International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Lupus Nephritis with Autoantibodies to Complement Alternative Pathway Proteins and C3 Gene Mutation

Dr. Boddepalli Madhuri

Sree Balaji Medical College

Abstract: ***Background**: Lupus is a systemic inflammatory disorder that affects several organs and causes tissue damage mostly via complement activation; one of the most serious consequences of lupus is glomerulonephritis. Because of this activation, hypocomplementemia is seen in active lupus patients during illness flares; however, levels of C3 and C4 are restored in between episodes. **Case presentation**: Here we depict a patient who had two episodes of lupus nephritis in five years, went into full reduction each time thanks to therapy, but whose C3 levels remained consistently low. The patient was found to have a mutation in the C3 gene, as indicated by the genetic analysis. Autoantibodies that complement proteins in the alternative route (Factor I, Factor B, C3, and Properdin) were discovered in serial sera samples. The results of the functional tests demonstrated that these autoantibodies activate the alternate route. **Conclusion**: Lupus nephritis and autoantibodies against supplement elective course proteins (Variable I, Component B, C3, and Properdin) had never been seen before until this first instance of a heterozygous C3 mutation was published. It is possible that the tissue damage is limited to the kidneys because these autoantibodies activate this route. **Electronic supplementary material**: Users with the proper authorization may access the additional materials included in the online version of this article (doi: 10.1186/s12882 - 015 - 0032 - 6).*

Keywords: Autoantibodies, Lupus nephritis, Complement C3, and the alternative complement pathway

1. Background

During the lupus flares that patients experience, C3 and C4 levels typically fall as a result of immune complexes (ICs) activating the complement system [1]. At remission times, nevertheless, complement levels return to normal. Deposition of ICs causes tissue damage when the complement system is activated. Then again, parts of the traditional pathway (CP) assume a defensive part by assisting with clearing ICs and apoptotic bodies. An absence of these parts expands the risk of systemic lupus erythematosus (SLE) [2, 3]. This association is explained by different mechanisms, such as the removal of ICs from circulation, reduced lymphocyte activation thresholds, and loss of self - tolerance [4, 5].

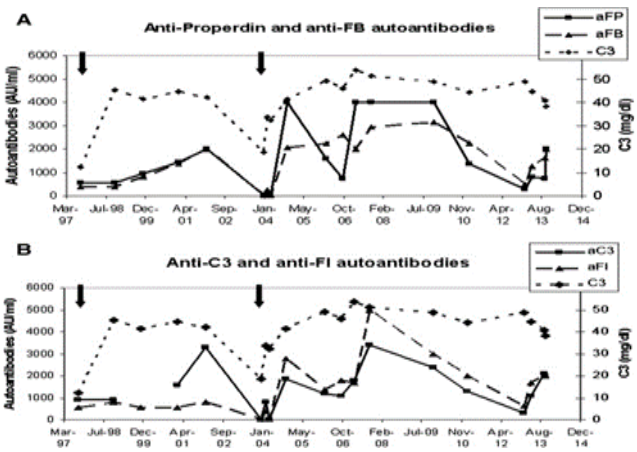
2. Case Presentation

A lady came to the hospital in 1997 at the age of 20 was suffering from nephrotic syndrome and renal insufficiency. She had signs of elevated blood pressure and swelling in her lower extremities, but no signs of inflammation in her joints or skin. Results from the laboratory tests revealed hematuria, proteinuria of 4.7 g/24 h, serum egg whites of 2.2 g/dl, and serum creatinine of 1.9 mg/dl. Positive outcomes for against atomic and hostile to DNA autoantibodies were seen, alongside diminished degrees of C3 and C4 (12.2 and 5.9 mg/dl, separately). There were no positive results for other autoantibodies, such as anti - GBM and C3NeF. The results of the renal biopsy revealed hyaline thrombi, endocapillary hypercellularity with luminal blockage, and widespread and extensive glomerular involvement. Acute inflammatory infiltration and moderate mesangial proliferation were also seen. Wire loop pictures revealed the presence of subendothelial deposits. The mesangium and capillary walls showed sporadic C3, C1q, IgM, IgG, and IgA deposits on direct immunofluorescence. Lupus nephritis class IV - G, which is dynamic, diffuse, worldwide, and proliferative, was the patient's diagnosis (Figure 1A).

During her one - year treatment, her doctors gradually reduced the amount of her intravenous steroids and oral prednisone and administered pulses of cyclophosphamide, with dosage changes in between. After a year of steady improvement in renal function, the patient achieved full remission and was no longer treated.

She maintained five years of clinical and analytical remission, with the exception of consistently low C3 levels. Once again, she ended up in the hospital in 2003 because to renal

See Figure 2 for a 16 - year follow - up of C3 levels and autoantibody titers. A shows C3 levels in conjunction with against FB and hostile to properdin autoantibodies, while B shows hostile to FI and hostile to C3. renal insufficiency - related hospitalizations and kidney biopsies are shown by black arrows. The healthy range for C3 is 75 - 150 mg/dl.



nephrotic disorder and inadequacy, with 5.9 g of proteinuria each 24 hours, serum creatinine 2.2 mg/dl, C3 10.3 mg/dl, and C4 1.8 mg/dl. Consistent with the first kidney biopsy, the results of the most recent one revealed evidence of chronic activity.

Following a 5 - month course of therapy that was similar to the original one, she was able to regain renal function, with no protein in her urine and all of her analytical parameters normalized except for her C3 levels (Figure 1B shows her progression over the last 7 years). Therefore, C3 levels were assessed in her surviving relatives; her mother's levels were also found to be low.

In 2013, the patient was researched with their informed permission in an effort to identify any changes in the complement alternative route (AP). The goal was to find mutations or autoantibodies that caused the blood C3 levels to be lower; the techniques utilized for this search are detailed in Additional file 1: techniques. A mutation in exon 2 of the C3 gene (c.131_146del; p. Leu44Argfs*19) was found to be present in both the patient and her mother, according to the genetic investigation. It is believed that this mutation results in a shortened, inactive protein and causes it to terminate too soon.

Along with the mutation, the patient's blood tested positive for autoantibodies against C3, complement Factor B (FB), Properdin, and Factor I (FI), while her mother did not. Over a sixteen - year period, autoantibodies were evaluated retrospectively using serial sera samples (Figure 2).

In addition to elevated degrees of circling IgG buildings with FB and Properdin, virtually all patient samples tested positive for autoantibodies to FI, C3, and FB (Additional file 2).

Due to lowered IgG levels (440 mg/dl) caused by excessive proteinuria and the immunosuppressive medication she got, the autoantibodies became undetectable during her second hospitalization and stayed that way for at least four months. Then autoantibodies spiked to high levels again, but this time modest doses of hydroxychloroquine prevented a relapse.

Although the patient had her mother's mutation, her C3 levels were consistently lower. To investigate whether AP - specific autoantibodies were to blame, functional investigations were conducted.

Both in fluid phase and on surfaces, assays were developed to assess these antibodies' ability to activate AP. When patient - derived IgGs were preincubated with NHS in AP - 50 hemolytic experiments, lysis was significantly decreased. Be that as it mayWhen additional NHS containing hare erythrocytes was added, lysis was restored. Following bring forth of NHS with patient's IgG, nephelometry estimations of C3 decline showed that AP enactment in the liquid stage was related with this rebuilding. The nephelometric estimations of C3 and C4 revealed that autoantibodies decreased C3 by approximately 10%, NHS kept up with ordinary degrees of C4. There was no change in the C3 and C4 measurements when IgG was isolated from normal human serum that had been pooled (data not shown). Western blotting revealed that the patient's IgG caused proteolytic cleavage of NHS C3, which led to a decrease in NHS C3 in the fluid phase (Additional file 3).

The results of these tests showed that this pathway is activated only in the fluid phase by autoantibodies targeting AP proteins. This information, together with the C3 mutation, might explain why this patient has low C3 levels and little renal impairment.

3. Conclusion

The complement system has a significant impact on pathogen identification and removal, but it also helps with clearing cellular debris and immunological complexes, learning to tolerate oneself, and regulating the immune system's adaptive response [4, 6] In autoimmune diseases, complement activation causes tissue damage and inflammation.; yet, it also plays a preventive function, since SLE is linked with total deficits of CP components [2, 3]. Although C3 deficits are very rare, those who do have chronic infections and, in rare instances, diseases associated with immune complexes [3, 6, 7]. Despite SLE being an immunological complexes disease, the only three Japanese patients who have been reported to have homozygous C3 deficiency have been studied [8]. Similarly, partial complement protein deficiencies have not been linked to SLE [5, 6].

Hypocomplementemia and diminished C3 levels attributable to the transformation in this understanding might advance the beginning of autoimmunity. This is on the grounds that C3 assumes a part in the foundation of self - resistance what's more to causing impaired immune complex clearance. In addition, autoantibodies against AP proteins cause a further drop in serum C3, which increases the buildup of supplement actuation items in renal glomeruli, causes inflammation locally, and damages tissues [9].

Statement of these flowing edifices and supplement initiation by means of the traditional route induce organ damage in illnesses mediated by immune complexes. It is possible that this patient's AP - recognizing autoantibodies build up as ICs in the glomerulus and enact AP locally, which could deteriorate renal harm and assume a part in the improvement of the disease.

In addition, the patient's serum supplement profile is low in C3, and there are no sores in different organs other than the kidneys. This may be because of supplement actuation in the liquid stage, which is caused by the persistent presence of autoantibodies against AP parts. Diseases like Dense Deposit also lead to restricted renal damage due to uncontrolled systemic complement activation. In addition, a lupus nephritis model (MRL - lpr mice) shows increased disease development when factor H is not present, leading to unregulated activation of AP [10]. This finding lends credence to the idea that activation of supplement AP plays an unsafe part in sicknesses brought about by safe edifices [2, 10].

We are unaware of any previous cases of lupus nephritis brought about by a heterozygous change in the C3 gene. The patient presented with autoantibodies against proteins in the complement alternative pathway, which trigger complement

activation; this may explain why the kidneys were the only organs affected.

Abbreviations

SLE	Systemic Lupus Erythematousus
ICs	Immunocomplexes
CP	Complement Classical Pathway
AP	Complement Alternate Pathway
FB	Factor B
FI	Factor 1

References

[1] Birmingham DJ, Irshaid F, Nagaraja HN, Zou X, Tsao BP, Wu H, et al. The complex nature of serum C3 and C4 as biomarkers of lupus renal flare. Lupus.2010; 19 (11): 1272–80. doi: 10.1177/0961203310371154. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[2] Bao L, Quigg RJ. Complement in lupus nephritis: the good, the bad, and the unknown. Semin Nephrol.2007; 27 (1): 69–80. doi: 10.1016/j. semnephrol.2006.09.009. [PubMed] [CrossRef] [Google Scholar]

[3] Chen M, Daha MR, Kallenberg CG. The complement system in systemic autoimmune disease. J Autoimmun.2010; 34 (3): 276–86. doi: 10.1016/j. jaut.2009.11.014. [PubMed] [CrossRef] [Google Scholar]

[4] Ballanti E, Perricone C, Greco E, Ballanti M, Di Muzio G, Chimenti MS, et al. Complement and autoimmunity. Immunol Res.2013; 56 (2–3): 477–91. doi: 10.1007/s12026 - 013 - 8422 - y. [PubMed] [CrossRef] [Google Scholar]

[5] Truedsson L, Bengtsson AA, Sturfelt G. Complement deficiencies and systemic lupus erythematosus. Autoimmunity.2007; 40 (8): 560–6. doi: 10.1080/08916930701510673. [PubMed] [CrossRef] [Google Scholar]

[6] Kościelska - Kasprzak K, Bartoszek D, Myszka M, Zabińska M, Klinger M. The complement cascade and renal disease. Arch Immunol Ther Exp.2014; 62 (1): 47–57. doi: 10.1007/s00005 - 013 - 0254 - x. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

[7] Rodriguez - Marco A, Bradbury M, Riley P, Arkwright P. Autoimmunity and recurrent infections in partial complement C3 immunodeficiency. Rheumatology.2010; 49 (5): 1017–9. doi: 10.1093/rheumatology/kep444. [PubMed] [CrossRef] [Google Scholar]

[8] Tsukamoto H, Horiuchi T, Kokuba H, Nagae S, Nishizaka H, Sawabe T, et al. Molecular analysis of a novel hereditary C3 deficiency with systemic lupus erythematosus. Biochem Biophys Res Commun.2005; 330 (1): 298–304. doi: 10.1016/j. bbrc.2005.02.159. [PubMed] [CrossRef] [Google Scholar]

[9] Sato N, Ohsawa I, Nagamachi S, Ishii M, Kusaba G, Inoshita H, et al. Significance of glomerular activation of the alternative pathway and lectin pathway in lupus nephritis. Lupus.2011; 20 (13): 1378–86. doi: 10.1177/0961203311415561. [PubMed] [CrossRef] [Google Scholar]

[10] Bao L, Haas M, Quigg RJ. Complement factor H deficiency accelerates development of lupus nephritis. J Am Soc Nephrol.2011; 22 (2): 285–95. doi: 10.1681/ASN.2010060647. [PMC free article] [PubMed] [CrossRef] [Google Scholar]