Post streptococcal glomerulonephritis (PSGN)

Introduction

Background

The most common form of acute glomerulonephritis is a diffuse proliferative glomerulonephritis that follows infections caused by group A beta-haemolytic streptococci. A classic case follows a streptococcal infection by 7-12 days. This is the time needed for the development of antibodies. Our case study focuses on this disease progression and series of graphics explains how the inflammatory response is caused by an immune reaction following the entrapment of immune complexes in the glomerular capillary membrane. The resulting proliferation of the glomerular capillary endothelial cells and the mesangial cells causing swelling of the capillary membrane and the accompanying signs and symptoms of post streptococcal glomerulonephritis.

Before we discuss the immune response in relation to disease progression we will first look at the pathology involved in this disease and the healthy functioning kidney.

Bacterial infection with Group A Streptococci

Group A Streptococcus bacteria, most commonly S. pyogenes, typically cause superficial infections of the throat (pharyngitis) or skin (impetigo). Bacteraemia is usually resolved within a few days, however, renal complications may develop a week or two later as a result of the humoral immune response to blood borne bacterial proteins that have specifically become deposited or “planted” in the kidneys (nephritogenic antigens). These nephritogenic antigens are thought to mediate damage to the glomerular basement membrane which disrupts the filtering function and allows antigens to cross into the Bowman’s space.

The innate and adaptive immune response to Streptococcal infection

Innate immune cells such as macrophages and neutrophils migrate to sites of infection and help to destroy bacteria. The adaptive immune system is also activated with the recruitment of CD4+ helper T cells and B lymphocytes responding to bacterial antigens. An important factor in the development of kidney dysfunction following a Streptococcal infection is the generation of antibodies that target the secreted bacterial antigens.
the secreted bacterial antigens

**Immune complex formation and deposition in the kidneys**

There are two possible explanations of how immune complexes become deposited in the kidney.

As plasma cells produce more and more antibodies, antibody-antigen complexes can form in the bloodstream due to the presence of secreted antigens and antibodies. These immune complexes can then become deposited in the kidneys via the circulation. Alternatively antibodies bind to free antigen already trapped in the glomerular basement membrane to form “in situ” immune complexes during glomerular filtration due to disrupted barrier function between the capillaries and the Bowman’s capsule.

To better understand the complications caused by immune complex deposition in the kidneys we will briefly look at the structure and functioning of a healthy kidney.

**Structure of kidney nephron**

The normal filtering of waste products from the blood is performed by thousands of nephrons located in the kidney. These are composed of several structures including renal corpuscles, responsible for filtering large amounts of fluid from the blood.

**Structure of the renal corpuscle**

The renal corpuscle consists of two main parts: the glomerulus and Bowman’s capsule. The glomerulus is a fine network of capillaries that are permeable to small molecules. The glomerular capillary membrane is similar to that of other capillaries except that it has three major layers instead of the usual two. The (1) endothelium, (2) basement membrane and (3) layer of epithelial cells (continuous with the epithelium lining the Bowman’s capsule) known as podocytes, that surround the outer surface of the capillary basement membrane. Podocytes have long processes (foot processes) that wrap themselves around the glomerular capillaries. Each component brings its own unique function- the endothelium is fenestrated, the basement membrane has a negative electrical charge and prevents the passage of plasma proteins and the podocyte foot processes form slit-pores - that together form a highly efficient filtration system. Fluid from the glomerular capillaries leaks out across these layers into Bowman’s capsule that surrounds the glomerulus. This glomerular filtrate contains only water and small molecules. Another important component of the renal corpuscle is the mesangium. This occurs in areas where the capillary endothelium and basement membrane do not completely surround each capillary. The mesangial cells instead provide support in these areas by producing an intercellular substance similar to that of the basement membrane. They also possess phagocytic properties and remove materials that enter the intercapillary spaces. Typically this area is narrow and contains only a small number of cells, however mesangial hyperplasia and increased mesangial matrix occur in a number of glomerular diseases.
Now that we have an understanding of the anatomy of the renal corpuscle we can look more closely at how streptococcal antigen is deposited in the kidney.

**Planting of Streptococcal antigen in the kidney**

Two “nephritogenic” proteins have thus far been identified in Streptococcal infections and include SpeB, a bacterial serine protease enzyme, and NAPiR, a secreted bacterial protein known as “nephritis-associated plasmin receptor”. It is thought that these proteins when present in the kidney precipitate enzymatic damage to the basement membrane and endothelial cell integrity, thus allowing plasma proteins, erythrocytes and immune complexes to cross into the bowman’s space i.e. the system becomes “leaky”. The bacterial antigens bind and activate plasmin or plasminogen which in turn activates the enzymes collagenase and matrix metalloproteinases that degrade the basement membrane and weaken endothelial cell tight-junctions. Disrupted membrane function allows bacterial antigens to be deposited inside the Bowman’s space.

**Complement activation in the kidney**

The deposition of immune complexes in the Bowman’s space activates the classical complement system by recruitment of C1 proteins from plasma. A loss of plasma C3 levels (see investigations) correlates with complement activation and deposits of C3 proteins can be detected along the basement membrane and in the Bowman’s space.

**Immune cell recruitment to the kidney**

Due to complement activation and generation of anaphylatoxins we then see an increased influx of immune cells such as macrophages and neutrophils. Deposits of C3, antibody and bacterial antigens accumulate at the basement membrane near the podocyte foot processes, known as “humps”. Kidney function is severely hampered by influx of immune cells, particularly neutrophils, that can block capillaries. There is also marked cell proliferation of mesangial and endothelial cells due to the presence of soluble inflammatory molecules.

**Immunological damage to the renal corpuscle**

Kidney function is compromised by the breakdown of the filtering function of the basement membrane and the influx of numerous immune cells due to complement activation. This results in plasma protein (proteinuria) and erythrocyte (haematuria) leakage unto the urine and a decrease in urine volume (oliguria). Oliguria which develops as the glomerular filtration rate (GFR) decreases is one of the first symptoms. Proteinuria and haematuria follow because of increased glomerular capillary wall permeability. The red blood cells are degraded and cola coloured urine is one of the early signs of the disorder. Sodium and water retention gives rise to oedema, particularly in the face and hands and the patient is also found to have hypertension due to salt imbalance.
findings include elevated antistreptolysin O titre (antibodies to a streptococcal exoenzyme) a decline in C3 complement and cryoglobulins. In most cases only mild damage to the kidneys is sustained and the patient will recover, but ongoing inflammation can result in complete and irreversible kidney damage that requires chronic dialysis and ultimately a transplant of a functional kidney.

Link to the associated Case Study

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