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Rapidly Progressive Glomerulonephritis

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1. Introduction

Rapidly Progressive Glomerulonephritis are a group of renal diseases which are still posing serious threat to human health and survival. They are all characterised by acute and rapid deterioration of renal function. Renal biopsy reveals extracapillary glomerulonephritis, most frequently circumferential and diffuse, and immunofluorescence findings continue to represent the most important clue toward precise diagnosis. In the last years, with the development of new technologies and more targeted animal models, several discoveries have been made, that can help in better understanding the pathogenesis and perspectively defining new molecular targets for novel therapies, which are still required to improve the prognosis of these patients.

2. Definition

Introduced for the first time by Ellis in 1942 (Ellis, 1942), the term Rapidly Progressive Glomerulonephritis (RPGN) clinically describes a heterogeneous group of glomerulonephritis characterised by worsening of kidney function that, if not adequately and timely treated, rapidly progresses to end stage renal disease. From the pathological point of view, these diseases are classified as extracapillary or crescentic glomerulonephritis, generally showing extracapillary proliferation in more than 50% of glomeruli. Besides renal biopsy, which is mandatory to make the diagnosis and guide therapeutic decisions, clinical symptoms, biochemical exams, and the observation of the urinary sediment are relevant to the diagnostic process.

Observation of the urinary sediment in the acute phase of disease allows to detect in the vast majority of cases marked erythrocytic cylindruria, mild to moderate leukocyturia, presence of tubular epithelial cells and tubular epithelial cell casts. Fatty casts and leukocyte casts can be detected in about one third of cases (Fogazzi, 2009). Progressive disappearance of these features follows successful therapeutic intervention, and their reappearance frequently precedes disease relapses, making the urinary sediment an important exam not only at diagnosis but also during the patient's follow-up.

Despite the amelioration of prognosis obtained with introduction of high doses of steroids, immunosuppressive agents, and plasma exchange, these diseases are still life-threatening and a high percentage of subjects have a poor renal outcome.

3. Classification

Along the years, different schemes for classifying RPGN have been proposed. Among them, the classification which is still largely accepted and mostly utilised was proposed by Couser (Couser, 1988), and defines disease groups on the basis of immunofluorescent findings. Clinical features and haematological exams are as well very important in reaching a precise diagnosis (Table 1).

Light microscopy	Necrotising extracapillary or pure extracapillary glomerulonephritis		
Immuno-fluorescence	Linear IgG staining	None or minimal deposits	Granular deposits
Hemato-chemical exams	Circulating anti-GBM antibodies	ANCA	Autoantibodies Complement components
Clinical features	Lung haemorrhage	Systemic symptoms	Systemic symptoms
Diagnosis	Anti-GBM disease Goodpasture's syndrome	Wegener's granulomatosis Microscopic polyangiitis Renal limited vasculitis Churg-Strauss syndrome	Post-streptococcal GN Post-infectious GN SLE nephritis IgA GN/HS syndrome Primary MPGN Other primary GN

Table 1. Classification of RPGN according to immunofluorescence findings

Linear deposition of IgG along the glomerular basement membrane associated to circulating anti-GBM antibodies allow the diagnosis of anti-GBM disease. If pulmonary haemorrhage is present, the diagnosis becomes of Goodpasture's Syndrome.

When immunofluorescence on renal biopsy material demonstrates absence of immune deposits or scanty immune deposition in the glomerulus, in association to the presence of circulating ANCA antibodies, a diagnosis of pauci-immune ANCA-associated renal vasculitis is made. In these cases, necrotising crescentic GN can be associated to clinical symptoms of systemic vasculitis. A prevalent involvement of the upper respiratory tract is highly suggestive for a diagnosis of Wegener's Granulomatosis, whereas the presence of only general systemic symptoms, such as fever, is highly suggestive of Renal Limited Vasculitis. Rarely presenting as RPGN, Churg-Strauss syndrome is diagnosed when asthma and increased circulating eosinophils are present.

Importantly, there is a percentage (10-30%, according to the literature) (Chen, 2009) of renal vasculitis which are negative for ANCA antibodies. A part from subjects with circulating AECA (anti-endothelial cell antibodies), that according to a recent study may be present in about 50% of cases (Cong, 2008), diagnosis is mainly based on clinical and biopsy findings and exclusion of other causes.

Among cases of RPGN with granular immune deposition in glomeruli, the most frequent are Post-Streptococcal/post-infectious nephritis and extracapillary GN observed in cases of Lupus Nephritis. In these diseases, besides clinical symptoms, diagnosis is made thanks to the presence of autoantibodies (ASLO and anti-DNAseB in PSGN, and ANA in SLE).

RPGN can also complicate any primary form of GN, most frequently MPGN and IgA nephropathy. A part from the immunofluorescence findings, diagnosis is also guided by clinical and biochemical exams, such as the evaluation of complement components for the diagnosis of MPGN, and the presence of purpura in cases of Henoch-Schoenlein syndrome.
It remains to be said, as a word of caution, that it is not infrequent to find a completely negative immunofluorescence or immunofluorescence findings particularly difficult to interpret in cases with very severe extracapillary proliferation or necrotic lesions, because of the consequent compression or destruction of the glomerular tuft.

4. Morphological findings

Though the common element characterising this group of diseases is the presence of extracapillary proliferation, morphological findings can be very diverse, according to the stage of the disease and also to the underlying disease, likely reflecting the different pathogenesis of glomerular lesions.

4.1 Anti-GBM nephritis and Goodpasture's Syndrome

By light microscopy, variable degrees of necrotising extracapillary lesions can be observed, which range from focal and segmental to global and diffuse (Fig 1).

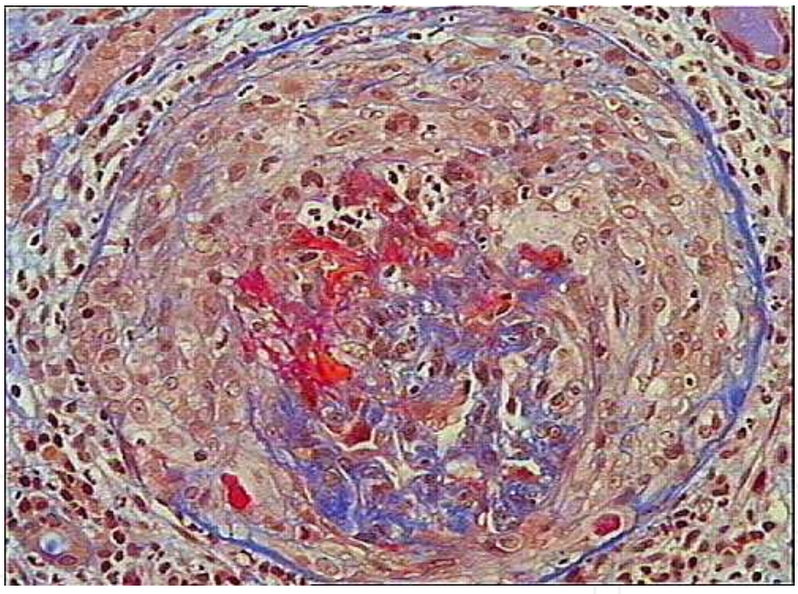

Fig. 1. Anti-GBM nephritis. A large area of necrosis of the glomerular tuft is surrounded by a circumferential crescent. Inflammatory cells surround the glomerulus.

Extracapillary lesions are composed by monocytes, epithelioid macrophages and epithelial cells. Glomeruli not involved by these lesions and the parts of the glomerulus not affected by necrosis can present normal features, but more commonly they show mild to moderate mesangial proliferation, some degree of mesangial matrix expansion, and increased leukocyte infiltration. Intraglomerular inflammatory cells are mostly monocyte-macrophages with variable numbers of T-lymphocytes (Ferrario, 1985; Bolton, 1987).
In about 50% of cases, multinucleated giant cells can be detected either in the crescent or in the periglomerular inflammatory infiltrate, forming the so-called granuloma-like lesions.

Generally well corresponding to the degree of glomerular damage, the tubulointerstitium shows variable extents of tubular atrophy, oedema, and interstitial inflammation. If the biopsy is timely performed, no interstitial fibrosis is observed.
Vascular lesions are not common, though necrotising arteritis and thrombotic microangiopathy have been reported occasionally in the literature (Dean, 1991; Stave, 1984).
Immunofluorescence is diagnostic, with the linear deposition of IgG along the glomerular basement membrane. This aspect can be best appreciated in glomeruli not particularly damaged, whereas it is more difficult to be seen when the glomerular capillary is largely destroyed by necrosis or compressed by extensive cellular crescents.
A combination of IgG and C3 can also be found, as well as a linear deposition of IgA or IgM (Gris, 1991; Peto, 2011) has been reported.
Linear IgG staining can be also detected along the Bowman's capsule, and along the tubular basement membranes. Additionally, the fibrinogen antiserum strongly stains the areas of necrosis in the tuft and within the crescents.

4.2 ANCA-associated renal vasculitis

Irrespective of diagnosis, identical renal microscopy features can be observed in Wegener's granulomatosis, microscopic polyangiitis, and renal limited vasculitis. Necrotising glomerulonephritis and extracapillary proliferation are the renal hallmark of these diseases, and can be found with variable degrees of association. Necrosis can be present alone in cases when renal biopsy is early performed, but more commonly is associated with segmental areas of extracapillary proliferation. Particularly compromised glomeruli show instead large areas of necrosis of the tuft and circumferential crescents, with frequent rupture of the Bowman's capsule and intense periglomerular leukocyte infiltration, so that the limit of the glomerular area is no more distinguishable (Fig 2), and the area has the aspect of a granulomatous reaction.

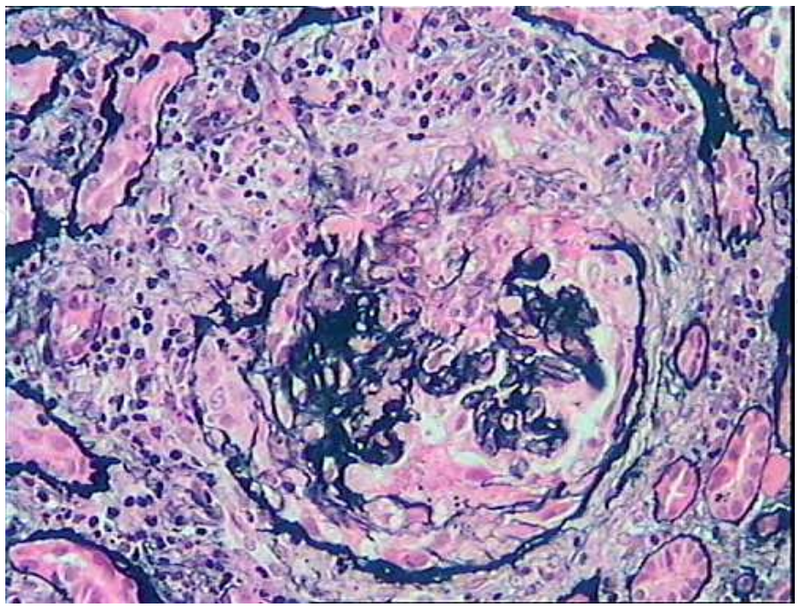

Fig. 2. ANCA-associated vasculitis. A large rupture of the Bowman's capsule can be observed.

Extracapillary and granuloma-like lesions are mainly made by inflammatory cells, mostly acutely activated monocyte-macrophages (Fig. 3, Fig 4) (Rastaldi, 1996; Rastaldi, 2000), whose entrance into the glomerulus seems to be facilitated by the de novo expression of the adhesion molecule VCAM-1 (Fig 5).

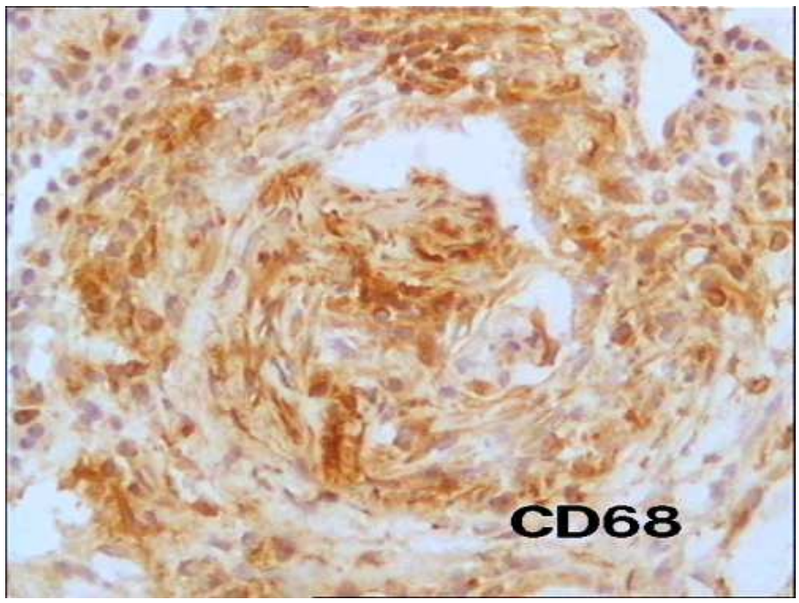

Fig. 3. ANCA-associated vasculitis. Glomerular damage and periglomerular granuloma-like reaction are mainly composed by monocyte-macrophages, as witnessed by the positivity for the marker CD68.

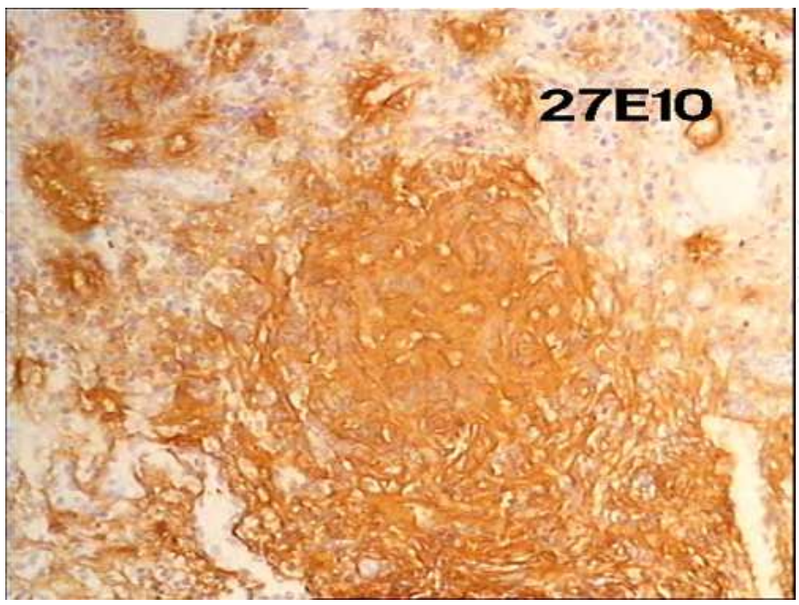

Fig. 4. ANCA-associated vasculitis. A vast glomerular granuloma-like reaction is strongly positive for the marker of acutely activated monocyte-macrophages 27E10.

The acute activation of cells composing the glomerular granuloma-like reaction differentiates this type of alteration from other kind of tissue granulomas, where acute macrophages have not been found (Bhardwaj, 1992).
Differently from those observed in other diseases, monocyte-macrophages present in renal vasculitis are proliferating cells, as we have shown by staining with antibodies against PCNA (Fig 6) and Ki67 (Rastaldi, 2000).

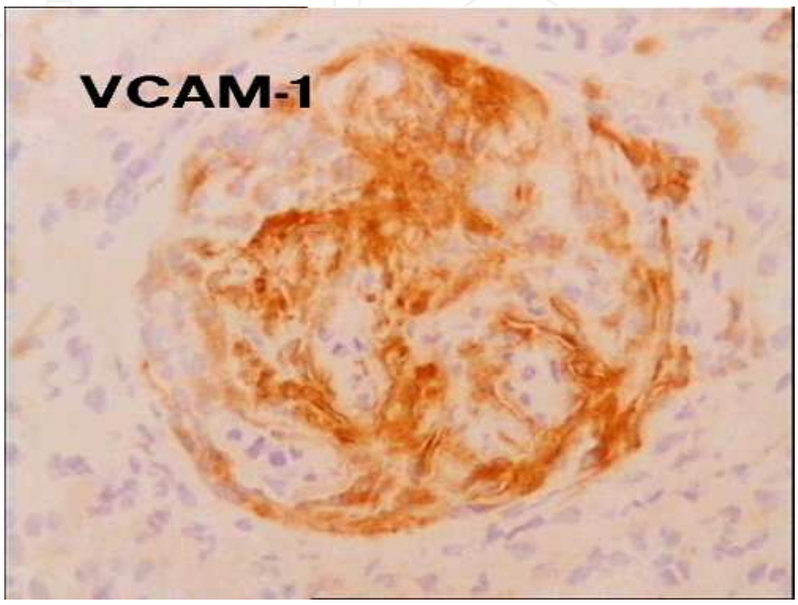

Fig. 5. ANCA-associated vasculitis. VCAM-1 de novo expression in damaged areas of the glomerulus.

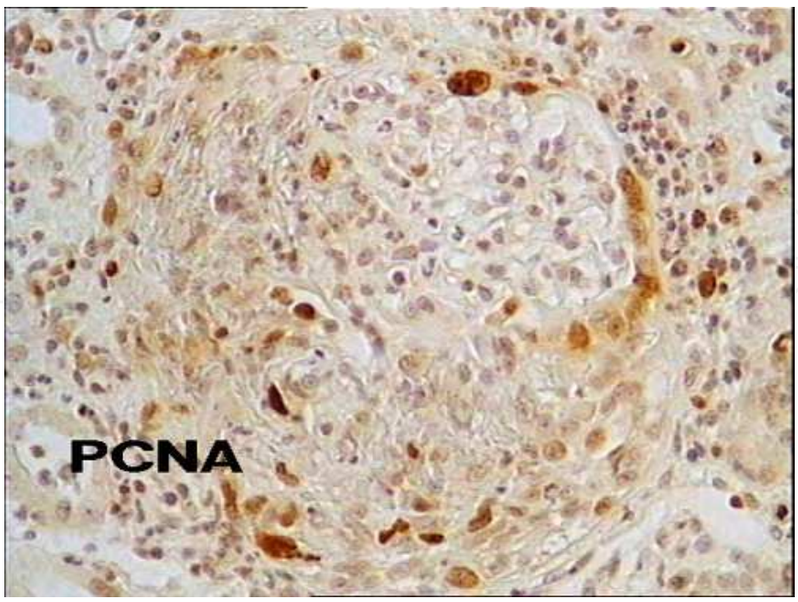

Fig. 6. ANCA-associated vasculitis. PCNA labels numerous cells in and around the glomerulus.

Depending on the timing of renal biopsy, glomeruli can be affected by active lesions or by more sclerotic alterations. It is not infrequent to observe both types of lesions in the same renal biopsy and even in the same glomerulus (Fig 7).

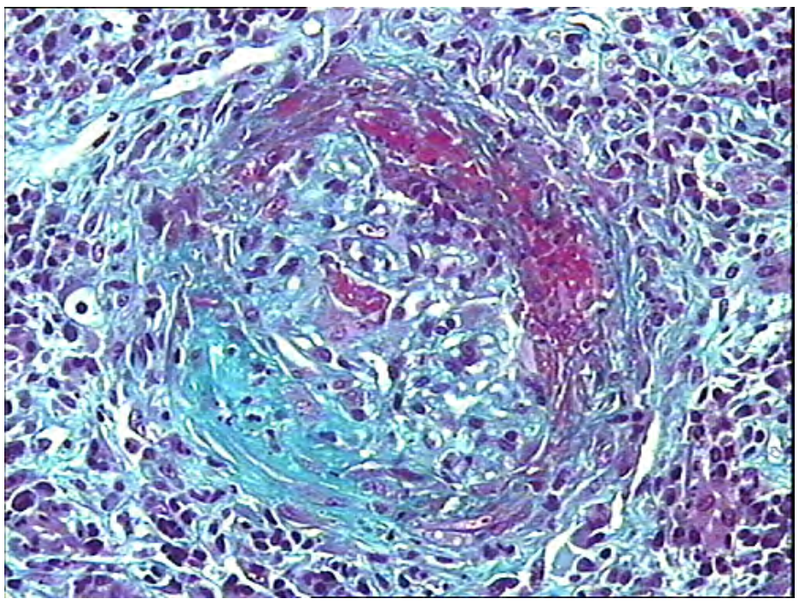

Fig. 7. ANCA-associated vasculitis. The glomerulus shows evident necrotic damage in the upper part of the crescent, whereas the lower part is already fibrous.

Besides periglomerular infiltrates, focal perivascular inflammatory cells are frequently detected in the interstitium, and a diffuse interstitial leukocyte infiltration is also present, whose degree well corresponds to the extent of glomerular damage. Interstitial cells are mainly monocyte-macrophages and T-lymphocytes.
Prevalence of eosinophils, in association to the clinical symptoms of asthma, and increased numbers of circulating eosinophils, stand for a diagnosis of Churg-Strauss syndrome.
By definition, in ANCA-associated renal vasculitis immune deposits are absent or few and scattered, hence the term pauci-immune glomerulonephritis. Instead, the fibrinogen antiserum strongly stains areas of necrosis of the tuft and fibrin deposits into the crescents.

4.3 Post-infectious glomerulonephritis

Either post-streptococcal and other post-infectious glomerulonephritis can present with a rapidly progressive course, which is indicative of a poor prognosis.
Several systemic infections, especially occult, such as infective endocarditis, infected atrio-ventricular shunts, visceral abscesses, and infected vascular prostheses, can be at the origin of RPGN. Blood levels of complement can be reduced.
By light microscopy necrotising lesions, but more frequently extracapillary damage without necrosis of the tuft are observed.
Especially in case of streptococcal infections, the presence of numerous intraglomerular granulocytes (so-called glomerular exudative lesions) (Fig 8) is useful for diagnostic purposes.

In post-streptococcal GN, granular IgG and C3 deposits are the most common finding. IgG, C3, and IgM deposits can be observed in other post-infectious GN, at various locations, but primarily subendothelial and mesangial.

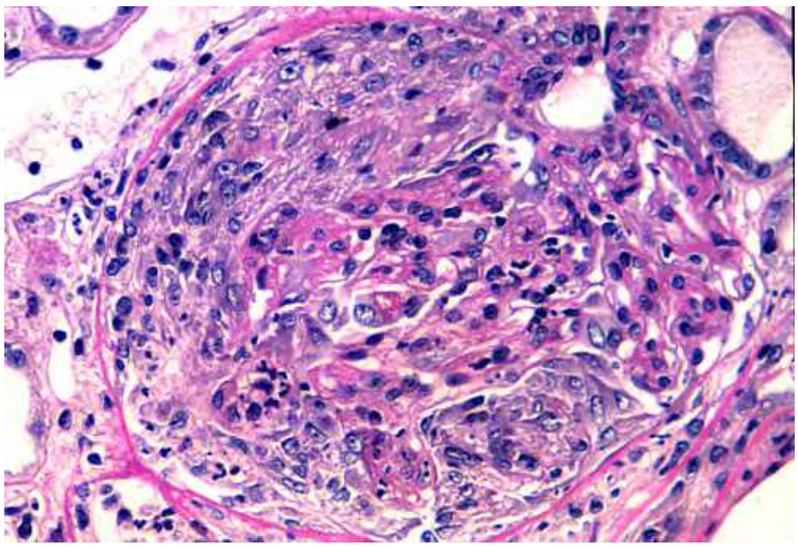

Fig. 8. Post-streptococcal GN. Numerous granulocytes can be observed in the glomerular tuft and in the crescent.

4.4 RPGN complicating primary and secondary glomerular diseases

Though rarely, any primary or secondary glomerular diseases can be complicated by a rapidly progressive course and display necrotising crescentic glomerulonephritis at light microscopy. Very recently, a report has shown for the first time the appearance of RPGN complicating the course of AL amyloidosis (Crosthwaite, 2010). Cases of association of primary or secondary glomerulonephritis and anti-GBM disease or renal vasculitis have also been published, as well as cases of association of anti-GBM disease and ANCA-positive renal vasculitis (Curioni, 2002; O'Connor, 2010). Diagnosis in these patients requires skilful and careful analysis of clinical features, renal biopsy findings, and hematochemical exams.

4.4.1 IgA nephropathy and Henoch-Schonlein purpura

Less than 10% of patients with primary IgA nephropathy or Henoch-Schonlein syndrome have been reported with a truly rapidly progressive course (Ferrario, 1997).

Clinical features of cutaneous purpura or abdominal and joint pain, accompanied by the finding of a small vessel leukocytoclastic vasculitis, most frequently detected in skin biopsies, help in making a diagnosis of systemic disease.

Focal segmental or global and diffuse necrotising and extracapillary lesions of the glomerulus can be found, or extracapillary lesions can be present without necrosis of the glomerular tuft (Fig 9), which always presents variable degrees of mesangial proliferation and expansion of the mesangial matrix.

Immunofluorescence shows prevailing IgA mesangial deposits, possibly in combination with IgG and C3 deposition, especially in the systemic disease.

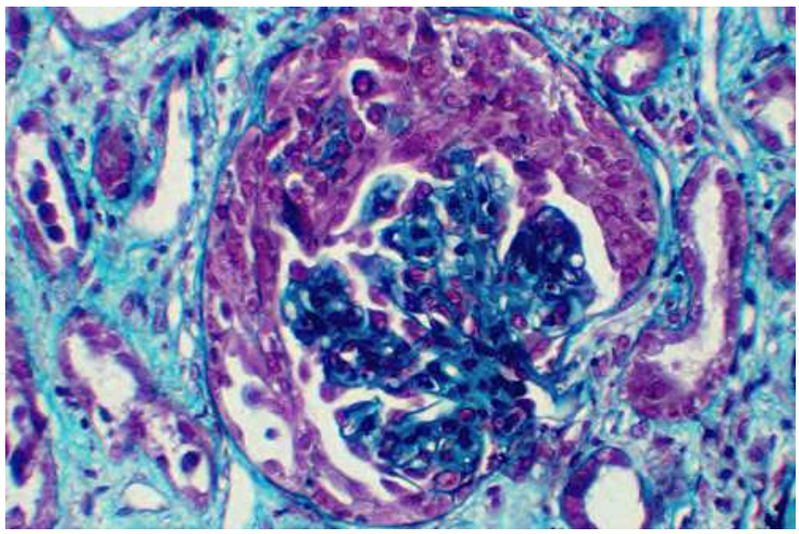

Fig. 9. Primary IgA nephropathy. A circumferential crescent surrounds a glomerulus affected by mesangial proliferation and mesangial expansion.

4.4.2 Systemic lupus erythematosus

Among the histological classes of SLE nephritis (Weening, 2004), RPGN is more frequently observed in classes III and IV. In these cases the occurrence of antineutrophil cytoplasmic antibodies is not uncommon and is thought to contribute to the development of necrotising and crescentic glomerular lesions (Sen, 2003).

Extensive extracapillary proliferation has been rarely reported (Fig 10), whereas segmental necrotising extracapillary alterations are a rather common finding, but not always translate in a RPGN clinical phenotype.

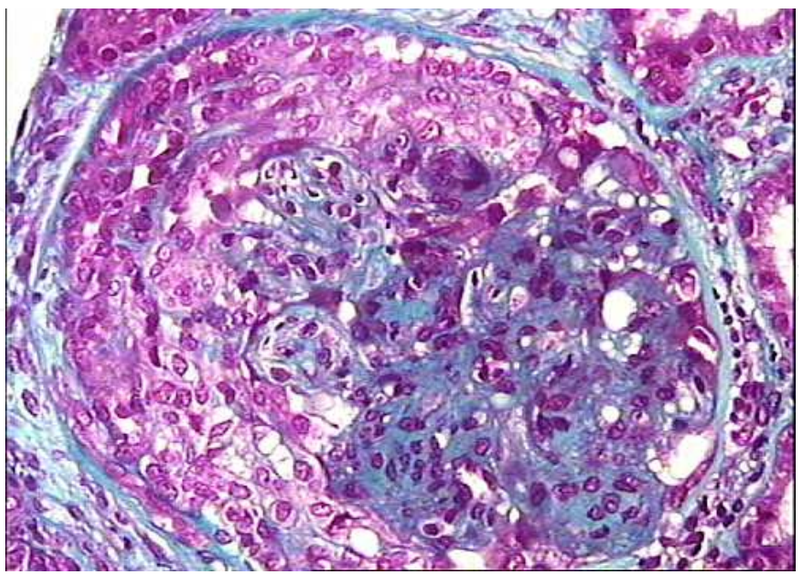

Fig. 10. Rapidly progressive class IV SLE nephritis. A circumferential crescent surrounds a glomerulus affected by intense intracapillary proliferation, mesangial expansion, and leukocyte infiltration.

Immunofluorescence has the typical findings of lupus nephritis, according to the class of disease, with frequent "full house" deposition, and fibrinogen positivity in necrotic areas and crescents.

5. Pathogenesis and experimental models

In recent years, thanks to the possibilities offered by molecular modelling, genetic studies, and the generation of novel animal models better reproducing human disease features, important advances have been made in understanding pathogenetic mechanisms underlying certain forms of RPGN, especially anti-GBM nephritis and ANCA-associated renal vasculitis.
Instead, it continues to be less clear why a rapidly progressive course can complicate virtually any type of primary and secondary glomerulonephritis.

5.1 Anti-GBM nephritis and Goodpasture's disease

The seminal discovery in understanding the pathogenesis of the disease was the identification of the antigen that causes production of pathogenic autoantibodies (Saus, 1988).
Thereafter, injection of the recombinant antigen, i.e. the noncollagenous domain (NC1) of the alpha3chain of collagen type IV, was shown to induce a severe glomerulonephritis in Wistar-Kyoto rats (Sado, 1998), hence proving a direct relationship between the self-antigen sustaining autoantibody production and the disease.
More recently, a second class of autoantibodies has been described, which are specific for the alpha5NC1 domain, occur in 70% of affected patients, and seem to be associated with a worse renal prognosis (Pedchenko, 2010).
In the normal glomerular basement membrane, the NC1 domain is assembled in alpha345NC1 hexamers, whose quaternary organisation has been shown in a three-dimensional model (Vanacore, 2008) as an ellipsoid-shaped structure composed by two NC1 trimers joined at the base by hydrophobic and hydrophilic interactions and reinforced by sulfilimine bonds. This crosslinked alpha345NC1 hexamer is inert to antibody binding. Anti-GBM antibodies in fact can bind only to dissociated monomer and dimer subunits that form after alteration of the hexamer and expose pathogenic neoepitopes. This explains why passive transfer of antibodies to the mouse, where hexamers in the GBM are completely crosslinked, does not result in glomerulonephritis (Luo, 2010).
The major epitopes within the alpha3 and alpha5 subunits have been identified as well, and named EA-alpha3, EA-alpha5, and EB-alpha3 (Netzer, 1999; Hellmark, 1999; Pedchenko, 2010).
Several questions, primarily regarding the causes of hexamer alteration that induce epitope exposure and antibody production, need to be answered. At present, the most accredited hypothesis is that environmental factors act in genetically predisposed subjects, leading to epitope alteration and antibody formation.
As for genetic predisposition, positive and negative associations with HLA molecules have been found, especially with the MHC class II HLA-DRB1*1501 allele (Yang, 2009), which is strongly associated to anti-GBM disease.
A number of experimental data are in favour of a role played by FcγR gene and the complement system, though their precise role in humans is still unclear.

Instead, several experimental models implicate T-cell mediated immunity in the pathogenesis of anti-GBM disease, which is based on the following findings. In rats, anti-GBM disease can be induced by injecting alpha3(IV)NC1-specific CD4+Tcells (Wu, 2002). Anti-CD8 monoclonal antibodies reduce disease severity and antigen-specific CD8+Tcell clones have been found in diseased patients (Reynolds, 2002). Invariant natural killer cells (iNKT) could have a role as well, because the disease has a worse course in iNKT cell-deficient mice (Mesnard, 2009). Finally, mice deficient in IL-23, which is important for the maintenance of Th17 cells, the CD4+Tcell subset producing IL17, are protected from anti-GBM disease (Ooi, 2009).

5.2 ANCA-associated renal vasculitis

The discovery of ANCAs (Falk, 1988) radically changed not only the diagnosis of small vessel vasculitis, but also introduced an important element for the study of the etiology and pathogenesis of this group of diseases. Major ANCA autoantigens are two proteins contained in azurophil granules of neutrophil granulocytes, MPO and PR3, which are mainly expressed during neutrophil development at the myeloblast and promyelocytic stage (Cowland, 1999). They are aberrantly expressed in mature neutrophils of ANCA patients, whereas are silenced in mature neutrophils of healthy subjects (Yang, 2004).

In vivo first evidence for a pathogenetic role of ANCA was demonstrated by injection of anti-MPO antibodies or anti-MPO lymphocytes, causing a pauci-immune focal necrotising extracapillary glomerulonephritis (Xiao, 2002). Subsequent research then showed that in this model neutrophil granulocytes are required, because mice depleted of neutrophils do not develop the disease, and disease worsening is obtained by priming neutrophils using a pro-inflammatory stimulus (Xiao, 2005). The model has been also useful in investigating the role of the alternative complement pathway, because the disease does not occur in C5 or Factor B null mice, but it fully develops in C4-KO animals (Xiao, 2007).

In an additional model, MPO-KO mice were first immunised with mouse MPO, determining production of anti-MPO antibodies. These mice having circulating anti-MPO antibodies were then irradiated and subsequently transplanted with MPO-wild type or MPO-KO bone marrow cells. A pauci-immune necrotising-crescentic glomerulonephritis developed only in mice engrafted with MPO-wild type cells, indicating the requirement for bone marrow derived cells in disease development (Schreiber, 2006).

5.3 Cells involved in crescent formation

Along the years, composition of glomerular extracapillary proliferation has been, and still remains, the object of intense investigation and discussion.

Though the exact mechanism/s of crescent formation remain elusive, novel animal models have recently added important information, that will lead to further clarification of the molecular pathways involved and the potential identification of possible novel therapeutic targets.

A word has first to be spent in stating that, morphologically speaking, extracapillary proliferation is a heterogeneous phenomenon. It has been shown by several investigators that presence or absence of necrosis of the glomerular capillary is relevant to the type of crescent. When necrosis is present, the crescent is more inflammatory, and mainly formed by monocyte-macrophages. In absence of tuft necrosis, the crescent has more epithelial and less inflammatory features.

If the presence of inflammatory cells and epithelioid macrophages has never been questioned either in animal models and in human disease, opposite data have been obtained when attempting to define the epithelial cell composition.

Until some years ago, both experimental and human studies aiming to study the cells contained in the crescents were mostly based on morphological findings and immunostaining. The conflicting results produced by these studies were due not only to the specific type of experimental model or of human disease under analysis, but especially to a dysregulated phenotype with loss of specific markers. In fact, both podocytes and parietal epithelial cells are likely to change their original resting phenotype once they start proliferating and filling the Bowman's space.

The advent of novel experimental models, though not generating unifying and conclusive data, is providing more convincing proofs of the participation of either podocytes or parietal epithelial cells, based on tagged expression of specific molecules.

Convincing evidence of podocyte contribution to crescent formation has been shown in a podocyte specific mouse model of Vhlh gene knockout (Ding, 2006). These mice showed rapidly progressive glomerulonephritis by 4 weeks of age and died by terminal renal failure after 3-4 weeks. Histology displayed a crescentic glomerulonephritis, and podocytes expressing tagged-ZO1 were found into the crescents. A part from showing podocyte participation in crescent formation, the model also identified a novel pathway potentially operating in extracapillary glomerulonephritis; deletion of Vhlh in fact resulted in stabilisation of hypoxia inducible factor-aplha (HIF1alpha) and consequent upregulation of target genes, among them the chemokine receptor CXCR4. Further, podocyte-specific expression of CXCR4 was sufficient to induce podocyte proliferation and crescent formation, and CXCR4 positivity was observed in glomeruli of human biopsies with necrotising extracapillary lesions, suggesting that the VHLH-HIF-CXCR4 pathway may have functional relevance also in humans.

The contribution of parietal epithelial cells to crescent formation has been recently shown in a mouse model where a construct containing 3 kb of the human podocalyxin (*hPODXL1*) 5′ flanking region and 0.3 kb of the rabbit *Podxl1* 5′ untranslated region were used to drive expression of rabbit podocalyxin, and transgene expression was detected exclusively within PECs but not in podocytes. In this model, injection of nephrotoxic serum caused extracapillary glomerulonephritis and cells within crescents could be clearly identified as of parietal origin (Smeets, 2009, a).

As a final consideration, recent work has demonstrated that the Bowman's capsule contains renal progenitors mainly located at the urinary pole of the glomerulus (Ronconi, 2009). If it is true that these cells are able to regenerate either tubular cells and podocytes, then their participation to crescent formation can be viewed as the pathological consequence of a tentative to repair glomerular damage in the course of inflammatory conditions (Smeets, 2009, b).

6. Conclusion

RPGN still constitute a threat for human health and survival. Despite numerous improvements in understanding the pathogenesis of these diseases, numerous questions still remain unanswered and will need clarification before providing targeted, pathway-based, novel therapeutics.

7. Acknowledgment

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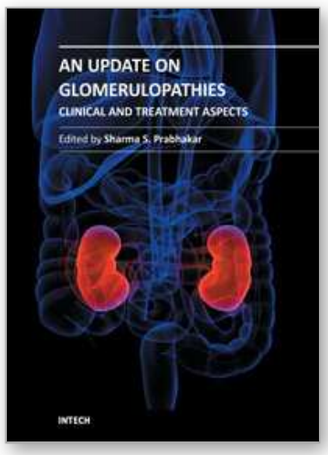

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An Update on Glomerulopathies - Clinical and Treatment Aspects is a systemic overview of recent advances in clinical aspects and therapeutic options in major syndromes of glomerular pathology. The book contains twenty four chapters divided conveniently into five sections. The first section deals with primary glomerulopathies, and the second section is devoted to glomerulopathies complicating infectious conditions. The third section deals with systemic autoimmune disorders and vasculitides which constitute major causes of glomerular disease and often renal failure. The fourth section includes chapters discussing the glomerular involvement in some major metabolic and systemic conditions. The final section has chapters which relate to some general aspects of glomerular diseases. This book will form an excellent reference tool for practicing and academic nephrology community.

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