# C3 GLOMERULONEPHRITIS: UNIQUE PRESENTATION AND ROLE OF GENETIC TESTING - NEW WINE IN A NEW BOTTLE

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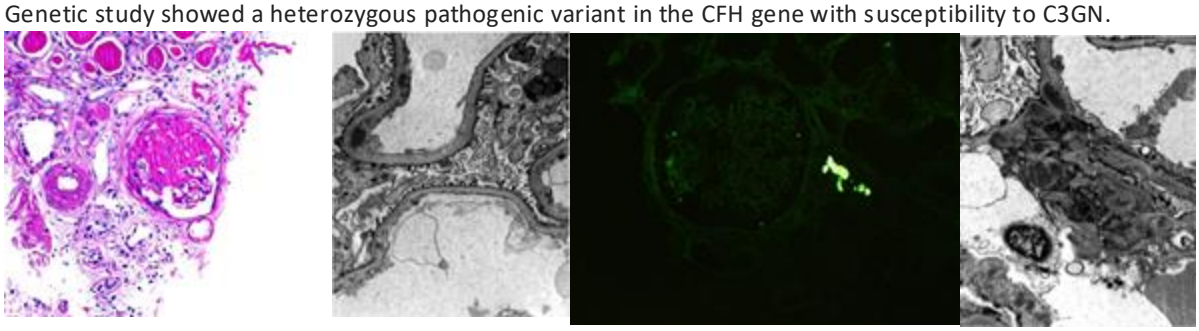
**Introduction:** C3 glomerulonephritis (C3GN) is a subtype of C3 glomerulopathy, a relatively rare kidney disease resulting from the dysregulation of the alternative pathway of the complement system, either due to acquired factors (autoantibodies such as C3 nephritic factors) or inherited mutations in complement regulatory proteins. We wish to highlight the unique presentation and the utility of genetic testing in a patient of ours with this condition.

**History:** 43-year-old Indian woman hospitalized with acute kidney injury. Twenty years prior to this presentation, she was presumed to have IgA nephropathy when she had an episode of gross hematuria. At the time, she did not undergo a kidney biopsy. She was treated with fish oil supplementation, her hematuria resolved, and she was reassured that her kidney function was normal. She was lost to follow-up locally. She relocated to the United States a year prior to the hospitalization, when she was noted to have normal kidney function as a part of her immigration paperwork. She developed an episode of sore throat 4 months prior to admission for which she was treated with antibiotics. Subsequently, she developed progressive lower extremity edema, fatigue, blurry vision, and worsening hypertension during the evaluation of which she was found to have acute kidney injury with a serum creatinine of 5.8 mg/dL and 7g/d proteinuria. She denied skin rash, tick bites, joint pains and denied NSAID use**.**

**Findings:** Her ultrasound was consistent with medical renal disease. Paraproteinemia screen was negative. IgA levels were normal but C3 levels were low at 69. Renal biopsy showed advanced C3 glomerulonephritis (C3GN) with global and segmental glomerulosclerosis. She was noted to have severe interstitial fibrosis and tubular atrophy. There was no mesangial matrix expansion, hypercellularity or crescent formation. Immunofluorescence staining was 3+ positive for C3 only in the glomerulus and all other stains were negative. Genetic study showed a heterozygous pathogenic variant in the CFH gene with susceptibility to C3GN.



**Course**: She was started on peritoneal dialysis and received a kidney transplant recently. She is doing excellent following kidney transplant. With knowledge of results of genetic testing, she has been advised on early allograft biopsy, with plan to consider Iptacopan (which binds factor B to regulate C3 cleavage) and PLEX in case of disease recurrence.

**Conclusions**: This patient's presentation has several unique features. She likely had an underlying GN years ago but was never biopsied. Subsequently, it appears to have been triggered by an upper respiratory infection prior to her hospitalization leading to a severe kidney injury resulting in ESRD. She also had a positive heterozygous mutation for CFH which is rare in Indian patients (Kumar, Outcome of C3 glomerulopathy patients: largest single-center experience from South Asia, 2020). This case illustrates the importance of obtaining definitive diagnosis with a biopsy, particularly in young patients as well as the importance of genetic testing which may help with planning to prevent recurrence in an allograft.

**Discussion**: C3 glomerulopathy (C3G) is a rare set of kidney diseases with 2 patterns: C3GN and dense deposit disease. Pathogenesis of both is due to complement dysregulation in the alternative pathway. Acquired or genetic alterations of the regulatory proteins of the complement pathway result in C3G. Other disease entities such as infection-related glomerulonephritis and masked monoclonal deposits can present similarly. Both the C3GN and dense deposit disease variants of C3G are progressive and recur in transplanted kidneys. While there is no definitive treatment now, these patients may benefit from immunosuppression or enrollment in clinical trials. There is limited data on ESRD modalities in C3GN; our patient remained relatively healthy with a good quality of life on peritoneal dialysis despite her underlying kidney disease.

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