Acquired disorders of the complement system

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INTRODUCTION

- Deficiencies in complement proteins may be inherited or acquired (secondary).
- Acquired deficiencies in complement proteins are **more common** than inherited complement disorders.
- **Reductions** in complement secondary to acquired disease processes are usually only **partial** and affect several complement components at once. (50 percent of patients with (SLE) will have reductions in C4 and C3, reflecting classical pathway activation
- These **acquired complement deficiencies** are most commonly encountered in diseases featuring **autoantibodies**.

CHALLENGES IN INTERPRETATION

- One problem clinicians may encounter when managing disorders featuring acquired deficiencies of complement components is that the **predisease levels** of proteins, such as C3, are rarely known.
- For example, the "normal" laboratory range of C3 in the population is from 80 to 160 mg/dL.
- A 17-year-old female with new-onset SLE may present with a C3 value of 92 mg/dL. Although this is considered in the "normal range," if her post-treatment C3 value rises to 125 mg/dL in six weeks,
- Measuring C4, which commonly parallels changes in C3 levels, is more complicated because of C4 copy number.

MECHANISMS OF ACQUIRED COMPLEMENT DISORDERS

- Accelerated consumption by immune complexes (common)
- Reduced hepatic synthesis (uncommon)
- Loss of complement components in the urine (rare)
- Somatic mutation in a complement gene (rare)

INCREASED CONSUMPTION BY IMMUNE COMPLEXES

- The most common pattern of complement protein deficiencies in disorders involving increased consumption by immune complexes is a low C4, a low C3, and CH50.
- In a large Japanese series of patients with low C4, C3, and CH50, SLE accounted for approximately two-thirds of the cases, while other **vasculitic** syndromes accounted for approximately **20 percent**.
- By comparison, activation by the lectin pathway is insufficient to substantially decrease C3 and C4 in blood.
- Alternative pathway activation usually resulting in the pattern of normal C4 and a low C3, include glomerulonephritis, partial lipodystrophy, acute rheumatic fever.

SLE

- Low C4 and C3 (C2 would also be reduced but is usually not measured) occur in about 50 percent of patients with SLE, reflecting activation of the classical complement pathway by immune complexes.
- Accelerated consumption outstrips synthesis and is the cause of hypocomplementemia in about 90 percent of such cases, while the remaining 10 percent also show signs of reduced hepatic synthesis. The mechanism for the latter is unknown.

- The usual pattern of complement activation in SLE involves the classical pathway, leading to low C3 and C4, while **factor B** of the alternative pathway is normal.
- However, a small percentage of patients (3 to 5 percent) demonstrate predominant alternative pathway activation, as evidenced by normal C4 but **low C3 and factor B**.
- In this situation, the **autoantibodies** are often subclasses that do not activate the classical pathway directly but coat the surface of the antigen, providing a surface for alternative pathway proteins to be protected from regulators.

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- Immune complex deposition has been documented in the pathogenesis of tissue damage in most organs afflicted in SLE, particularly the skin, kidneys, joints, and serosal surfaces.
- Low complement values tend to correlate with more severe SLE, especially with renal disease, and with antibodies to double-stranded DNA.
- A return to normal levels with treatment is a good prognostic sign.
- Antiphospholipid syndrome

  Hypocomplementemia can be observed in patients with (APS), analogous to what is seen in SLE.

CRYOGLOBULINEMIA

- Cryoglobulins are serum proteins that precipitate at subphysiologic temperatures.
- Mixed cryoglobulins commonly consist of immune complexes that contain immunoglobulins, antigen, rheumatoid factor, and complement components (particularly fragments of C3 and C4).
- Cryoglobulinemia may be either essential or secondary (in association with another disease).
- Chronic hepatitis B and C account for most all of the formerly idiopathic cases of mixed cryoglobulinemia.
- Monoclonal paraproteins that precipitate in the cold may also **activate complement** .
- Although rare, an association of mixed cryoglobulinemia with certain malignancies has been described.

- The usual complement profile in the setting of essential or secondary cryoglobulinemia is that of classical pathway activation.
- The complement profile shows decreased levels of C4 and C2 with normal or slightly lowered C3. C3 levels are usually only modestly altered because it is **harder to form C3 convertases on** a soluble or precipitated immune complex than on a cell membrane.
- In rheumatic disorders, the presence of cryoglobulins is usually associated with more severe disease. As an example, in SLE, there is a correlation of mixed cryoglobulins with renal involvement, vasculitic manifestations, and hypocomplementemia.

VASCULITIC SYNDROMES

- **Systemic vasculitides** are characterized by **inflammation of *the arterial and/or venous walls*** *leading to* *stenosis or thrombosis*.
- *Many vasculitic* syndromes are caused by immune complexes.
- Classical pathway activation by *immune complexes* initiates inflammatory processes and tissue destruction, primarily affecting blood vessels.
- Complement activation is usually not as marked as in SLE, although up to 50 percent of patients with polyarteritis may have decreased serum complement levels.
- As in SLE , complement values can be helpful in assessing the clinical course, especially the response to therapy.

Hypocomplementemic urticarial vasculitis

- In hypocomplementemic urticarial vasculitis, classical pathway activation by immune complexes initiates inflammatory processes and tissue destruction, primarily affecting blood vessels.
- Complement activation is usually not as marked as in SLE. As in SLE, complement values can be helpful in assessing the clinical course, especially the response to therapy.

ANCA -ASSOCIATED VASCULITIS

- In anti-neutrophil cytoplasmic antibody-associated vasculitis (ANCA-AAV), plasma levels of C3a, C5a, soluble C5b-9 and Bb can be elevated in active stages of disease compared with remission .
- In addition, lower serum C3 levels at diagnosis were associated with poorer patient and renal outcomes in one study .
- Note that **avacopan**, an orally administered antagonist to C5a, has been approved to treat ANCA-AAV.

RENAL DISEASES

- **Many nephritides** result from an inflammatory reaction within the kidney glomerulus that features leukocyte infiltration and cellular proliferation.
- Antibodies in the kidney may result **from local immune complex** formation or originate in the **circulation as immune complexes** that then lodge in the glomerulus. In either instance, the result can be **activation of the complement system**, with recruitment of inflammatory cells and subsequent **tissue damage** .
- The complement system is involved in multiple renal diseases, including acute PSGN, IgA nephropathy, membranous nephropathy, **hemolytic uremic syndrome**, types I and II MPGN, SLE nephritis, tubulointerstitial nephritis, and Goodpasture's disease.

C3 NEPHRITIC FACTOR

- Secondary C3 deficiency may arise when an autoantibody stabilizes the **alternative pathway C3 convertase,** increasing the half-life of the convertase and causing **excessive C3 activation**.
- The autoantibody against the alternative pathway convertase is called C3 nephritic factor. The typical **complement profile** is a **normal C4 with** a low C3, factor B, and alternative pathway AH50, indicating alternative pathway activation .
- Patients with C3 nephritic factor typically present in **childhood with MPGN** that may be accompanied by partial lipodystrophy as well as frequent infections with encapsulated bacteria.
- Nephritic factor levels do not correlate predictably with disease activity, and progressive renal damage can occur in patients who are persistently normocomplementemic.

DENSE DEPOSIT DISEASE

- Dense deposit disease (DDD) is a rare but devastating glomerular illness that **primarily** affects children.
- Dysregulation of the alternative pathway of complement has been associated with pathology .
- Most patients with DDD present with hypocomplementemia that persists throughout the course of disease. C3 and factor B levels are low, while **C4 is normal**.
- More than 80 percent of patients demonstrate a C3 nephritic factor. Genetic analyses have identified **mutations** in complement regulatory proteins (factors H and I) in these patients.

C4 NEPHRITIC FACTOR

- C4 nephritic factor is an autoantibody that reacts with an epitope expressed on C4 within the classical pathway C3 convertase (C4b2a).
- It leads to deficiency of C3 that is consumed by the stabilized classical pathway C3 convertase. the patient may present with recurrent bacterial infections secondary to the low C3 .
- The C4 nephritic factor also has been found in a few patients with PSGN and SLE, although its role in pathogenesis has not been defined.

AUTOIMMUNE HEMOLYTIC ANEMIA

- In cold agglutinin disease, (IgM) autoantibodies react with RBC antigens at reduced body temperatures, such as in the extremities.
- The antibodies activate the classical pathway, leading to the deposition of large quantities of C4, C3, and C5b-9. The red blood cell may be either phagocytosed or lysed.
- Cold agglutinins are associated with lymphoid malignancy or arise transiently following viral and mycoplasma infections.
- In approximately 20 percent of (IgG-warm antibody-mediated) **hemolytic anemias**, complement fixation also occurs and tends to correlate with more severe disease.

IgG4–positive multiorgan lymphoproliferative syndrome

- This syndrome features (IgG_4) that reacts with antigens on a variety of tissues, including the pancreas (autoimmune pancreatitis) and salivary glands in Mikulicz's disease .

  Other idiopathic inflammatory conditions, including sclerosing cholangitis, autoimmune hypophysitis, retroperitoneal and mediastinal fibrosis, interstitial nephritis.

- A hallmark pathologically is: IgG_4-positive plasma cell infiltration. The antibodies are not directly activating like those of IgG subclasses 1 and 3 but rather provide an altered surface on which the alternative pathway can be engaged.

NEUROMYELITIS OPTICA SPECTRUM DISORDERS

- NMOSD represent autoimmune inflammatory diseases of the central nervous system.
- In many cases, antibodies against the water channel protein, AQP4, lead to antibody-associated complement activation with concomitant pathology .
- Eculizumab has been approved for treatment of AQP4-positive NMOSD .

Myasthenia gravis

- In myasthenia gravis (MG), many patients exhibit autoantibodies against the acetylcholine receptor (AChR), which drive complement activation and lead to disease pathology .
- Eculizumab has also been approved for treatment of adult patients with generalized MG who are AChR positive.

VIRAL INFECTIONS

- Hepatitis B and C infections are associated with immune complex formation secondary to the release of antigen from the infected liver.
- These immune complexes often manifest as cryoglobulins. Also, parvovirus and flavivirus infections featuring large antigenic loads, can develop a transient hypocomplementemia as the antibodies combine with viral antigen ,
- These forms of hepatitis represent an example of a chronic serum sickness-like reaction (antigen binding by an immune host making antibody, leading to complement activation.

Acquired C1 inhibitor deficiency

- A deficiency of C1 inhibitor (C1-INH) causes the autosomal dominant disorder hereditary angioedema (HAE).
- C1-INH deficiency also can be acquired. in patients with B cell lymphoproliferative disorders who present with new-onset **swelling of the skin, abdominal viscera, and/or larynx.**
- Most patients demonstrate an autoantibody to the C1-INH that blocks its function or causes its premature removal. Others feature a monoclonal autoantibody on the B cell surface that activates C1 and consumes the C1-INH.

- Acquired C1-INH deficiency should be considered in patients with angioedema in which complement studies show low C4, low C1q, low or normal C1-INH antigenic levels, and reduced C1-INH function.
- **Serum protein electrophoresis** should be considered in acquired C1-INH deficiency as basic testing for **lymphoproliferative disease**.
- C1q levels are normal in the hereditary form, and this test is important in distinguishing the two disorders.
- Otherwise, complement profiles are similar in hereditary and acquired C1-INH deficiency.

REDUCED HEPATIC SYNTHESIS

- The liver is the synthetic site of most complement components and inhibitors, and reduced hepatic synthesis may lead to hypocomplementemia in various types of advanced liver disease .
- As an example, low C3 and C4 levels may be seen in severe alcoholic liver disease.
- C3 and C4 are easily measured, CH50 and AH50 would also likely be impaired.
- However, because complement abnormalities are only detectable with **severe liver disease**, the coagulation system provides a more clinically useful measurement of hepatic synthetic function.

LOSS OF COMPLEMENT COMPONENTS IN THE URINE

- In severe forms of nephrotic syndrome, several complement components can be lost in the urine, although factor D is the only component that can be lost in substantial amounts.
- Factor D has a molecular weight of **25,000 daltons** and is the smallest component of the alternative pathway.
- Its loss would be detected as a decrease in the alternative pathway **AH50 titer**. No clinical consequences have been reported in association with this laboratory observation.