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Postinfectious glomerulonephritis

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Introduction

Postinfectious glomerulonephritis (PIGN) [1,2] is associated with bacterial, viral, fungal, and parasitic infectious agents and histologically appears most often as acute diffuse endocapillary or proliferative GN (group A streptococcus, streptococcus viridans, *Staphylococus aureus, Diplococcus pneumoniae, Brucella melitensis, Salmonella typhi, Yersinia enterocolitica, Mycobacterium leprae, Plasmodium falciparum,* meningococcus, Mycoplasma, Klebsiella, measles, mumps, varicella, vaccina, variola, cat scrats, etc.). Less commonly, it appears as diffuse crescentic GN (streptococcus, staphylococcus, legionella, varicella, *Treponema pallidum*) and focal crescentic GN (streptococcus A). It rarely appears as mesangiocapillary GN (streptococcus viridans, hepatitis C virus), diffuse or focal mesangial proliferative GN (diplococcus, salmonella, hepatitis B virus, influenza virus, adenovirus), focal segmental, necrotizing and sclerosing GN (bacterial endocarditis), membranous GN (syphilis, hepatitis B virus, filaria, Schistosoma, Mycobacterium, *Plasmodium falciparum*), focal proliferative (Mycoplasma), mesangiolytic GN (ECHO), and HUS (Epstein–Barr virus, handavirus).

Poststreptococcal GN

Poststreptococcal GN (PSGN) [1,2] is the most common form of PIGN. It affects mostly children after an infective episode or a skin infection with a latent period of 2–6 weeks. Its incidence is lower in western (10–40%) than eastern (40%) countries. PSGN may be asymptomatic (subclinical) or may present with haematuria (100%), proteinuria (80–92%), oedema (75–90%), hypertension (60–80%), oliguria (10–58%), and other symptoms (heart failure, nephrotic syndrome, azotaemia) manifested more often in elderly patients. Low serum complement is found in over 90% of cases of PSGN. Indications for renal biopsy are massive proteinuria, normal serum complement levels or persistent low levels and progressive increase in serum creatinine levels.

Histopathology-light microscopy

All glomeruli are affected by infiltration initially of polymorphonuclear and in later stages of mononuclear leucocytes and CD4 + T lymphocytes. In addition, there is activation and proliferation of endothelial cells and, to a lesser degree, of mesangial and epithelial cells. All these transient and native cells occlude the capillary lumina and enlarge the glomerulus, producing expansion of its lobularity. The capillary walls are segmentally thickened. Under high power magnification, tiny subepithelial fuchinophilic dots can be identified on thin paraffin and plastic semi-thin sections. In some patients focal crescent formation may be found. Tubular changes are not usually pronounced, unless there is florid glomerular involvement. Vacuolation of the proximal tubular epithelial cells, intraluminal erythrocytes, polymorphs and casts, focal tubulitis, dilation and atrophy can be observed. Interstitial involvement is variable, but usually not remarkable. Oedema and focal inflammation may be found.

Immunofluorescence

Immunofluorescence reveals coarse granular deposits of C3 (predominantly) and IgG or IgM on the glomerular capillary wall and sometimes in the mesangium early in the course of the disease ('starry sky' pattern). These deposits may be densely packed or confluent or look linear in some areas of GBM ('garland' pattern). Later, C3 deposits are confined to mesangial areas (mesangial pattern). In a few cases linear deposition of IgG and C3 on TBM has been described when severe tubular damage was accompanying PSGN.

Electron microscopy

Electron microscopic examination reveals glomerular subepithelial bulging, electron dense deposits (humps)

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numerous in the first few weeks and gradually resolving and disappearing within 6 weeks. Some intramembranous (lamina densa), subendothelial, mesangial and along Bowman's capsule dense deposits may also be seen. Endothelial cells are disrupted and polymorphs are adjacent to the denuded GBM, which may show rare gaps.

Pathogenesis

Streptococcal antigens are gradually released during infection and can be incorporated in the GBM. A transient acute PIGN has been induced in rabbits by infection with streptococci bearing the (extracellular) nephritis strain-associated protein (NSAP), which was then found in the glomerular deposits. NSAP is considered to have nephrotoxic properties and can convert plasminogen to plasmin. Streptococcal M-protein shows cross-reactivity to GBM, binds to fibrinogen and localizes in the glomeruli. Endostreptosin (intracellular) may act as planted antigen and has been found in glomeruli during the early phase of the disease in association with high titers of circulating antibody. Nephritogenic streptococcal streptokinases can be bound into renal tissue and facilitate further antigenic planting via certain molecular domains. Streptococci trigger an autoimmune complex disease by releasing enzymes, such as neuraminidase.

Circulating or *in situ*-formed immune complexes containing streptococcal antigens are deposited within glomeruli. Plasmin, converted by NSAP, activates the alternate pathway of complement, whereas plasma fibrinolytic hyperactivity with decreased plasminogen has been demonstrated in children with PSGN. Activation of the classical pathway of complement also occurs during the early stages of PSGN. Low serum levels of complement are almost always found, but rise to normal values within 3 weeks to 4 months from the acute onset of the disease. Low complement is another sign of ongoing antigen–antibody reactions. Streptococcal neuraminidase causes depletion of sialic acid and renders normal IgG autoimmunogenic. This altered IgG stimulates the production of anti-IgG antibody and the formation of IgG–antiIgG complexes. There is a similar situation with other autologous proteins (e.g. GBM antigens, see below). Persistent antiDNA antibodies and DNA–antiDNA complexes are found in some patients with PSGN. In the setting of immune complex pathogenesis, human PSGN shows many clinical, laboratory, histological, immunofluorescence, and electron microscopy similarities to acute 'one shot' serum sickness in the rabbit.

Cell-mediated mechanisms play an important role in maintaining the glomerular lesion. The patient's lymphocytes can activate normal human immunoglobulins while the monocytes exhibit increased secretion of IL1 and TNFα. There is also elevated concentration of monokine (e.g. IL8) in the patient's urine. Altered lymphocyte transformation and disturbances in lymphocyte functions have also been observed. As previously mentioned, nephritogenic streptococcal proteins can alter the normal composition of GBM so that 'new' GBM antigens are found. Antibodies to these antigens can sensitize T lymphocytes to develop specificity for these 'new' GBM antigens.

There are some associations with the major histocompatibility complex antigens in patients with PSGN. An increased familial incidence has been noted. PSGN was found in 38% of the siblings with sporadic disease. HLA-DR4 was found to be more common in unrelated patients, while HLA-DR1 seems to be associated with PGSN. However, at present no definite conclusions have been drawn on the association of HLA antigens with PSGN development.

Clinicopathological correlations and clinical outcome

Increased glomerular hypercellularity is correlated with low glomerular filtration rate, very low levels of serum complement, an increase in the number of 'humps', and a more protracted clinical picture. Subendothelial deposits are not associated with any particular findings in the urine. 'Garland' deposits are most often observed in patients with severe proteinuria or nephrotic syndrome. 'Starry sky' deposits are seen in early cases in association with increased cellularity (some correspond to subendothelial electron dense deposits). Mesangial deposits are related to the resolving stage of PSGN and to the subsequent mesangial proliferation. Acute PSGN may change to a membranoproliferative pattern or may be transformed to membranous GN or may rapidly progress to crescentic GN, especially when associated with severe infections. The last form of GN is the most significant lesion correlated with poor outcome when (i) crescents are large and affect more than 40% of the glomeruli and (ii) there is global glomerulosclerosis and interstitial fibrosis. The severity of the tubulointerstitial damage is correlated with increasing of serum creatinine levels. Arterial and arteriolar sclerosis, together with considerable glomerular obsolescence, contribute to an unfavorable prognosis (as it happens in other diseases).

Complete clinical and morphological recovery (which may be delayed) has been observed in children (92%) and adults (60%). Some patients continue to have proteinuria, haematuria, hypertension, and renal failure for several months or years. Histology usually shows mesangial hypercellularity or a chronic form of GN. End-stage renal disease is the aftermath of a crescentic or complicated chronic GN. However, death from renal or cardiac failure, hypertensive encephalopathy, or infection itself can occur. The mortality rate is higher in adults (5–9%) than in children ($<1\%$).

Conclusion

PSGN is an immune-complex mediated renal disease with significant participation of cellular immunity and

has a favourable prognosis for the majority of the patients. Of course, continuing and severe infections may cause permanent renal damage and worsen the prognosis.

References

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