hydrochlorothiazide 12.5 mg, one tablet daily, and amlodipine 10 mg, one tablet at dinner. He has chronic low back pain treated with analgesics. He does not take NSAIDs regularly or continuously, nor does he have any known toxic habits (smoking, alcoholism, etc.). He does not report any significant family medical history.

A patient presented to the Emergency Department of our Hospital with a one-month history of general malaise, nausea, and JCTCS| Volume 8 |Issue 3|APR, 2026

nonspecific abdominal discomfort, predominantly in the epigastric region. He also reported coughing and whitish expectoration due to "chronic pharyngitis" that he has been experiencing for many years (no history of smoking), which had worsened in recent weeks. He also presented dyspnea and greenish sputum, although he denied any traces of blood or black sputum. He also reported having urine "the color of red wine," with no clots and no associated urinary discomfort. She visited her primary care physician, who advised her that it could be a viral infection. She underwent laboratory tests, which revealed leukocytosis of 19,600 and thrombocytosis of 419,000, with a marked elevation of CRP to 35.83 mg/dL (procalcitonin negative), and elevated HbA1c, in addition to isolated urinary glycosuria, without hematuria or proteinuria. She has come to the emergency room 9 days earlier with general malaise, neck pain, and back pain, reporting a respiratory infection several days earlier, with no associated fever. A chest X-ray revealed no abnormalities. He was administered 50 mg of intramuscular dextetopfen and prescribed tramadol, metamizole, and diazepam for home treatment. During his stay in the emergency room, he experienced paroxysmal nocturnal dyspnea. His baseline hypertension (220/100 mmHg) worsened, with tachypnea (31 breaths per minute) in the emergency critical care unit. Physical examination revealed intercostal indrawings (no subcostal indrawings). Cardiac auscultation revealed arrhythmic heart sounds, no murmurs, and lung auscultation revealed fine crackles in the lower legs and lung fields. Pulmonary auscultation revealed pitting edema up to the middle third of both legs. An ECG revealed an unknown rapid AF (records in the patient's medical records with sinus rhythm), which reverted to sinus rhythm with the administration of digoxin.

Blood and chemistry tests revealed acute renal failure (2.4 mg/dL, creatinine within normal range), decreased CRP compared to the previous test, normal leukocyte count, and persistent thrombocytosis, with elevated proBNP (6366, normal prior value). The rest of the blood parameters (sodium, potassium, calcium, phosphate, and venous blood gas) were unchanged. Urinalysis revealed persistent sediment with microhematuria (no dysmorphic red blood cells). The urine test strip showed protein (1000 mg/dl), with the albumin/creatinine ratio reported as incalculable and the protein/creatinine ratio at 5.1 mg/g. Chest X-ray revealed bilateral pulmonary infiltrates, predominantly on the right side. A pinched costophrenic sinus impression was seen on the lateral projection.

The patient's progress was poor, with worsening overall clinical status and desaturation up to 88% (98% on admission) despite oxygen therapy. The patient also had increased breath sounds on lung auscultation. Therefore, high-flow oxygen therapy was initiated due to GN. Nitroglycerin infusion was started, with little response (the dose had not been adequately adjusted), and several doses of furosemide were administered due to oliguria. The patient was admitted to the Cardiology department due to suspicion of decompensated congestive heart failure. Cardiac Doppler echocardiography revealed preserved biventricular systolic function, elevated filling pressures, mild mitral regurgitation (apparently functional), and ultimately probable mild-moderate pulmonary hypertension. Intravenous nitroglycerin perfusion, is optimized, and continuous furosemide infusion (250 mg/24 h) was started, with good control of arterial hypertension, but with no diuretic response, so we were referred for consultation.

Due to the poor diuretic response to furosemide infusion, it was decided to start thiazide (50 mg daily chlorthalidone) and aldosterone antagonists (spironolactone) were associated with the patient's combined therapy. The patient presented progressive worsening of renal function, with moderate hypoalbuminemia and hypoproteinemia, and increased cholesterol and triglyceride levels. Fluid and electrolyte balance and acid-base parameters were preserved and a persistent albumin-creatinine and protein-creatinine ratio in a range similar to that seen in the emergency room laboratory tests. Autoimmune tests detected IgG and IgA hypergammaglobulinemia (see laboratory results in the appendix) and antinuclear antibodies were positive (1/320, homogeneous nuclear pattern). C3 (9 mg/dl, normal range 80-100 mg/dl) and C4 (14 mg/dl, normal range 20-40) hypocomplementemia. The rest of the autoimmune tests (antineutrophil cytoplasmic antibodies, antibodies, serum and urine protein electrophoresis, ant glomerular basement membrane antibodies, rheumatoid factor and cryoglobulins, antiphospholipid antibodies) were negative. A diagnosis of rapidly progressive renal failure associated with nephritic syndrome/nephrotic syndrome is therefore established, taking into account as diagnostic possibilities glomerulonephritis associated with previous pharyngeal infection/glomerulonephritis associated with HBV infection and/or autoimmune disease (most likely lupus nephropathy).

The patient poor clinical evolution, with increased respiratory work, desaturation despite high-flow oxygen therapy and increased edema in the lower extremities to the point of anasarca and the establishment of anuria, with deterioration of renal function (cr 2.96 mg/dl), and it was decided to transfer to the intensive care unit, start noninvasive mechanical ventilation and start continuous renal replacement therapy.

Results

Upon admission to the Intensive Care Unit, a temporary non-tunneled catheter was placed in the right temporal femoral vein, and a dialysis machine was connected to initiate continuous renal replacement therapy. Non-invasive mechanical ventilation was maintained and, according to the main diagnoses of the kidney disease mentioned above, treatment was empirically initiated with intravenous boluses of 500 mg of methylprednisolone, 1 daily for 3 days and then oral prednisone at a dose of 1 mg/kg, subsequently progressively tapered. The patient began to present spontaneous diuresis, so it was decided to restart furosemide at high doses. Presenting a diuretic rhythm, which was increasing, being able to suspend continuous renal replacement therapy, stabilized blood pressure levels and improved respiratory failure, being able to discontinue invasive mechanical ventilation and switch to nasal prong oxygen therapy. From an analytical point of view, renal function improved, with creatinine at discharge from the Intensive Care Unit of 2.25 mg/dl.

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Therefore, the decision was made to discharge the patient from the Intensive Care Unit and transfer him to the inpatient ward. During his stay in the inpatient ward, and given his hemodynamic and respiratory stabilization, a kidney biopsy was performed, which was performed without complications. The laboratory results reported the HBV viral load at 317 IU/ml (normal range is below 200). The case was discussed with the gastroenterology department, who decided to initiate antiviral treatment (entecavir).

Renal biopsy (optical microscopy and immunofluorescence) reports Endocapillary proliferative (exudative) glomerulonephritis with intense C3 deposits. The histological presentation is compatible with postinfectious glomerulonephritis or C3 glomerulonephritis, although the negative CD4d count is more in favor of C3 glomerulonephritis (See anexes) Ultrastructural examination (electron microscopy) reveals glomerulonephritis with a mesangiocapillary (membrane-proliferating) pattern and unorganized deposits (See anexes).

Considering the immunofluorescence findings, the findings are consistent with C3 glomerulonephritis. After starting entecavir and gradually tapering off prednisone, the patient showed progressive clinical improvement, with improvement of the edematous state with bolus administration of diuretics (furoemide) and aldosterone antagonist diuretics (spironolactone), progressive improvement of renal function (1.45 mg/dl), improvement of proteinuria (RAC), sediment with only 21 red blood cells per field, which is why it was decided to discharge home and follow-up in the Nephrology EC. After one year of follow-up, renal function normalized (Cr 1.15 mg/dl), absence of proteinuria in the urine and completely unremarkable urinary sediment and normalization of complement and IgG and IgA levels. The patient is still under follow-up in our service.

Discussion

GPC3 is a rare clinicopathological kidney disease entity, distinguished by dominant C3 deposition in the glomeruli with minimal or no Ig [1]. It is further classified into C3GN and dense deposit disease (DDD) based on electron microscopy findings [2]. It has an incidence of between 1 and 3 cases per million inhabitants/year and is mainly diagnosed in childhood and adolescence, although it can also be seen in adults and the elderly.

C3G is thought to result from dysregulation in the alternative complement pathway, identified in 59% and 40% of patients with DDD and C3GN, respectively, and is usually caused by genetic abnormalities affecting complement components or regulatory proteins such as complement factor H (CFH), or by autoantibodies such as anti-CFH antibodies (anti-CFH Ab) or C3 nephritic factors (C3NEF). Since C3 glomerulopathy is caused by a dysregulation of the alternative complement pathway, it is thought that there are humoral factors involved that can cause this process. The acquired type is caused by unchecked complement activation, primarily by autoimmune processes. About 30% of individuals with C3G would have experienced a past respiratory or urinary tract infection [3].

Alternative complement pathway dysregulation can occur due to genetic mutations of factor H or the presence of autoantibodies. C3NeFs are present in 40-50% of patients with C3GN. Nephritic factors are persistently present and associated with complement activation, but their serum levels can be variable over the course of C3GN (68). High levels of C3NeFs are associated with active disease. It should be noted that autoantibodies against factor H are usually associated with homozygous deletions in the genes encoding factor H. Both C3GN and Ig-associated MPGN can exhibit antibodies directed against factor B and/or C3b, leading to the activation of alternative pathways, suggesting similar pathogenetic mechanisms (Figure 1).

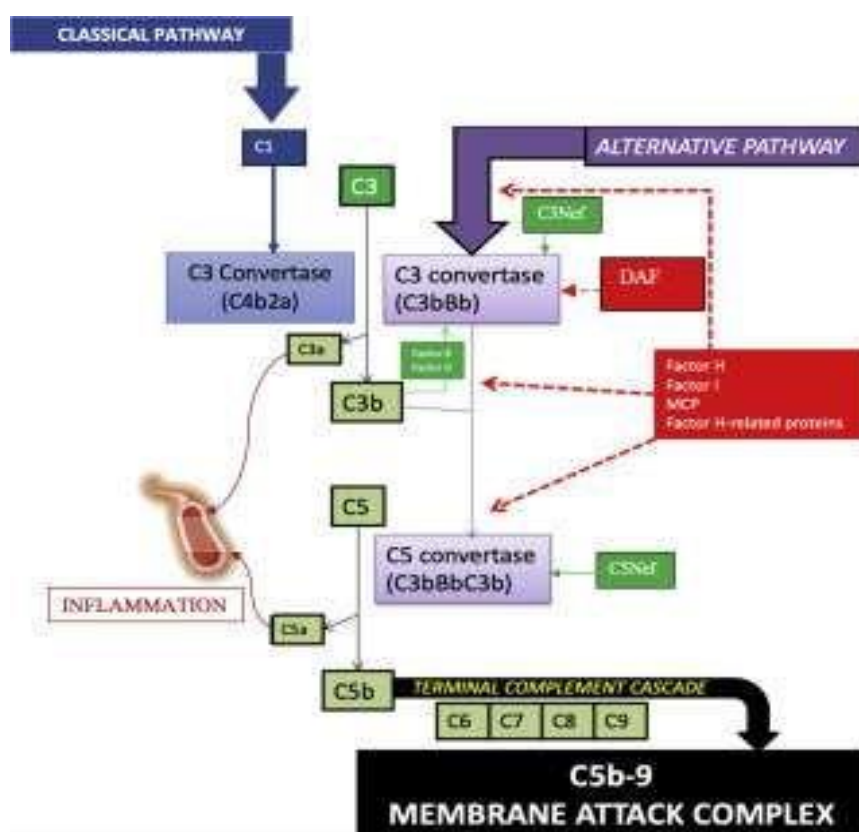


Figure 1: Alternative complement pathway dysregulation in C3 glomerulonephritis and Ig-associated membranoproliferative glomerulonephritis mediated by genetic mutations and autoantibodies.

It should be noted that both C3 GN and Ig-associated MPGN can be displayed directed against factor B and/or C3b, leading to the activation of alternative pathways, suggesting similar pathogenetic mechanisms and, in the case of our patient, antibodies directed against HBV could act as "autoantibodies" capable of inhibiting the regulatory action of factor H (stabilization of C3 convertase or inhibition of C3 factor activation) or of factor I (inhibition of factor B activation). which is evidenced by the absence of genetic alterations in the study of the alternative pathway of complement, the absence of C3Nef and the negativization of the viral load with antiviral treatment with entecavir and the concomitant use of steroid treatment, caused a progressive reduction of hematuria, proteinuria, renal failure and significant improvement of the clinical picture of nephritic and nephrotic syndrome [4, 5] (Figure 2).

Hereditary and Acquired Etiologies of C3 Glomerulopathy	
Hereditary and Acquired Etiologies for C3 Glomerulopathies	
Acquired Drivers and Frequency (%)	Hereditary Drivers
C3 nephritic factors (50-80)	<i>C3</i>
C4 nephritic factor (2.4)	<i>CD46</i>
C5 nephritic factor (50)	<i>CFB</i>
Factor H autoantibodies (1.0)	<i>CFH</i>
Factor B autoantibodies (2.5)	<i>CFHR1</i>
C3b autoantibodies (1.5)	<i>CFHR5</i>
Monoclonal immunoglobulins (rare)	<i>CFI</i>

Figure 2: HBV-associated autoantibody-mediated alternative complement pathway activation with clinical improvement following antiviral and steroid therapy.

The clinical presentation is variable, almost identical to that seen in DDD. Patients with C3GN tend to be older and have less renal impairment at presentation compared to DDD. C3NeF is found in ~ 45% of patients with C3GN. However, hematuria, severe proteinuria, hypertension, and low complement C3 levels are common in both diseases. Acquired partial lipodystrophy and Bruch's membrane involvement are specific to DDD and are not seen in C3GN. Differential diagnosis can be challenging in older patients with C3GN who may have a monoclonal gammopathy, requiring additional diagnostic testing such as serum protein electrophoresis, serum and urine immunofixation, and investigation of serum free light chain levels to assess the presence of an underlying pathological plasma cell or B cell clone (59, 60). In addition, postinfectious glomerulonephritis can mimic GN3, but hypocomplementemia and proteinuria tend to normalize and C4d staining is positive in postinfectious glomerulonephritis. A proposed diagnostic workup for C3G is outlined in Figure 3.

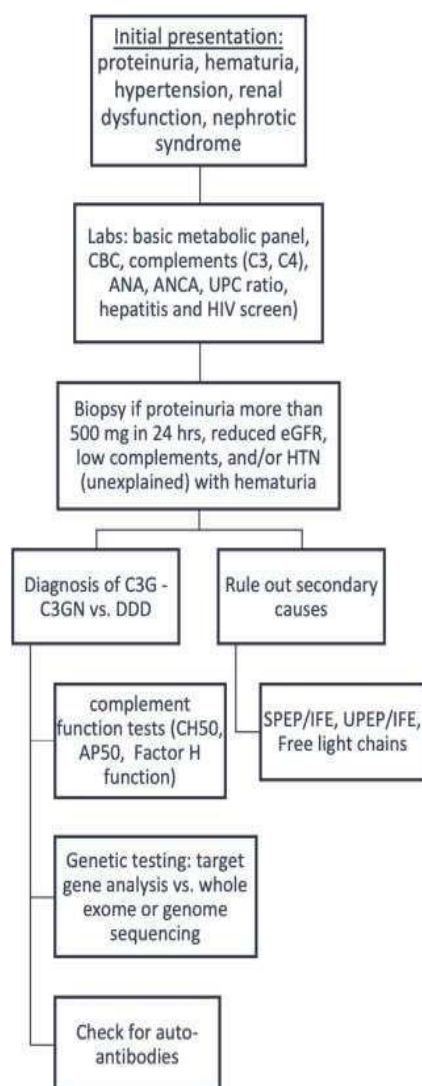


Figure 3: Proposed diagnostic workup and differential diagnosis of C3 glomerulopathy distinguishing C3GN, dense deposit disease, and mimicking conditions.

The diagnosis is based on the presence of intense, isolated, or clearly predominant C3 deposits on immunofluorescence. It is considered secondary to dysregulation of the alternate complement pathway (ACP), which manifests with the deposition of C3 and its cleavage products in the glomeruli. Abnormal complement activation is due to mutations in the ACP regulatory proteins or to the presence of autoantibodies against them (mainly nephritic C3 or factor H (NAD) [6].

GC3 are rare diseases, and there are no prospective, randomized studies that guide our therapeutic decision. The goal of GC3 treatment should be aimed at eliminating antibodies directed at complement regulatory proteins (C3Nef or anti-FH), restoring deficient or dysfunctional regulatory proteins, or eliminating mutant or hybrid proteins. As general measures, patients with GC3 who have hypertension and/or proteinuria greater than 500 to 1000 mg/day should preferably receive a renin-angiotensin-aldosterone system blocker, although the benefits of renin-angiotensin system inhibition have not been demonstrated in studies specific to GC3. Furthermore, dyslipidemia should be evaluated and treated in these patients to reduce the risk of cardiovascular disease. For patients with moderate to severe disease (proteinuria ≥ 1.5 g/day and/or abnormal renal function [but not rapidly progressive disease] considered to be due to active DDD or C3GN), initial therapy with a complement inhibitor (either iptacopan [an oral complement factor B inhibitor] or pegcetacoplan [a subcutaneous complement C3 inhibitor]) plus supportive measures is suggested instead of supportive measures alone or in combination with other immunosuppressive agents. If iptacopan or pegcetacoplan is unavailable, mycophenolate mofetil (MMF) plus oral glucocorticoids is a reasonable alternative. Patients with moderately severe disease: In patients with more severe proteinuria, nephrotic syndrome, and/or impaired renal function, treatment should be based on the underlying etiology, if known [7, 8].

In the event that the cause is unknown and cannot be determined, plasma infusion is suggested, since this therapy could be

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effective if the patient has a genetic mutation that leads to deficiency of a serum factor, isolated or combined with immunosuppressive treatment (corticosteroids in combination with cyclophosphamide or mycophenolate mofetil) [9]. Given the growing evidence of infectious processes in which antibodies produced as part of the humoral response may act against regulatory factors of the alternative complement pathway, it is necessary to consider the diagnosis of C3 glomerulonephritis when glomerulonephritis associated with infection is suspected. If this entity is diagnosed in the renal biopsy data, the combination of antimicrobial treatment with immunosuppressive therapy could be considered as a therapeutic regimen [10].

Conclusion

In conclusion, HBV infection can cause sustained CAP activation, leading to C3G. For patients with HBV infection, if there is a continuous decrease in complement C3 level and a progressive increase in serum creatinine, and in the presence of exclusively C3 deposits, it is crucial to be alert for possible C3G and the use of immunosuppressive therapy along with antiviral treatment should be considered to prevent continued CAP activation, as in the case of our patient, in whom the combination of glucocorticoids and antiviral treatment with entecavir produced significant clinical improvement and also improvement of proteinuria, hematuria and acute renal failure until complete resolution.

NGC is a disease process rather than a specific disease, caused by a variety of causative agents. Identifying the specific etiology early in the process is important from a therapeutic perspective for making clinical decisions regarding treatment modality and, therefore, achieving a better outcome. Although biopsy diagnosis with basic light microscopic categorization of NGC is essential, complementary evidence by immunofluorescence and MS is invaluable for arriving at a specific diagnosis. Knowledge of the genetic basis of the disease and its practical application to the diagnostic and therapeutic process are important today in the evaluation of patients with NGC, although the required facilities are not well established in most settings.

But on the other hand, it is important to highlight and even establish the possibility that certain infectious processes of any kind (viruses, bacteria, parasites, etc.), in our case subclinical HBV infection, may be involved as triggering agents of the pathophysiological processes that lead to the development of a C3 glomerulopathy by inhibiting the regulatory factors or stimulating the promoting factors of the alternative complement pathway by the antibodies produced during the immune response in the ongoing infectious process.

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