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# Biomarkers in Renal Vasculitis

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## Abstract

The use of biomarkers in glomerular diseases has been subject of investigation during the last decades, as it can provide worthwhile evidence in diagnosis, but also, it can guide treatment and give information about prognosis and response. Renal biopsy is still the compulsory technique to establish diagnosis, and also to offer information about the severity of renal damage. However, as an invasive method, it cannot be regularly performed during follow up, so the need to find and establish measurement of molecules, easily collected, which are associated with disease pathogenesis and predict renal function outcome seems very attractive to nephrologists. The renal complications of systemic vasculitis are very important for the outcome of the disease, and several substances and molecules, such as inflammatory cells, autoantibodies, cytokines, chemokines and growth factors are produced and may serve as biomarkers to provide useful information for diagnosis, follow up of the disease.

**Keywords:** vasculitis, biomarkers, cytokines, growth factors, outcome

## 1. Introduction

The classical presentation of a primary or secondary glomerular disease (GD) is the triad of microscopic hematuria, proteinuria and impaired renal function.

A patient who presents with microhematuria, 2 g of proteinuria and a GRF of around 35 ml/min is possible to have IgAN, focal segmental sclerosis (FSGS) or membranous nephropathy (MN) or focal necrotising glomerulonephritis, due to vasculitis, and the diagnosis will be established with renal biopsy, which is the typical and standard method in diagnosing GN.

However, renal biopsy is an invasive method, which is usually mandatory for diagnosis, but, carrying the probability of complications, it cannot be repeated regularly during follow up. This is the reason, why the need to find and apply biomarkers that could help in diagnosis and follow up of the GNs is imperative.

## 2. Biomarkers: which are the characteristics of an ideal biomarker?

The precise characteristics of an ideal biomarker depend upon the disease of investigation, but certain features are considered as important, and are depicted in **Table 1**.

Primary and secondary GDs have some unique advantages; first of all kidneys produce urine, and urine are easy to collect in order to repeat measurements during follow up, but also excreted molecules in the urine represent histological changes in the kidneys. Nevertheless, kidneys are highly perfused organs, meaning that any

1.	High sensitivity
2.	High specificity
3.	Biological plausibility
4.	Associated with pathogenic mechanisms
5.	Prognosis and response to treatment
6.	Biomarker sources should be easily available

**Table 1.**  
*Specific characteristics, an ideal biomarker should carry.*

substances in the serum may have a direct effect on them. On the other hand, there are major disadvantages. Pathogenesis of GDs, especially of vasculitis affecting kidneys, is not a simple issue, it is complicated and in most cases not completely identified. Histological lesions are the result of different synergistic or counteracting pathways, which lead to proliferation, inflammation and fibrosis. In addition, the same molecule will not have the same effect in all glomerular diseases [1–5].

All the above mean that all the information provided by kidney biopsy cannot be easily substituted by one biomarker, and the question that comes up is: do the biomarkers have something to offer which is beyond the renal biopsy results and beyond the classical approach of glomerular diseases, including estimation of renal function impairment, degree of proteinuria, microhematuria and active urine sediment, or do they just correlate with these parameters and reflect renal damage?

In the present chapter, we are going to describe biomarkers involved in pathogenesis and outcome of systemic vasculitis affecting the kidneys, and we shall investigate possible advantage instead of using classical parameters.

### 3. ANCA-associated vasculitides

ANCA-associated vasculitides (AAV) are a group of systemic pauci-immune diseases, characterized by inflammatory necrosis of the small vessels (arterioles, capillaries and venules) and the presence of antineutrophil cytoplasmic antibodies (ANCA) [6–11]. There are four clinical and pathological phenotypes of AAV: granulomatosis with polyangiitis (GPA, formerly known as Wegener’s granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA, also known as Churg-Strauss syndrome), microscopic polyangiitis (MPA) and, finally, renal limited vasculitis (RLV), also known as idiopathic rapidly progressive glomerulonephritis (RPGN) [9, 11]. Contrary to other small-vessel vasculitides, which are immune-complex-mediated, in AAV there is no significant immunoglobulin deposition [6, 9–11].

### 4. ANCA

ANCA are IgG autoantibodies directed against proteinase 3 (PR3-ANCA), expressed in neutrophil granules, and myeloperoxidase (MPO-ANCA), expressed in monocyte lysosomes. PR3 and MPO are also expressed in the neutrophil extracellular traps (NET), localized to inflammatory lesions within the affected organs [6–11]. Because of their immunofluorescence pattern, PR3-ANCA are also described as cytoplasmic ANCA (c-ANCA), whereas MPO-ANCA are referred to as perinuclear ANCA (p-ANCA) [5, 9–11]. Indirect immunofluorescence and enzyme-linked immunosorbent assay (ELISA) methods are used to detect ANCA in the

serum of patients [9, 11]. The type of ANCA (PR3-ANCA or MPO-ANCA) defines the serotype of the AAV [8, 11].

There is a correlation between the serotype and the phenotype of AAV. PR3-ANCA are most common (75%) in patients with GPA and least common (5%) in patients with EGPA. MPO-ANCA occur more frequently in patients with RLV (70%), while they appear in 60% of patients with EGPA and 50% of patients with MPA. The occurrence of seronegativity is 5 and 30% in GPA and EGPA, respectively, and 10% in MPO and RLV [9]. ANCA-positive patients present either PR3-ANCA or MPO-ANCA, whereas the occurrence of both ANCA in the same individual is extremely rare and related to infection-induced or drug-mediated vasculitis [5, 9–11].

However, autoantibodies against different antigenic targets, such as lysosome-associated membrane protein-2 (LAMP-2), plasminogen, moesin, have been demonstrated recently, and they were related to different precipitating causes, as well as different disease presentation and severity. Specifically, anti-LAMP-2 antibodies have been found in most patients with RLV linked to *E. coli* urinary tract infection (UTI), suggesting that molecular mimicking mechanisms may be responsible for the formation of antibodies [6–10].

## 5. Pathogenesis

PR3 and MPO antigens are presented by autoreactive antigen-presenting B cells to autoreactive T cells, thus stimulating their activation and polarization, with the formation of pro-inflammatory Th1, Th2 and Th17 cells. In that environment, T cells activate B cells, promoting the formation of ANCA. Autoreactivity of B and T cells is presented in patients with genetic susceptibility, as shown by correlation of the disease with specific HLA gene loci, while both SNP in certain genes and epigenetic factors are associated with increased antigenic expression in neutrophils and monocytes. That increased expression of PR3 on the monocyte cell surface causes macrophage activation, while binding of MPO-ANCA promotes the release of pro-inflammatory cytokines, such as IL-1 $\beta$ , IL-6 and IL-8. On the other side, increased PR3 expression on the neutrophil surface, in patients with GPA, promotes diminished macrophage phagocytosis of neutrophils that have undergone apoptosis, leading to uncontrolled necrosis and release of more antigens and pro-inflammatory cytokines, including IL-6, IL-8 and TNF- $\alpha$ , which further amplify the previous pathological immune mechanism [6–11].

The involvement of immune cells in pathogenesis of AAV, through impaired immune tolerance and balance between immune response and immune regulation is crucial. As mentioned, B cells are responsible for antigen presentation and antibody production, but also for cytokine production and activation of T cells. That is why rituximab, a chimeric monoclonal anti-CD20 antibody, is successfully administered as therapy for AAV. Besides that, regulating B cells, which act suppressing immune response, are found numerically normal, but with impaired function. This also applies for regulating T cells, while, on the contrary, effector T cells are found infiltrating affected tissues, alongside with macrophages, neutrophils and monocytes. These cells are responsible for direct tissue damage, releasing reacting oxygen species. Neutrophils, specifically, appear to be the main participating cell in vessel damage, via the respiratory burst and the release of proteolytic enzymes and NET [6–11].

There are recent data from animal and patient studies suggesting that the complement is also involved in AAV. Altered levels of C3, C4, and CH50 are found in some patients during presentation and are associated with adverse outcome. Moreover, C5a and its receptor are implicated in neutrophil activation, thus establishing the alternative complement pathway as a promoting disease factor and a possible therapeutic target [6–11].

As far as genetic susceptibility is concerned, genome-wide association studies (GWAS) have documented a close relation between the phenotype and serotype of AAV and specific HLA gene loci. In detail, studies on Northern European and American populations have shown that GPA and PR3-ANCA are strongly associated with HLA-DP loci (with HLA-DP 0401 being associated with PR3-ANCA vasculitis and recurrence of disease, regardless of phenotype or serotype), while MPO-ANCA are related to HLA-DQ loci. HLA-DR B1501 is associated with AAV presentation in African American patients and HLA-DR B4 with EGPA. Besides HLA genes, SNP in genes PRTN3, coding for PR3, and SERPINA1, coding for  $\alpha$ 1-antitrypsin (A1AT), a protein regulating PR3, are associated with the formation of PR3-ANCA, while SNP in gene PTPN22, coding for a protein tyrosine phosphatase, regulating B and T cell receptor-mediated cell activation, is implicated in the dysregulation of immune response [6–11].

## **6. Clinical presentation**

AAV is, as mentioned before, a necrotizing inflammation of the small vessels. Therefore, it is considered a systemic disorder, affecting all tissues and organs. The clinical presentation depends on the activity and the chronicity of the disease and the specific system involvement and determines, together with the pathology, the phenotype of the disease [9].

The onset of the disease may be accompanied by non-specific systemic symptoms, such as fever, fatigue, malaise, anorexia, weight loss, arthralgia and myalgia. These symptoms, reminiscent of flu-like illness, may precede weeks or even months before the occurrence of specific systemic manifestations [9, 12].

Renal involvement is the most significant and severe of AAV clinical presentation. It affects almost every patient with MPA (90%) and GPA (80%), but less than half of the patients with EGPA (45%). The most common presentation is with RPGN, thus featuring typically microscopic or gross hematuria, subnephrotic proteinuria, hypertension, edema and, finally, renal failure, while examination of the urine reveals active urinary sediment, with dysmorphic red blood cells and red blood cell casts. Another presentation, common to patients with MPO-ANCA, is indolent glomerulonephritis, featuring a more chronic presence of microscopic hematuria and a slower decline of renal function. Interestingly, 5% of the patients with ANCA vasculitis (mostly MPO-ANCA) are also positive for anti-glomerular base membrane (anti-GBM) antibodies, suggesting concomitant glomerular lesions of AAV and anti-GBM disease. Renal involvement is the only manifestation of RLV [9, 11, 12].

Lower respiratory system involvement is more frequent in GPA (90%) and EGPA (70%) and less frequent in MPA (50%). Pulmonary manifestations vary from transient infiltration of the alveoli to severe pulmonary hemorrhage. Clinical, laboratory and imaging findings include dyspnea, cough, hemoptysis, acid-base balance and blood gases disorder, lung functional tests disorder, as well as radiological ground-glass pattern, with nodules and diffuse infiltrates [9, 11, 12].

Upper respiratory system is also involved in the clinical presentation, concerning mostly patients with GPA (90%), but also half of the patients with EGPA and 35% of the patients with MPA. Patients present sinusitis, rhinitis, ocular inflammatory disorders, such as episcleritis, necrosis and perforation of the nasal septum and subglottic stenosis. Interestingly, EGPA, is less associated with RPGN and pulmonary hemorrhage and is characterized by a prodromal phase of atopic manifestations, asthma and allergic rhinitis, followed by an eosinophilic phase of increased eosinophil counts in the blood and eosinophilic perfusion of affected tissues, before evolving to active vasculitis [9, 11, 12].

Involvement of the central and peripheral nervous system accompanies 70% of patients with EGPA, 50% of patients with GPA and 30% of patients with MPA and manifests usually as mononeuritis multiplex, while the inflammation of the meninges is less frequent [9, 11, 12].

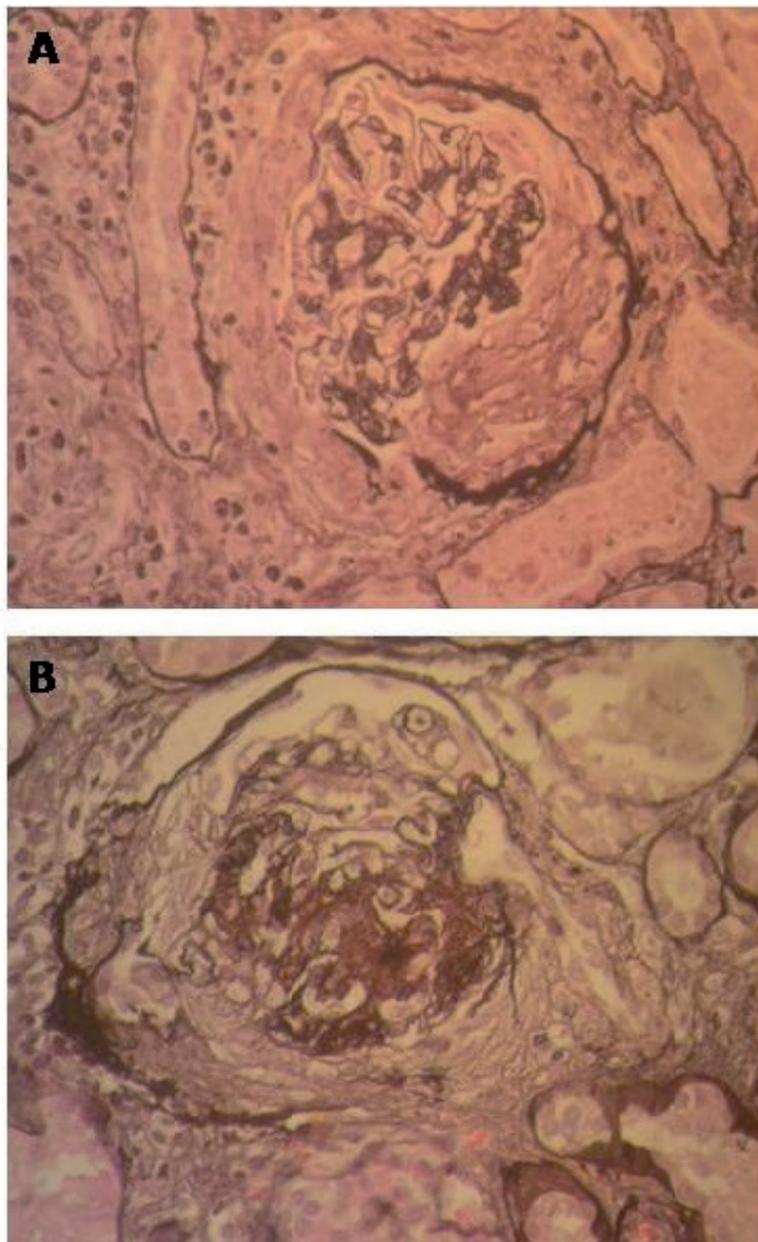
Cardiovascular involvement, mainly in ANCA-negative EGPA patients, presents as endocarditis, pericarditis or myocarditis, hypokinesia of the ventricles arrhythmias, such as atrioventricular blocks, and, lastly, as acute myocardial infarction [9, 11, 12].

Gastrointestinal involvement, affecting half of the patients with AAV, presents as an acute abdomen, with abdominal pain, hematochezia and sometimes even perforation, due to mesenteric ischemia and ulceration [9, 12].

Finally, AAV present with a plethora of cutaneous lesions, such as purpura, petechiae, ecchymoses, ulcers, nodules and more [9].

## 7. Renal pathology

Renal biopsy is the gold standard for the diagnosis of renal disease, and this also applies for AAV. The classical histopathological feature in renal biopsy of AAV patients



**Figure 1.**  
*Histology of renal involvement in ANCA associated vasculitis (A) and IgAV-N (B).*

is segmental necrotizing glomerulonephritis. Characteristic findings include inflammatory perfusion of both glomeruli and interstitial tissue, fibrinoid necrosis of glomeruli, glomerular capillary obstruction and crescents. Granulomas are also found in GPA and EGPA. It is worth mentioning again that, because AAV are pauci-immune vasculitides, immunofluorescence is negative, that meaning there is a paucity or absence of glomerular immune deposits. Nevertheless, there are patients who demonstrate atypical histopathological features, such as interstitial nephritis with vasa recta vasculitis. These patients eventually develop the classical lesions of AAV [9, 11, 12] (**Figure 1**).

## **8. Biomarkers in AAV**

Any substance that can be objectively measured and evaluated as an indicator of normal and pathogenic processes or response to an intervention can be used as a biomarker [13].

Inflammatory markers, such as erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP), are non-specific and, although they can be used in the diagnosis of AAV, when evaluated together with clinical and pathological presentation, they are of no value in the differential diagnosis and assessment of disease activity and relapse in diagnosed patients [14].

On the contrary, research on platelet (PLT) counts, which are an acknowledged inflammatory marker, found elevated PLT counts in patients with active disease, compared to patients in remission, and also elevated PLT counts in AAV patients with active disease, compared to AAV patients with infection, thus highlighting their role as an AAV specific marker of disease activity [15].

## **9. ANCA as biomarkers**

Although ANCA are important in the diagnosis of AAV, there are seronegative patients with clinically and pathologically established disease. Furthermore, because diagnosed patients tend to remain ANCA-positive during clinical remission, the use of ANCA as a marker of disease activity and relapse is also limited. Nevertheless, increased values of ANCA in seropositive patients or emergence in seronegative patients, can be evaluated as a marker of disease relapse [14]. Studies have suggested that increase of ANCA titer should not be taken into consideration in terms of changing treatment decisions, but could be used to select patients requiring closer monitoring [14, 16].

## **10. LAMP-2**

Unlike PR3 and MPO, LAMP-2 is also expressed in glomerular endothelial cells, an important site of inflammatory injury [17]. As mentioned before, anti-LAMP-2 antibodies are believed to be formatted through molecular mimicking of bacterial proteins, proposing the implication of this mechanism in the pathogenesis of disease.

One study indicated that anti-LAMP-2 antibodies are present in 80–90% of untreated patients, including PR3-ANCA negative and MPO-ANCA negative patients, while being undetected in healthy controls. Interestingly, anti-LAMP-2 antibodies become rapidly undetectable after immunosuppressive therapy, thus suggesting a possible role in the diagnosis and monitoring of AAV patients. However, these findings were not replicated by other investigators, meaning that the use of these antibodies as a biomarker of disease activity is rather inappropriate [10, 14, 17].

## 11. Plasminogen

The presence of anti-plasminogen antibodies, in about 18–26% of AAV patients, depending on the study, is strongly correlated with glomerular lesion severity, but only weakly correlated with ESR, renal function and renal histopathology [14].

## 12. Moesin

Moesin, a heparin-binding protein linking actin to the plasma membrane of the cellular cortex, is identified as a possible molecule responsible for the formation of MPO-ANCA, using molecular-mimicking mechanisms, similarly to LAMP-2. Anti-moesin antibodies are found increased in both active AAV disease and remission, but are associated with renal damage, as assessed by correlation to blood urea nitrogen, serum creatinine and proteinuria [14, 18].

## 13. NET

The contribution of NET in the pathogenesis of AAV is already mentioned. Excessive NET formation is observed in both PR3-ANCA and MPO-ANCA positive patients with active AAV compared to healthy individuals, which is interestingly independent of ANCA titers. Moreover, excessive NET formation is presented in hospitalized AAV patients for disease relapse, but not for infection, suggesting a specificity of NET as a marker of autoimmunity, rather than infection [19].

## 14. Leucocytes

Regulatory B cells (Bregs) have been investigated as a potential biomarker of AAV. A research group found CD25<sup>+</sup> B cells to be increased during disease remission, compared to active disease and healthy controls. Another study revealed CD5<sup>+</sup> B cells numerical deficiency in AAV patients, compared to healthy controls. These data, however, are insufficient for the establishment of Bregs as biomarkers in AAV [14, 17].

A study attempted to clarify the role of CD8<sup>+</sup> T cells as a biomarker of AAV. The presence of particular gene expression profiles of CD8<sup>+</sup> T cells were associated with disease relapse, among patients with the same disease activity, inflammatory markers and treatment. If validated, these data could be used to identify patients in need of customized therapeutic regimens [14, 17, 20].

Regulatory T cells (Tregs) have also been studied by researchers. Decreased number and impaired functionality of Tregs was found in patients with active AAV. Furthermore, the proportion of Tregs was found inversely correlated with relapse and positively associated with time of remission. Based on these data, Tregs could be used as a biomarker of therapeutic and prognostic importance [14, 17].

## 15. Monocytes

The role of monocytes in the pathogenesis and tissue damage in AAV has already been discussed. Soluble and cell surface markers of monocyte activation are increased in AAV patients, even during disease remission. Furthermore, monocyte-derived macrophages and giant cells within affected tissues and granulomas may be responsible for maintaining autoimmunity. These data suggest

that monocytes may account for disease relapse, thus be used as a prognostic biomarker of negative outcome [21].

## 16. Inflammatory response

- **Complement:** Plasma levels of C3a, C5a, soluble C5b-9 and Bbare found increased in patients with active disease, compared to patients with disease remission and healthy controls [14, 17]. C5a receptor (C5aR) expression is found lower in renal tissue of patients with active disease [17, 22]. Furthermore, plasma levels of Bb, which is indicative of alternative pathway activation, is associated with serum inflammatory markers and the presence of crescents in renal biopsy. Similarly, urinary levels of Bb are positively correlated with serum creatinine levels, indicative of renal function, and negatively correlated with the percentage of normal glomeruli in renal biopsy [14, 17].
- **Monocyte chemotactic protein-1:** Monocyte chemotactic protein-1 (MCP-1), as declared by its name, affects the monocyte/macrophage migration to the tissues. It is also related to the number of circulating monocytes and T cells. Serum MCP-1 is measured significantly higher in patients with AAV, compared to healthy controls. Interestingly, in AAV patients, MCP-1 is found elevated in those with renal involvement, compared to patients without renal involvement. Moreover, serum MCP-1 levels are correlated with serum creatinine levels and proteinuria severity [23].
- **Calprotectin:** Calprotectin is a heterodimer complex of two calcium-binding proteins, expressed on neutrophils, monocytes and early differentiated macrophages [14, 24]. Serum calprotectin is found increased in patients with active AAV and decreased, but not normalized, during remission, thus implicating subclinical disease [24]. Calprotectin levels are, additionally, elevated in patients who discontinued treatment [24] and in patients who relapsed [9, 19], with the elevation predictive of relapse happening during remission [14]. Correlation between calprotectin expression and renal biopsy indicates higher expression of calprotectin in patients with focal lesions and crescents and lower expression in patients with sclerotic findings. Furthermore, neutrophil and monocyte cell surface calprotectin expression is, also, higher in patients with AAV, compared to healthy individuals [24].
- **Neutrophil gelatinase-associated lipocalin:** Neutrophil gelatinase-associated lipocalin (NGAL) is a protein contained in neutrophil granules and, because of its primary secretion, is considered a marker of neutrophil degranulation. Serum levels of NGAL are higher at initial onset and disease relapse of AAV, compared to disease remission, thus suggesting a role in AAV diagnosis and evaluation of activity. Moreover, they are associated with disease severity, ESR, CPR and ANCA titers [25].
- **Angiopoietin-2:** Angiopoietin-2 (Ang-2), an important regulator of endothelial activation, is also positively associated with AAV severity. However, levels of Ang-2 do not decline after successful therapy, thus are not predictive of response to therapy, and, moreover, levels during remission are not predictive of relapse onset [26].

## 17. Other serum inflammatory proteins

Among many serum inflammatory proteins, such as cytokine, chemokines, soluble receptors, etc., CXCL13 (BCA-1), matrix metalloproteinase-3 (MMP-3) and tissue inhibitor of metalloproteinases-1 (TIMP-1) report the strongest correlation with AAV. Specifically, higher levels of these proteins are found in patients with active disease, compared to healthy individuals, and are also able to distinguish active disease from disease remission. Additionally, lower levels are measured after successful therapy of AAV [14, 27].

## 18. Urinary biomarkers

A study investigated the role of four urinary proteins [ $\alpha$ -1 acid glycoprotein (AGP), kidney injury molecule-1 (KIM-1), MCP-1 and NGAL (with the last two being already mentioned above as serum biomarkers)] as biomarkers of active disease. All four proteins were found increased in the urine of patients during active renal disease, compared to remission, with MCP-1 being the most accurate discriminator between the two [23]. MCP-1 levels were also strongly indicative of poor outcome and disease relapse [14, 17, 28].

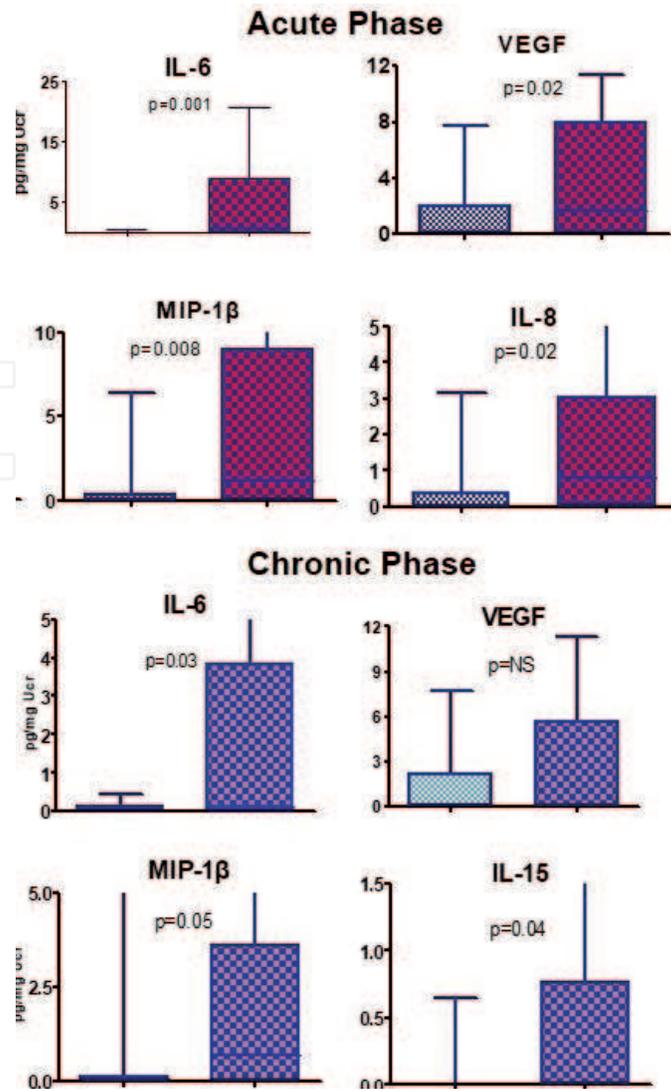
Another research studied the possible use of urinary soluble CD163 (sCD163), secreted by monocytes and macrophages, as a biomarker in small vessel vasculitis (SVV). Glomeruli of patients with SVV contained remarkably higher levels of CD163 RNA, thus presented increased expression of CD163, than those of patients from disease controls (lupus nephritis, diabetic nephropathy, nephrotic syndrome) [29]. In addition, patients with active SSV had higher levels of urinary sCD163, compared to patients in disease remission [14, 29], disease controls and healthy controls [29].

Urinary excretion of angiogenic factors (VEGF, EGF), cytokines with known pro-inflammatory (IL-6, MCP-1, MIP-1b), anti-inflammatory (IL-2, IL-4, IL-15), and pro-fibrotic activity (TGF- $\beta$ , IL-6) have been evaluated as biomarkers in renal

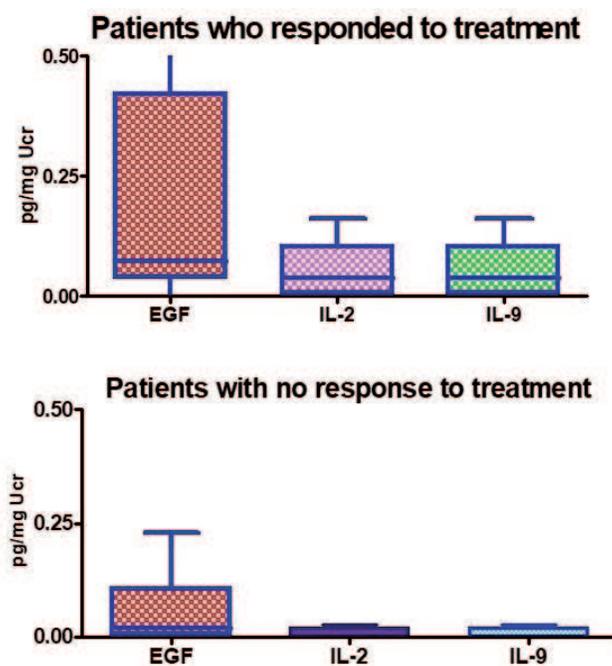
Cytokine (pg/mg Ucr)	RPGN n = 38	Controls n = 10	p
IL-2	0.003 $\pm$ 0.01	0	0.04
IL-4	0.003 $\pm$ 0.006	0.008 $\pm$ 0.001	0.04
IL-6	1.2 $\pm$ 0.03	0.001 $\pm$ 0.001	0.05
IL-8	0.94 $\pm$ 2.8	0.04 $\pm$ 0.09	0.05
IL-9	0.9 $\pm$ 0.0001	0.04 $\pm$ 0.09	0.02
IL-15	0.2 $\pm$ 0.5	0	0.03
TGF- $\beta$ 1	275 $\pm$ 79	0.02 $\pm$ 0.05	0.04
VEGF	4.3 $\pm$ 3.6	0.001 $\pm$ 0.0007	<0.0001
MCP-1	2.5 $\pm$ 0.001	0.1 $\pm$ 0.04	0.01
MIP-1 $\beta$	1.6 $\pm$ 0.001	0.06 $\pm$ 0.05	0.02
EGF	0.15 $\pm$ 0.3	0.14 $\pm$ 0.07	NS

**Table 2.**

*Differences in the urinary excretion between patients with rapidly progressive glomerulonephritis due to vasculitis and controls.*



**Figure 2.**  
Impact of cytokines during the acute and chronic phase of vasculitis.



**Figure 3.**  
Favorable influence of cytokines in renal function outcome.

vasculitis. Most of them were significantly increased compared to controls (**Table 2**). Cytokines with possible impact to histologic findings were TGF- $\beta$ 1, IL-15, MCP-1, MIP-1b and EGF. Several factors, such as IL-6, VEGF, MIP-1b and IL-15 could predict worse outcome of renal function, while others, including EGF, IL-2 and IL-9 were correlated with a favorable outcome (**Figures 2 and 3**). The above findings suggested that these factors may act synergistically or competitively during the progression of the disease [30, 31].

## 19. IgA vasculitis-nephritis

Immunoglobulin A vasculitis-nephritis (IgAV-N), formerly known as Henoch-Schonlein purpura nephritis (HSPN) is the most common vasculitis in childhood, with an annual incidence of 13–20/100,000 children under 17 years of age, but also affects adults and elderly patients with increasing incidence. IgAV is a small vessel vasculitis, usually presents by palpable purpura on the lower legs, arthritis, abdominal pain, and nephritis, while less frequent are manifestations from pulmonary involvement, such as alveolar hemorrhage and neurologic involvement [32–34].

Diagnosis of the IgAV-N is mainly based on the criteria defined by The European League Against Rheumatism (EULAR), Paediatric Rheumatology International Trials Organization (PRINTO) and Paediatric Rheumatology European Society (PRES) (EULAR/PRI NTO/PRES) [35, 36].

Among children with IgAV a proportion of 20–60% will show renal complications, most of them occur at disease onset. Manifestations of renal involvement cover a wide spectrum of symptoms ranging from urinary abnormalities, such as hematuria or/and proteinuria, to rapidly progressive glomerulonephritis and acute kidney disease. Although disease is considered as mild and self-limited, a considerable proportion reaching to 15% will develop chronic kidney disease. The presence of nephritic syndrome, impaired renal function at presentation, increased levels of proteinuria, severe histology and no response to treatment are considered as parameters predicting adverse outcome of renal function [32, 34].

## 20. Renal pathology

Histology of IgAV-N is characterized by mesangial hypercellularity and mesangial deposition of IgA and C3, with or without IgG. Fibrinoid necrosis and crescents are a common finding, while the presence of segmental or global sclerosis, endocapillary hyperplasia, severity of tubulointerstitial fibrosis and inflammatory infiltration may vary between cases (**Figure 1**) [35, 36].

Several classification systems have attempted to organize histological findings and evaluate their significance. The classification proposed by the International Study of Kidney Disease in Children (ISKDC), mainly based on the presence and extent of crescents, is widely used, although lately there have been attempts to apply Oxford classification system in IgAV-N, in the same way as this is used for IgAN classification [35].

According to ISKDC classification, optical microscopy findings are categorized into six histological grades. Grades I-V are based on the extension of crescents, grade VI describes a membranoproliferative type glomerulonephritis. The system was designed to estimate vasculitic lesions and inflammation, therefore it took into account the state of glomeruli only and not tubulointerstitial lesions. This seems to be the main disadvantage of the system, as presence and percentage of crescent

formation merely reflect active inflammation, and their predictive value has been doubted in recent studies, which showed that patients on higher grades may experience spontaneous remission, while those with low grade histologic lesions may develop chronic renal failure [37–40].

The Oxford classification system, available since 2009, has been designed to estimate histology in IgAN, and it was based initially on four morphologic features: mesangial hypercellularity (M), endocapillary proliferation (E), segmental glomerulosclerosis (S) and tubular atrophy/interstitial fibrosis (T), which formed the MEST score [41–43]. More recently, the system was revised to MEST-C score, including the present of crescents, as crescent score (C) [44]. Although patients with IgAV-N were not included in the validation cohort, and therefore, the classification system cannot officially be recommend for patients with this condition, there have been few recent attempts to apply Oxford classification in IgAV-N. The presence of endocapillary proliferation and tubulointerstitial fibrosis were the main histologic findings associated with worse outcome of renal function [44–46].

Renal biopsy is essential for diagnosing IgAV-N, probably guide treatment and predict outcome, but, the procedure cannot be used repeatedly during follow up of the patients. The use of biomarkers is again mandatory to estimate disease outcome. IgAV-N share the same pathogenic pathway with IgAN, mediated by aberrant O-linked glycosylation of IgA1 hinge region, they are considered similar diseases that share common pathophysiologic mechanisms. Based on this fact, researchers tried to evaluate the utility of IgAN biomarkers in the assessment of the clinical course of IgAV-N. It was thus found that several of them could be used in IgAV-N patients as well [47, 48].

## **21. Biomarkers in IgAV-N**

### **21.1 Serum and urine immunoglobins and immune complexes**

Since IgA deposition in various tissues is an important parameter of the disease pathophysiology, several studies have tried to examine immunoglobulin production in IgAV patients. It has been found that IgA and IgE serum concentrations are higher in individuals with IgAV compared to normal controls, although it has not been proven that they can be useful in distinguishing patients with and without nephritis [47]. Moreover, serum Gd-IgA1 and IgA-IgG complexes, as well as urine IgA and IgA-IgG complexes are potential biomarkers for IgAV-N. More specifically, elevated levels of Gd-IgA1 in the blood of IgAV patients have been correlated with the presence of nephritis [47]. It has been proposed that recognition of the under galactosylated IgA1 hinge region by IgA or IgG antibodies induces the production of circulating immune complexes [47, 48]. Indeed, high concentrations of IgA-IgG complexes have been found in the serum of all IgAV-N patients, while in urine, the levels of these complexes are increased only in patients who have developed nephritis [47, 48]. It seems though that deterioration of renal function is not associated with the serum levels of Gd-IgA1 and IgA-IgG complexes. Recently, a French multicenter prospective study showed that urinary IgA concentration can be used as an additional index in order to improve patient risk stratification for poor outcome at disease onset. This is an important finding, since only a small percentage of IgAV patients finally develop severe deterioration of renal function and can benefit from intensive care, monitoring and follow-up and for the time IgAV outcome assessment is based on conventional clinical factors [48].

## 22. Cluster of differentiation (CD) antigens

Concerning CD antigens that could be used as biomarkers, CD89 has been found to be useful in the assessment of IgAV. CD89 is the human myeloid specific IgA Fc receptor. It is expressed on neutrophils, eosinophils, monocytes/macrophages, dendritic cells and Kupffer cells [49, 50]. In IgAN patients, cleavage of the CD89 extracellular domain and release of IgA-soluble CD89 (IgA-sCD89) complexes is caused by the binding of IgA to CD89. Therefore, high levels of circulating IgA-sCD89 complexes are observed in these patients. The complexes are trapped in the mesangium by the transferrin receptor. Their deposition, as well as mesangial activation, is facilitated by transglutaminase 2 (TG2) [48, 51]. IgAV patients demonstrate decreased expression of CD89 at their monocyte and granulocyte cell surface. This finding is combined with increased blood concentration of IgA-sCD89 complexes. Urinary levels of these complexes are more elevated in individuals who develop nephritis [47, 48]. Furthermore, according to the findings of a 2016 multicenter study, urinary CD89 and TG2 concentrations are significantly lower in patients with active IgA vasculitis with nephritis (IgAV-N) compared to individuals whose disease has gone into complete or partial remission. More specifically, urinary CD89 and TG2 levels were found to be positively correlated with each other and negatively correlated with the level of proteinuria. It has been proposed that this decrease is consistent with the reduction in CD89 and TG2 urinary excretion as a result of the mononuclear-cell mediated inflammatory reaction that is induced by IgA-sCD89 deposition in the kidney. During this active phase, large multimolecular complexes containing CD89, TG2, CD71 and IgA1 are stabilized on the mesangial cell surface, thus causing CD89 and TG2 molecules to remain in the renal tissue. Interestingly, there seems to be a stronger negative correlation between proteinuria and urinary CD89 levels in comparison to TG2 levels, thus suggesting that CD89 might decrease earlier in the urine of patients with IgAV-N [51].

CD62L (L-selectin) and CD11b are also found to be upregulated in IgAN patients and are considered to be involved in IgAV pathogenesis. CD62L, is an adhesion molecule observed on the neutrophil surface that mediates the initial adhesion of neutrophils to the endothelium and could consequently be important in the early development of IgAV. CD11b is a predominant  $\beta$ 2 integrin, also expressed on neutrophils. High CD11b and IgA levels possibly promote vascular damage through induction of antibody-dependent cellular toxicity (ADCC) [52].

## 23. Cytokines and other inflammatory factors

Regarding pro-inflammatory cytokines, IgAV patients with or without nephritis present high serum concentrations of IL-1b, IL-6 and IL-8 compared with normal controls, with the increase in IL-6 and IL-8 levels being very significant in individuals with renal involvement. Urine IL-6, IL-8 and IL-10 concentrations appear to be more elevated in IgAV-N patients, in the same way as in patients with IgAN [53, 54]. These cytokines possibly play a role in mesangial cell activation, proliferation, crescent formation and glomerulosclerosis. Additionally, increase in IL-6 blood concentration seems to be an index of the acute phase of IgAV [47, 48]. Tumor necrosis factor (TNF) blood levels, that have also been associated with the development of interstitial fibrosis and tubular atrophy regardless of renal function, are higher in IgAV patients who present with nephritis [47]. Furthermore, several other inflammatory parameters, including C-reactive protein (CRP), Serum Amyloid A (SAA) and Neutrophil-Lymphocyte ratio (NLR), also seem to be upregulated in IgAV patients in comparison

to healthy individuals [55]. Of all these inflammatory indexes, NLR seems to present the strongest diagnostic value concerning the development of extracutaneous manifestations in adult IgAV (gastrointestinal and/or renal). The severity of the systemic involvement has been found to be associated with high NLR before treatment [56]. There is also a possible connection between high SAA levels also has a possible connection with the presence of gastrointestinal manifestations [52].

#### **24. Neutrophil gelatinase-associated lipocalin (NGAL)**

NGAL protein, a member of the lipocalin superfamily initially found in activated neutrophils, is produced in various cell types including renal tubules. It is a factor promoting kidney cellular proliferation and differentiation that is significantly upregulated in response to epithelial injury, thus serving as an index of kidney damage [47, 57]. It can possibly predict the appearance of acute renal impairment and the acute deterioration of unstable nephropathies. Furthermore, it may also be implicated in the pathophysiology of some chronic kidney disease (CKD) conditions, such as polycystic kidney disease and glomerulonephritis, while its levels are directly associated with the degree of renal damage [25]. In IgAV, NGAL concentrations seem to be high in both patients with and without nephritis, while its levels in urine, found more elevated in patients with nephritis, are useful in distinguishing them from individuals without kidney impairment [47, 48].

#### **25. Soluble transferrin receptor (sTfR)**

sTfR consists of a single polypeptide chain and has been found to be upregulated in IgAV-N and IgAN patients, perhaps as a result of IgA1 polymer-mediated induction. Its overexpression is thought to be associated with the disease severity. Normally, it cannot cross the glomerular membrane because of its molecular size. However, when non-selective glomerular proteinuria is present, it is possible that the molecule can passively cross the membrane and then be detected in the urine. Interestingly, it has been found that in IgAV-N and IgAN patients the sTfR/creatinine ratio is higher than the ratio measured in healthy individuals or patients with other glomerulopathies. Therefore, it can possibly be used as a non-invasive tool to distinguish those two diseases from other pathologies that cause proteinuria. It has also been proposed that sTfR can additionally be further evaluated as a potential prognostic and activity marker for IgAV-N and IgAN [58].

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