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# **Immune Complex Small-Vessel Vasculitis with Kidney Involvement**

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Additional information is available at the end of the chapter

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## **Abstract**

The term immune complex small-vessel vasculitis encompasses anti-glomerular basement membrane disease, cryoglobulinemic vasculitis, IgA vasculitis and hypocomplementemic urticarial vasculitis. These disorders affect predominantly small vessels, and renal involvement is frequent. In this chapter, we shall discuss thoroughly anti-GBM disease, cryoglobulinemic and IgA vasculitis with respect to the criteria required for the establishment of diagnosis, the specific characteristics of renal histopathology, the clinical picture, prognosis, and therapeutic management.

**Keywords:** vasculitides, immune complex, immunoglobulin A (IgA) vasculitis, cryoglobulinemia, anti-glomerular basement membrane disease

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## **1. Introduction**

Immune complex small-vessel vasculitis (SVV) refers to vasculitis, which is characterized by the deposition of immunoglobulin and/or complement on the vessel wall. It affects predominantly small vessels, and renal involvement is common. According to the Chapel Hill consensus conference nomenclature of vasculitides [1], disorders included in the group of immune complex SVV are anti-glomerular basement membrane (anti-GBM) disease, cryoglobulinemic vasculitis (CV), IgA vasculitis (IgAV), and hypocomplementemic urticarial vasculitis.

Anti-GBM disease is a vasculitis, which affects glomerular and/or pulmonary capillaries. It is caused by autoantibodies against the basement membrane. Renal involvement typically causes acute or rapidly progressive glomerulonephritis.

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Cryoglobulinemic vasculitis is characterized by the presence of cryoglobulins, which are immunoglobulins or immune complexes that precipitate in the cold and dissolve upon rewarming. Common sites of deposition are the skin, the joints, the peripheral nerves, and the kidneys. The main etiological factors are chronic viral infections, particularly autoimmune disorders and B-cell lymphoproliferative disorders.

IgA vasculitis is a systemic vasculitis characterized by the deposition of IgA1-dominant immune complexes. It affects predominantly the skin, the joints, and the gastrointestinal tract. Renal involvement with glomerular hematuria and mild proteinuria may be observed.

## 2. Anti-glomerular basement membrane disease

### 2.1. Introduction

Anti-glomerular basement membrane (anti-GBM) disease, also known as Goodpasture's syndrome, is an immune complex small-vessel vasculitis first identified by Dr. Ernest Goodpasture in 1919 [1, 2]. It is characterized by autoantibodies directed against the alpha-3 chain of type IV collagen of the glomerular and alveolar basement membrane. In 1951, Krakower and Greenspon discovered the antigenic properties of the glomerular basement membrane (GBM) [3], whereas, in 1967 Lerner, Glasscock and Dixon found that autoantibodies eluted from kidneys with acute glomerulonephritis produce the disease in animal models [4]. Patients typically present with glomerulonephritis alone or in association with alveolar hemorrhage that can be life threatening.

### 2.2. Epidemiology

Anti-GBM disease is rare. The annual incidence is estimated to be about 0.5–1 cases per million inhabitants in Europe [5, 6]. The White race is affected more commonly than the Black race. Age distribution is bimodal, with a peak incidence in the third and seventh decades. A slight male predominance is recorded in the younger age group and a female predominance in the older [7].

### 2.3. Pathogenesis

Exposure to an exogenous stimulus leads to autoantibody production and circulation of antibodies, which are directed against an antigen of the glomerular basement membrane (GBM). This antigen has been identified as a particular region of the NC1 domain of the  $\alpha 3$  chain of type IV collagen.

Type IV Collagen is the main constituent of most basement membranes and is encoded by six genes (COL4A1-A6) each for six distinct  $\alpha$  chains ( $\alpha 1(IV)$  to  $\alpha 6(IV)$ ), which are selectively expressed in membranes of different organs through embryonic development. This selectivity explains the specific lung and renal involvement in Goodpasture's disease, since  $\alpha 3IV$  collagen is expressed primarily in the GBM of the glomeruli and the pulmonary alveoli [8].

Each  $\alpha$  chain consists of three domains: a short 7C domain at the N-terminal, a long collagenous domain in the middle, and a noncollagenous domain (NC1) at the C-terminal. During development, the six  $\alpha$  chains form three sets of triple helical molecules called promoters:

$\alpha1\alpha1\alpha2(\text{IV})$ ,  $\alpha3\alpha4\alpha5(\text{IV})$  and  $\alpha5\alpha5\alpha6(\text{IV})$ . These promoters subsequently form three-dimensional organized networks consisting of only three sets of hexamers:  $\alpha1\alpha1\alpha2(\text{IV})$ - $\alpha1\alpha1\alpha2(\text{IV})$ ,  $\alpha3\alpha4\alpha5(\text{IV})$ - $\alpha3\alpha4\alpha5(\text{IV})$  and  $\alpha1\alpha1\alpha2(\text{IV})$ - $\alpha5\alpha5\alpha6(\text{IV})$ .

The autoantigen in anti-GBM is the  $\alpha3\text{NC1}$  domain which is located in the network of  $\alpha3\alpha4\alpha5(\text{IV})$ - $\alpha3\alpha4\alpha5(\text{IV})$  hexamers. Two major antigenic epitopes  $E_A$  and  $E_B$  in the  $\alpha3\text{NC1}$  domain of the hexamer have been identified as targets for the autoantibodies [9, 10].

These epitopes are hidden and are only accessible to the autoantibodies after dissociation of the hexamer as a result of oxidative stress. This could explain the initiation of anti-GBM after an extrinsic insulting event as, for example, after a respiratory tract infection or after urinary tract obstruction or lithotripsy [11].

Anti-GBM autoantibodies are most often of the IgG class (usually IgG1 or 2 subclass) and rarely IgA. The pathogenicity of the autoantibodies has been demonstrated by induction of the disease after passive transfer of circulating or tissue autoantibodies in animal models. The high and rapid binding affinity to alveolar and glomerular capillary basement membranes is consistent with the fulminant disease course though variable pathogenicity according to autoantibody titers, different IgG subclass and epitope specificity has also been reported [12, 13].

Besides autoantibody production, there is growing evidence for the contribution of autoreactive T cells to the pathogenesis of anti-GBM. In some instances, autoantibodies alone are not sufficient to induce disease. Furthermore, T cells with reactivity against the  $\alpha3\text{NC1}$  antigen have been isolated from patients with the disease. In animal models, it has been demonstrated that CD4<sup>+</sup> T cells specific for the Col4 $\alpha3\text{NC1}$  epitope can target the autoantigen and induce glomerular injury in the absence of autoantibodies, suggesting a direct causative role of T cells [9, 14].

### 2.3.1. Genetic susceptibility

The susceptibility to the development of the disease is genetically determined and restricted by the major histocompatibility complex (MHC): HLA-DR15 and HLA-DR4 haplotypes increase susceptibility while HLA-DR1 and HLA-DR7 seem to be protective [8, 15].

Moreover, anti-GBM autoantibodies occur after kidney transplantation in patients with hereditary nephritis (X-linked Alport's syndrome). This can be explained by the genetically defective organization of the  $\alpha$  chains of type IV collagen. The genetic defect in hereditary nephritis results in the absence of  $\alpha3\alpha4\alpha5(\text{IV})$ - $\alpha3\alpha4\alpha5(\text{IV})$  hexamers and the presence of networks comprising only of  $\alpha1\alpha1\alpha2(\text{IV})$ - $\alpha1\alpha1\alpha2(\text{IV})$  hexamers. After transplantation, the normal collagen IV, which consists of all the three sets of hexamers, may be recognized as a previously "unseen" antigen with subsequent autoantibody production. However, this autoantibody recognizes a different antigenic epitope and rarely leads to the initiation of overt nephritis [3].

## 2.4. Clinical presentation

### 2.4.1. Glomerulonephritis

The commonest disorder is that of the rapidly progressive glomerulonephritis (RPGN). Acute renal injury and oliguria-anuria may evolve within days, whereas slower progression of the renal impairment occurs in a minority of patients. Features of RPGN occur in 80–90% of

patients. Macroscopic hematuria may present; however, microscopic hematuria of glomerular origin and red cell casts are the most prominent features. Proteinuria is usually modest. Kidney disease is the only manifestation in 20–40% of patients [16, 17].

#### 2.4.2. Lung hemorrhage

Pulmonary and renal involvement occurs in 60–80% of the patients [16]. Cough, dyspnea, hemoptysis, chest pain, hypoxia, iron deficiency and anemia are the presenting manifestations. Pulmonary involvement may precede renal disease by weeks to months [18].

#### 2.4.3. Systemic manifestations

Systemic symptoms such as fatigue, arthralgias and fever are infrequent and suggest the coexistence of antineutrophil cytoplasm antibodies (ANCA) vasculitis. Sufficient data regarding the incidence of these symptoms do not exist.

### 2.5. Renal pathology

Light microscopy reveals diffuse proliferative glomerulonephritis with rupture of the GBM, areas of fibrinoid necrosis and crescent formation in severe disease. Crescents involve approximately 75% of the glomeruli and typically show the same features of activity and chronicity in contrast to other causes of crescentic glomerulonephritis. Tubular injury is proportionate to the degree of crescents. In mild disease, segmental proliferative injury with infiltrating neutrophils and monocytes is observed.

Immunofluorescence demonstrates linear deposition of immunoglobulin G along the GBM. IgA or IgM deposition is rare. Deposition of C3 in a granular pattern is found in approximately 75% of the biopsies. Electron microscopy examination reveals GBM fractures, necrosis and crescents [19].

### 2.6. Diagnosis

Diagnosis is based on the detection of circulating anti-GBM antibodies in conjunction with the identification of anti-GBM nephritis by kidney biopsy. Anti-GBM antibodies can be detected by indirect immunofluorescence or by direct enzyme-linked immunosorbent assay (ELISA), which has a high sensitivity (95%) and specificity (97%). Positive results are confirmed by Western blot. Indirect immunofluorescence is rarely performed; it has a false-negative rate of 40% and requires an experienced pathologist [20]. ANCA antibodies, mainly with specificity for myeloperoxidase, are found in 10–38% of patients with anti-GBM disease. These patients are characterized as “double positive” [21].

Pulmonary involvement is investigated by chest radiograph and CT scan, broncho-alveolar lavage and pulmonary function testing. Bilateral, patchy consolidations that spare the apices are found on the chest film. A computed tomography (CT) scan reveals widespread areas of ground glass morphology which are not pathognomonic of the disease. Broncho-alveolar lavage shows the characteristic hemosiderin-laden macrophages.

## 2.7. Therapeutic management

Given the rarity of the disease, the therapeutic management is based on a small number of studies, mainly retrospective ones. The treatment of choice in anti-GBM disease is immunosuppression consisting of corticosteroids and cyclophosphamide in combination with plasma exchange [22].

### 2.7.1. Immunosuppressive therapy

When the diagnosis is highly suspected, immediate administration of high dose pulse corticosteroids is recommended [22]. Methylprednisolone 500–1000 mg/day for 3 consecutive days, followed by prednisone 1 mg/kg/day orally is the regimen most commonly used. Once the diagnosis is established, oral cyclophosphamide (CYC) at a dose of 2 mg/kg/day must be instituted. Although oral and intravenous CYC have not been compared in this patient population, the latter is used only in unreliable patients or those with severe renal injury to reduce bladder toxicity. Timing of immunosuppression withdrawal is not well established, although maintenance treatment is not recommended [22]. Cyclophosphamide is continued for approximately 3 months and steroids for 6 months. Some experts suggest a shorter duration of therapy (2–3 months) in the case of disease remission and negative antibody titers that persist. In patients with active disease at 3–4 months, immunosuppression comprising steroids and azathioprine may be prolonged up to 6–9 months.

Plasma exchange is generally performed after the diagnosis is confirmed. However, in patients with severe pulmonary hemorrhage, plasmapheresis may begin immediately. Among 17 patients with anti-GBM-induced renal disease, 9 were randomized to prednisone and CYC, whereas 8 also received plasmapheresis. At the end of the therapy, two patients in the plasmapheresis group became dialysis dependent compared to the six patients in the control group [23]. These results were confirmed by a large retrospective study of 221 patients from China [24]. Patient and renal survival rates were better among those who were treated with plasmapheresis in addition to standard immunosuppression. The usual prescription is daily or alternate-day exchanges for 2–3 weeks.

According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, this intense therapeutic regimen applies to all patients with anti-GBM disease. However, dialysis-dependent patients at presentation with approximately 100% crescents on kidney biopsy seem to have a low probability of renal recovery [22, 24]. Therefore, plasma exchange is not advised unless concurrent lung hemorrhage occurs, since the potential complications may exceed the benefits of therapy. Our approach is to perform plasmapheresis regardless of the crescent ratio in:

- Young patients with less comorbidities
- Patients with recent onset of the disease
- Patients with concurrent clinical and laboratory manifestations of ANCA vasculitis

Rituximab has been used as first- or second-line therapy in a limited number of patients with anti-GBM disease, with variable effect on renal function [25, 26].

## 2.8. Prognosis

In the past, mortality rates of patients with anti-GBM disease due to pulmonary hemorrhage or renal failure were approximately 100%. The combination of aggressive immunosuppression with plasmapheresis has dramatically changed patient survival. Levy et al. have conducted a retrospective study of 71 patients with anti-GBM disease followed for up to 25 years [27]. The therapy consisted of plasmapheresis, high dose oral prednisone and CYC. Serum creatinine (sCr) at presentation seemed to be associated with patient and renal outcome. If the initial sCr was <5.7 mg/dl, the 1-year patient and renal survival rates were 100 and 95%, respectively. At 5 years, the patient and renal survival approached 94%. In the case of severe renal impairment not requiring dialysis at presentation with sCr >5.7 mg/dl, the patient and renal survival rates were 83 and 82%, respectively, at 1 year, and 80 and 50% at 5 years, respectively. Dialysis dependence at presentation correlated to reduced patient survival, 65 and 44% at 1 and 5 years, respectively. Renal recovery was rare in this group and occurred in 8% of the patients at the first year and in 13% of them at 5 years. The proportion of glomerular crescents strongly correlated to the degree of renal impairment. The need for immediate dialysis initiation and 100% crescents on kidney biopsy resulted in irreversible kidney damage despite aggressive treatment.

An interesting study by Yang et al. showed that high levels of anti-GBM antibodies against epitopes EA and EB occur in patients with severe renal damage and correlate to poor prognosis [28].

Patients with positive anti-GBM and ANCA antibodies have a poor renal outcome despite adequate treatment [17]. Relapses are more common in this population, in whom the vasculitis is incriminated [29].

## 2.9. Renal transplantation

Renal transplantation in patients with anti-GBM disease is delayed until clinical and laboratory quiescence. It is our practice to delay kidney transplantation for at least 6 months after immunosuppression discontinuation. Biopsies of renal allografts show linear deposition of IgG, without symptomatic disease in many patients. Disease recurrence posttransplantation is reported to be 2.7% [30].

De novo anti-GBM disease may develop in 3% of patients with Alport syndrome after renal transplantation [30].

Mutations in the *COL4A5* gene located on the X chromosome are the most frequent as it has already been mentioned, although autosomal recessive and dominant disease have been found. An alloimmune response against the antigens of the kidney allograft leads to the development of anti-GBM antibodies. In this patient group, a second kidney transplantation is associated with a more aggressive disease [31]. Recent guidelines advise the implementation of genetic testing for the evaluation of the risk of de novo disease posttransplantation [32].

## 2.10. Summary

Anti-GBM disease is an organ-specific autoimmune disorder characterized by the production of autoantibodies against the basement membrane of glomeruli and alveoli. Dominant manifestations are crescentic glomerulonephritis and pulmonary hemorrhage that may be life-threatening. The severity of renal impairment at presentation as well as the need for dialysis

and the percent of glomerular crescents are factors prognostic of renal and patient survival. Therefore, early and timely diagnosis is of major importance. Treatment is based on the removal of pathogenetic antibodies by plasma exchange and the prevention of antibody production by a short course of immunosuppressants, namely cyclophosphamide and steroids.

### **3. Cryoglobulinemic vasculitis**

#### **3.1. Introduction**

Cryoglobulinemic vasculitis (CV) is a small-vessel vasculitis that affects mainly the skin, the joints, the peripheral nerves and the kidneys. Medium-sized vessels may also be involved. Cryoglobulins are immunoglobulin or immune complexes that precipitate in vitro at temperatures below 37°C and dissolve upon rewarming [33].

Brouet et al. in 1974 [33] developed a classification system based on the immunoglobulin composition of cryoglobulins:

Type I cryoglobulins are single monoclonal immunoglobulins most often of the IgG or IgM isotype, found in lymphoproliferative disorders, usually Waldenstrom's macroglobulinemia, multiple myeloma and monoclonal gammopathy of unknown significance (MGUS). Type II cryoglobulins are composed of monoclonal IgM with rheumatoid factor (RF) activity in association with polyclonal immunoglobulins (usually IgG). The commonest cause is hepatitis C virus (HCV) infection. Other causes include infection from hepatitis B virus (HBV) or human immunodeficiency virus (HIV), autoimmune diseases and lymphoproliferative disorders. Type III cryoglobulins consist of polyclonal IgM with RF activity and polyclonal IgG. They are linked to autoimmune disorders and infections, mainly due to HCV. Types II and III are associated with mixed cryoglobulinemia (MC) syndrome. In the case of no identifiable cause, type II or III cryoglobulinemia is characterized as essential.

#### **3.2. Epidemiology**

The prevalence of CV has been reported to be 1:100,000 individuals [34]. The disease usually occurs between the ages of 45 and 65, with a female predominance (2–3/1). Racial preference has not been recorded. Type I cryoglobulinemia accounts for 10–15% of cryoglobulinemia cases [35]. This type of cryoglobulinemia is most frequently attributed to malignancies of the hematopoietic cells. According to the French nationwide CryoVas survey, among 64 patients with type I CV, 56% suffered from a hematologic malignancy, while MGUS was present in 44% of them [36].

Mixed cryoglobulinemia is reported to be present in approximately 75% of cryoglobulinemias. HCV is the main underlying disorder in 80–90% of individuals with MC [37].

#### **3.3. Pathogenesis of kidney injury in cryoglobulinemic vasculitis**

In chronic viral or bacterial infections (hepatitis C, hepatitis B, endocarditis), defective handling of antigenic peptides whether due to high antigenic load or abnormally functioning immune regulatory mechanisms might contribute to a state of persistent antigenemia. The result is the stimulation of an immune response with subsequent release of antigen-directed antibodies and

the formation of immune complexes. Impaired antigen clearance due to complement deficiency or to a defect in the reticuloendothelial system may result in the deposition of immune complexes in the glomeruli either by passive trapping of circulating immune complexes or by in situ formation [38]. Monocytes isolated from patients with active cryoglobulinemic glomerulonephritis display delayed processing of cryoglobulins and reduced ability of catabolism, thus favoring tissue deposition [39]. The mesangium and subendothelial space are the sites of immune complex localization.

Subsequent complement activation generates the chemotactic factor C5 $\alpha$  which promotes the accumulation of circulating neutrophil and monocytes-macrophages [38]. The association between C5 activation and neutrophil accumulation has been shown in a murine model of cryoglobulin-induced immune complex glomerulonephritis [40]. Moreover, the formation of the terminal membrane attack complex (C5b-9) activates inflammatory cells of the glomerulus to act similarly [40–42]. Leucocytes release acute inflammatory mediators (oxidants, proteases) that damage the capillary wall leading to proteinuria and the decrease of the glomerular filtration rate (GFR). On the other hand, glomerular cells release chemokines and growth factors that mediate direct damage of the glomerulus through matrix accumulation and *mesangial* cell proliferation [6]. The magnitude and severity of glomerular injury seem to be associated to monocyte chemotactic protein-1 (MCP-1) expression [43].

Healthy mice that have been injected with a monoclonal antibody exhibiting both cryoglobulin and rheumatoid factor properties develop cutaneous and glomerular lesions. Moreover, the loss of the rheumatoid factor activity may protect from the development of skin but not glomerular vasculitis, indicating that cryoglobulins alone are sufficient to induce nephritic damage [44].

Pathogenetic mechanisms involved in HCV-associated cryoglobulinemic glomerulonephritis have been more extensively studied. It seems that a nonenveloped core protein, HCV E2, exhibits nephritogenic properties and binds to the complement-fixing antibody IgG3 [45–47]. The complex that is formatted activates the classic complement pathway through C1q and stimulates the production of B-cell clones through binding to B-cell receptors (i.e., CD81 molecule) [47–49]. Monoclonal B lymphocyte expansion seems to be associated to the development of nephritis [50]. Subsequently, monoclonal IgM $\kappa$  and polyclonal IgG antibodies with rheumatoid factor activity are elicited. Immune complexes consisting of IgG, IgM (identical to those of the cryoprecipitates), viral proteins and complement deposit in the mesangium and subendothelial space causing inflammation and mesangial expansion [46, 49, 51]. It is noteworthy that the autoimmune response may persist even after complete suppression of viremia [52]. Finally, the increased expression of vascular cell adhesion molecule 1 (VCAM-1) has been associated to severe vasculitic lesions in patients with HCV and mixed cryoglobulinemia, a finding that has not been confirmed in patients with kidney involvement. Cryoglobulins act as anti-endothelial antibodies and induce platelet aggregation [45, 53].

### 3.4. Clinical presentation

#### 3.4.1. Extra-renal manifestations

The “Meltzer’s triad” consisting of weakness, purpura and arthralgia is reported in 80% of the patients early in the course of the disease [54]. Palpable purpura of the lower extremities occurs in 70–90% of patients, but Raynaud’s phenomenon, acrocyanosis and necrotic

ulcers have been described. Arthralgias usually symmetric, involving mainly the large joints, develop in 40–72% of the cases. Sensory or sensory motor polyneuropathy presents with painful paresthesias and motor deficit of the lower limbs in 58–70% of the affected individuals. A minority of the patients may present with mononeuritis multiplex [36, 54–56]. However, hepatic, gastrointestinal, pulmonary, cardiovascular and central nervous system involvement, as well as sicca symptoms, have also been reported [57]. The CryoVas study showed that type I CV seems to be characterized by a higher incidence of severe cutaneous lesions compared to mixed cryoglobulinemia syndrome (50 vs. 30%), whereas severe skin involvement is even more infrequent in HCV-related mixed cryoglobulinemia (5%) [36, 54, 55, 58].

### 3.4.2. Renal manifestations

Renal damage is present at the time of diagnosis in approximately 20–35% of the patients, whereas 10–35% of them will eventually develop renal disease at some point during the course of the disease [36, 53–55, 59]. Renal manifestations vary. Microscopic hematuria and mild proteinuria occur in nearly 41% of the patients. Nephrotic or nephritic syndrome is less frequent accounting for 22 and 14% of the cases, respectively. The incidence of hypertension is approximately 65%. Other clinical features include acute renal injury or chronic kidney disease [36, 54, 59]. The main pathological pattern, in over 80% of affected individuals, is that of type-I membranoproliferative glomerulonephritis (MPGN) with subendothelial deposits. It seems to be strongly related to type II IgMκ mixed cryoglobulinemia [60].

### 3.5. Renal pathology

Membranoproliferative glomerulonephritis (MPGN) is the characteristic histopathological pattern observed in mixed cryoglobulinemia. The lesions may be histologically identical to MPGN type I.

Light microscopy reveals varying degrees of glomerular hypercellularity because of the influx of leucocytes. It is often global and diffuse with a predominance of monocytes/macrophages, whereas neutrophils are observed during the acute phase. Monocyte infiltration of the interstitium may also be seen. Mesangial and endocapillary cell proliferation leads to enlargement and lobular accentuation of the glomerular tuft which is typical of the disease. Subendothelial, Periodic acid–Schiff (PAS)-positive eosinophilic deposits are present. Intraluminal thrombi consisting of precipitated cryoglobulins are not a rare finding. However, complete lumen obstruction is uncommon. The severity of clinical manifestations seems to be related to the extent of endocapillary proliferation and the abundance of glomerular deposits. Mesangial matrix expansion and accumulation and the interposition of mesangial cells, monocytes and endothelial cells lead to the appearance of double-contoured glomerular basement membrane (GBM) which is recognized by PAS and silver staining. Extracapillary proliferation is a rare finding. Vasculitic lesions of small- and middle-sized renal arteries are described in approximately 30% of the cases. They comprise vascular PAS-positive deposits, endoluminal accumulation of leucocytes and fibrinoid necrotizing vasculitis in more advanced stages of the disease.

Direct immunofluorescence examination shows granular glomerular and luminal deposits that stain positive for both IgM and IgG in type II, III cryoglobulinemia. Subendothelial and

mesangial deposits may also contain C3 and less frequently components of the classical complement pathway (C1q, C4).

Electron microscopy reveals the deposits that can be either amorphous or organized into curved and annular fibrils with a tubular appearance in cross-section and a diameter of 20–35 nm [60, 61].

### 3.6. Diagnosis and laboratory findings

Criteria for the classification of CV have been proposed [62]. Three parameters (questionnaire, clinical, laboratory findings) have been taken into account.

1. Patients are classified as having CV, if at least two of the three items are positive.
2. The patient must be positive for serum cryoglobulins in at least two determinations at 12 weeks' interval or less.
3. Questionnaire item: at least two out of the following: (1) Do you remember one or more episodes of small red spots on your skin, particularly involving the lower limbs? (2) Have you ever had red spots on your lower extremities, which leave a brownish color after their disappearance? (3) Has a doctor ever told you that you have viral hepatitis?
4. Clinical item: at least three out of the following four (present or past) (1) Constitutional symptoms: fatigue, low-grade fever, or fever  $>38.8^{\circ}\text{C}$  of no other cause, fibromyalgia. (2) Articular involvement, namely arthralgias, arthritis. (3) Vascular involvement: purpura, skin ulcers, necrotizing vasculitis, hyperviscosity syndrome, Raynaud's phenomenon. (4) Neurologic involvement of the peripheral or central nervous system.
5. Laboratory item: at least two out of the following three (present) (1) Low serum C4. (2) Positive serum rheumatoid factor. (3) Serum M component present.

The diagnosis of CV with kidney involvement is based on clinical manifestations in the presence of cryoglobulinemia and biopsy-proven MPGN type I.

In type I cryoglobulinemia, precipitation at  $1-4^{\circ}\text{C}$  occurs within hours, whereas in the mixed types precipitation may be delayed. Therefore, samples should be stored for 7 days. When the test is negative in the context of high suspicion, it should be repeated after assuring the correct technique for sampling and handling of the blood. In the case of cryoglobulinemia, the cryocrit, which is the centrifuged volume of the precipitate as a percentage of the original serum volume should be measured if possible. Cryoglobulin concentration  $> 20-50$  mcg/ml or a cryocrit  $>0.5-1\%$  is considered positive. Cryocrit levels do not correlate with response to the treatment. Furthermore, electrophoresis and immunofixation are performed to determine the exact type of cryoglobulins.

Other surrogate markers indicative of this disorder are RF, acute phase reactants (erythrocyte sedimentation rate and C-reactive protein) and complement components (C1q, C4, CH50). Serological studies for viral infections, urinalysis with examination of the sediment, assessment of renal function and proteinuria should always be included in the evaluation of patients with mixed cryoglobulinemia.

### 3.7. Prognosis

Cryoglobulinemic vasculitis is associated with significant morbidity and mortality. In HCV-related mixed CV, 1-year and 10-year survival rate is estimated to be 96 and 63%, respectively. Factors prognostic of a poor outcome are severe liver fibrosis, central nervous system and kidney and/or cardiac involvement [58]. In noninfectious mixed CV, age > 65 years, pulmonary and gastrointestinal involvement and renal impairment with GFR < 60 ml/min seem to be independently linked to death [56]. Main causes of death are infections and cardiovascular disease [56, 58]. In type I CV, 1- and 10-year survival rate is higher, 97 and 87%, respectively [36].

### 3.8. Therapeutic management

The therapeutic management of glomerulonephritis in CV depends on the underlying etiological disorder and the severity of the disease.

#### 3.8.1. Therapeutic management of mixed cryoglobulinemic vasculitis

The therapeutic regimen comprises immunosuppression in selected cases as well as treatment of the underlying disorder.

##### 3.8.1.1. Immunosuppressive therapy

The main indication for immunosuppressive therapy in patients with renal involvement is glomerulonephritis associated with a rapidly progressive pattern and/or nephrotic syndrome. In the case of severe, organ-threatening disease, immunosuppression is instituted immediately, even prior to disease-specific therapy. This does not apply to patients with HIV or HBV infection who should always receive effective antiviral treatment in order to eradicate viremia before immunosuppression use.

Immunosuppression consists of Rituximab and/or corticosteroids. Data supporting the use of cyclophosphamide are limited, whereas plasmapheresis should also be considered in severe disease [63].

##### 3.8.1.2. Rituximab

Cryoglobulinemic vasculitis, especially in the case of HCV infection, is characterized by clonal B-cell expansion, production of IgM and IgG antibodies and immune complex deposition. Rituximab is a chimeric IgG1 $\kappa$  monoclonal antibody targeted against CD20, which is an antigen expressed on the B-cell surface from the early pre-B-cell stage to the activated mature cell stage. The rationale behind the use of rituximab in this patient population is that B-cell depletion may decrease the production of pathogenic cryoglobulins. Moreover, there is evidence that rituximab therapy is not associated with HCV replication, although there are data of HCV viremia without clinical manifestations after Rituximab infusion [64, 65].

In a single-center randomized controlled trial (RCT) [64], 24 patients with HCV-associated mixed cryoglobulinemia were randomized either to receive rituximab (375 mg/m<sup>2</sup>/week

for 4 weeks) or to continue their current immunosuppressive medications (control group). Antivirals had failed to induce clinical remission in all the patients. At the study entry, 33% of the patients had active glomerulonephritis (four patients in each group). After 6 months, remission defined by a Birmingham Vasculitis Activity Score of zero, was achieved in significantly more patients in the rituximab group (83 vs. 8.3%,  $p < 0.001$ ). Remission sustained for a median of 7 months. In addition, during the 6-month period, patients with nephritis in the control group experienced a decline in renal function whereas rituximab-treated patients had a stable or improved estimated glomerular filtration rate (GFR). However, only three patients in the control group received immunosuppressants, namely low dose corticosteroids (mean dose of 10 mg prednisone daily). On the other hand, of the 12 patients in the intervention group, 6 also received glucocorticoids (mean dose of 26 mg prednisone daily), 1 received cyclophosphamide and 2 were also treated with plasmapheresis. Clinical or laboratory findings indicative of hepatitis were not recorded in either group.

De Vita et al. [66] evaluated the use of Rituximab in 59 patients with CV and severe manifestations (skin ulcers, active glomerulonephritis or peripheral neuropathy). The majority of the patients (93%) had HCV-associated disease, but antiviral therapy failed to achieve remission or was contraindicated. Enrolled patients were randomized either to rituximab therapy (1000 mg at baseline and at day 14) or to conventional treatments (either glucocorticoids, azathioprine or cyclophosphamide, or plasmapheresis). At 12 months, success of the initial treatment was achieved in significantly more patients in the rituximab arm (64.3 vs. 3.5%,  $p < 0.0001$ ). Among seven patients with glomerulonephritis treated with rituximab, complete or partial response was recorded in four of them after 6 months of therapy. Of eight patients with renal involvement under conventional therapy who had a treatment failure, six had a favorable response to rituximab.

The abovementioned studies indicate that rituximab may be a safe and effective treatment in patients with mixed cryoglobulinemia and severe manifestations, especially when HCV antiviral therapy fails to induce remission.

Data regarding the use of rituximab in non-HCV infectious cryoglobulinemia syndrome are scarce. Prompt initiation of antiviral therapy is mandatory in the case of HBV- or HIV-infected patients, since rituximab has been associated with virus reactivation in untreated patient populations [67, 68]. In our opinion, this monoclonal antibody should not be used in patients with HIV infection who are not receiving antiretroviral agents and/or have not achieved a virological response. In the case of HBV infection, rituximab should be administered in patients with suppressed viremia under appropriate antiviral therapy. In these patients, the use of immunosuppression alone is associated with a poor response to therapy, whereas remission was reached with antiviral medications. Especially in refractory disease, the combination of anti-infectious agents with immunosuppressants leads to a favorable response [69].

Finally, limited data exist regarding the use of Rituximab in noninfectious CV. The CryoVas survey analyzed data of 242 patients with mixed CV [55]. Causative disorders were connective tissue diseases, essential disease and hematologic malignancies. The therapeutic management was evaluated in 209 patients. Corticosteroid monotherapy or steroids in conjunction with an alkylating agent resulted in lower response rates compared to rituximab with corticosteroids. First-line treatment with rituximab and glucocorticoids allowed for reductions in steroid dosing and was more efficacious in achieving complete renal and clinical response. However, this combination was related to a ninefold higher rate of infections

compared to the other regimens. Therefore, although rituximab seems to be a valuable and effective treatment for noninfectious CV, cautiousness regarding the incidence of infections is warranted.

#### 3.8.1.3. Corticosteroids

The use of corticosteroids for the treatment of HCV-associated CV is controversial as there are no randomized controlled trials evaluating their safety and efficacy in this disease. In patients with severe renal involvement, we and other centers administer a short course of high-dose pulse corticosteroids (500–750 mg for 3 consecutive days) followed by oral prednisone 1 mg/kg/day for 2–4 weeks and a rapid tapering to a maintenance dose of 5–10 mg/day, depending on the clinical response. The abovementioned randomized controlled studies [64, 67] included different steroid regimens applied by different investigators in all patients with severe disease and renal injury. Therefore, we cannot conclude regarding potential benefits and the safety profile.

In a small cohort study, five patients with HCV-related cryoglobulinemic glomerulonephritis received rituximab without steroids. Although they all experienced remission of the disease, relapse occurred in four of them from month 5 to month 12 of follow-up [70].

Given the lack of convincing evidence regarding the use of steroids in mixed CV, we believe that high-dose corticosteroids should be used in the management of renal disease. Rapid tapering and concomitant administration of antiinfectious agents are of major importance, since steroid use carries the risk of enhancing viral reactivation.

#### 3.8.1.4. Cyclophosphamide

The benefits and risks of cyclophosphamide (CYC) use in patients with mixed CV cannot be evaluated from the current literature. Cyclophosphamide is not routinely used in patients with HCV cryoglobulinemic vasculitis, since it may increase viral replication or aggravate liver injury. In clinical practice, it may be considered when rituximab therapy fails or when it is unavailable or poorly tolerated. According to the European League Against Rheumatism (EULAR), noninfectious CV can be treated with immunosuppressants including cyclophosphamide [71]. When used, CYC is combined with plasma exchange and it is administered orally at a dose of 2 mg/kg/day for 3 months [67].

#### 3.8.1.5. Plasma exchange

Case reports or small case series have shown that after plasma exchange response occurs in 70–80% of patients with mixed CV. It is performed in cases of organ and/or life-threatening diseases [72], such as:

- Symptomatic hyperviscosity syndrome
- Rapidly progressive glomerulonephritis, MPGN with renal impairment
- Alveolar hemorrhage or acute gastrointestinal vasculitis

It is advised to warm the albumin solution, since acute kidney injury due to cryoglobulin precipitation has been reported [72].

Plasma exchange is always used in combination with immunosuppressive therapy in order to remove circulating cryoglobulins but also to prevent further formation.

#### *3.8.1.6. Treatment of the underlying disorder*

##### *3.8.1.6.1. Treatment of hepatitis C or hepatitis B infection*

During the past decades, patients with HCV-related cryoglobulinemic vasculitis have been treated with interferon-containing regimens. The introduction of direct acting antiviral agents (DAAs) has radically changed the treatment of patients with HCV infection. These drugs target nonstructural (NS) viral proteins and inhibit HCV replication [73]. Although the efficacy of DAAs in HCV-associated cryoglobulinemic vasculitis has not been confirmed, they are more potent regimens with a better safety profile and a shorter duration of therapy. Taking into account that DAAs are first-line agents in HCV treatment according to current guidelines [74], we believe that they should be offered to patients with CV and hepatitis C. In a prospective study, Gragnani et al. [75] evaluated the efficacy, safety and virological response of different combinations of DAAs in 44 patients with HCV-related cryoglobulinemic vasculitis. Concurrent immunosuppression was given to two patients. Kidney involvement was recorded in four cases. Sustained virologic response and complete clinical remission was achieved in all patients at week 24. Renal function as well as proteinuria ameliorated substantially in patients with renal disease. Adverse events were mild and did not lead to drug discontinuation.

The optimal timing for initiation of antivirals is not clear. It has been recommended to delay antiviral therapy for 1–4 months [63, 71]. The purpose of this approach is to avoid immune-mediated events attributed to interferon regimens. On the other hand, immunosuppression may improve renal function, enhancing the use of DAAs. The proper timing of DAAs' introduction needs to be determined.

Patients with hepatitis B-associated CV and nephritis are treated with entecavir which is associated with less nephrotoxicity and lower rates of resistance. Antiviral therapy not only prevents from HBV replication but it may also induce disease remission [76]. Ideally, it should precede immunosuppressive therapy, which is not recommended in active hepatitis.

#### *3.8.2. Therapeutic management of type I cryoglobulinemic vasculitis*

The treatment of type I CV is that of the causative hematological disorder. Rituximab, bortezomib, CYC, lenalidomide and thalidomide have been used with satisfactory results.

More specifically, a bortezomib-based regimen is used in patients with deteriorated renal function, whereas lenalidomide is preferred in cases of neurologic involvement [77]. Rituximab infusion, which has been hypothesized to induce B-cell apoptosis and cryoglobulin release in these patients, seems to be associated with a rapid disease flare [34]. Therefore, rituximab is suggested for use after inducing an initial remission with other treatment regimens [78].

### 3.9. Summary

- Cryoglobulinemic vasculitis is a small-vessel vasculitis which mainly affects the skin, the joints, the peripheral nerves and the kidneys.
- Etiological factors include chronic viral infections particularly HCV, autoimmune disorders and B-cell lymphoproliferative disorders.
- Renal involvement may be manifested as mild proteinuria with microscopic hematuria, nephrotic or nephritic syndrome and varying degrees of renal impairment. Hypertension is common.
- The predominant histological pattern is MPGN type I. Recent studies have identified prognostic factors that need to be evaluated in clinical trials.
- Treatment strategy is individualized according to the underlying disorder and the severity of the disease. The therapeutic regimen comprises immunosuppression mainly Rituximab in selected cases as well as the treatment of the underlying disorder.

## 4. IgA vasculitis (Henoch-Schonlein purpura)

### 4.1. Historical background

IgA vasculitis (IgAV), until recently known as “Henoch-Schonlein purpura,” has actually first been described by Heberden in 1806. Later on, in 1837, Schoenlein first described the association of purpuric rash with arthritis, and his student, Henoch, in 1874, added the renal and gastrointestinal involvement to the entity [79–81].

### 4.2. Nomenclature/organ involvement

According to the 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, the term “Henoch-Schoenlein Purpura” was replaced by “IgA vasculitis” on the basis of the pathophysiological mechanism which is characterized by circulation and tissue deposition of abnormal IgA [1].

According to the new classification, IgAV is an immune complex small-vessel vasculitis (SVV). IgAV may present as a single-organ disease, for example, as isolated cutaneous vasculitis or as renal-limited IgAV which is indistinguishable from IgA nephropathy (IgAN), or as a systemic disease with multiorgan involvement. Patients with initial single-organ involvement may subsequently develop systemic manifestations.

The “classic triad” of organ involvement in IgAV comprises skin involvement manifested as palpable purpura mostly of the lower extremities, arthralgia or arthritis and gastrointestinal manifestations including abdominal pain and occult or overt GI bleeding. Though

not included in the classic triad, renal involvement is frequent, occurring in 45–50% of adult patients with IgAV, and is the most important determinant of outcome [82].

### 4.3. Epidemiology

IgAV is the most common vasculitis in childhood with an annual incidence of 13–20 cases per 100,000 children, affecting most commonly children in the age group of 4–7 years, with a predominance in boys. In children, there is a peak incidence in autumn and winter and the clinical presentation is often preceded by a respiratory infection, suggesting a possible implication of viruses and bacteria as a trigger for the disease [83].

Of these pathogens, the most studied is group-A  $\beta$  hemolytic streptococcus, found in 20–50% of children with IgAV, either as positive throat cultures or by serology as elevated antistreptolysin titers [84].

In adults, IgAV occurs far less frequently and has an annual incidence of 0.8–1.8 per 10,000. There is no seasonal variation in incidence. There is a male predominance with a male to female ratio of 5:1 [82].

IgAV is described worldwide and in all ethnic groups, but its annual incidence, as examined in a worldwide study by Garner-Medwin et al. including children of all origins, has been reported to be lower in the Black race. The ethnic variation of its renal limited counterpart, IgAN, with increased frequency in Japan and East-Asia, less prevalence in Europe and Australia and the lowest prevalence in Africa, has not been detected in IgAV [83, 85, 86].

### 4.4. Pathophysiology

In recent years, an association between adulthood IgAV and malignancy, as with other autoimmune diseases, has been reported. In a retrospective study including 200 patients with ANCA-associated vasculitis (AASV) and 129 patients with IgAV, the relative risk of malignancy was increased at 6.02 in AASV and 5.25 in IgAV patients, respectively, compared to an age-matched control group of the general population [87].

In the largest cohort of adult patients with IgAV with long-term follow-up, Pillebout et al. report a mortality rate of 26% at 15 years. Malignancy was the leading cause of death in 30% of patients. Almost all of them were solid tumors, most of them being lung and GI carcinomas [88].

Besides solid tumors, IgAV has also been described in the setting of hematologic malignancies as lymphoma and IgA myeloma but also as secondary to infections, vaccines and medications [89–92].

Though there is no proven causal relationship, it seems that, irrespective of the trigger, extrinsic factors, in the presence of a specific genetic background, lead to initiation of the pathogenetic mechanism in IgAV [93].

As for IgAN, the key pathogenetic mechanism includes aberrant glycosylation of the IgA1 isotype of IgA. According to the “multihit hypothesis,” this galactose-deficient IgA1

induces autoantibody production toward the neoantigen. These antiglycan antibodies bind to the abnormal IgA1 leading to complement activation via the alternate or the lectin pathway and to the subsequent formation of immune complexes, which deposit in the affected organs [94].

#### **4.5. Differential diagnosis and diagnostic criteria**

The typical presentation of IgAV includes palpable purpuric rash of the lower extremities, gastro-intestinal bleeding and/or abdominal pain, arthralgia or arthritis and in case of renal involvement, microscopic hematuria and subnephrotic proteinuria with or without renal function impairment.

In cases of more atypical presentation, especially in adulthood, other diseases with similar clinical features must be excluded. Immune thrombocytopenic purpura (ITP) and thrombotic microangiopathies may present with a hemorrhagic rash but can easily be excluded by the absence of thrombocytopenia or hemolysis [95].

Cryoglobulinemic, urticarial and hypersensitivity vasculitides may also present with skin lesions, arthritis and renal involvement. In this setting, a skin biopsy, when performed adequately involving active lesions, may confirm the diagnosis of IgAV. The typical histologic features are those of leukocytoclastic vasculitis with fibrinoid necrosis and perivascular infiltration of leukocytes and monocytes. On immunofluorescence, there is IgA deposition along with C3 and fibrin [96].

In the minority of cases with predominance of GI symptoms that may precede the other manifestations, causes of surgical abdomen must be ruled out.

There are no distinctive laboratory parameters for the diagnosis of IgAV. Serum levels of IgA may be increased in about 50% of patients and rarely complement components C3, and C4 might be decreased [97].

A series of diagnostic criteria including clinical and laboratory parameters and histologic features of skin biopsy for the diagnosis of IgAV have been proposed. The first attempt was in 1990 by the American College of Rheumatology (ACR) which were revised and extended first by Michel in 1992, later on by Helander, de Castro and Gibson in 1995, coming to the more recent EULAR/PRINTO/PRESS Criteria in 2010. The extended description and comparison of the sensitivity and specificity of these criteria have been published by Yang et al. in 2014. Most data for the diagnostic criteria have been derived from studies in pediatric populations [98].

#### **4.6. Clinical manifestations**

##### *4.6.1. Purpura*

The typical presentation is palpable purpura, often symmetric, predominantly affecting the lower extremities, at pressure sites, but it can extend to the whole body. In children, rash most often resolves spontaneously after 2–3 weeks and may relapse in about one-third of patients. In adults, in about 30% of patients, it may present with more severe forms including blisters, hemorrhagic and necrotic lesions [99].

#### 4.6.2. *Joint involvement*

The second most common manifestation affecting about 75% of patients is joint pain, most often of the knees and ankles, impairing walking. Overt arthritis is less common [97].

#### 4.6.3. *Gastrointestinal involvement*

GI involvement occurs in about 50–75% of patients with IgAV. The presenting symptom is most often colicky abdominal pain which occurs typically soon, in about 2–10 days after the onset of rash. In a minority of patients (10–20%), abdominal symptoms may precede the onset of purpura; in this setting diagnosis may be difficult. Occult GI bleeding is common in IgAV, while gross bleeding with melanotic or hemorrhagic stools occurs in less than 10% of patients. The most frequently involved sites of the GI tract are the duodenum and the small intestine. Esophagogastroduodenoscopy (EGD) is the preferred diagnostic procedure in patients with suspected IgAV. The typical findings are irregular ulcers and petechiae in the duodenum. Small intestine radiography and colonoscopy may also be necessary. Severe GI complications as intussusception and perforation occur in 1–5% of patients [100].

#### 4.6.4. *Renal involvement*

Renal involvement occurs in about 25–54% of children and in 45–85% of adults with IgAV. In adults, it is a rare entity, which accounts for 0.6–2% of all biopsy-proven glomerulonephritides. In adults, there is not only increased frequency of renal involvement but also a worse outcome compared to children. Reported progression rates to ESRD in children range from 5 to 10%, while in adults they reach 30% and more [101].

#### 4.6.5. *Clinical presentation*

The most common clinical manifestation is microscopic hematuria with subnephrotic proteinuria in 80% of patients. In contrast to IgAN, macroscopic hematuria is less common in IgAV. Arterial hypertension and impaired renal function are present in about 30% of adults at disease onset. About 10–20% of adult patients present with nephritic or nephrotic syndrome [82].

Renal biopsy is performed more often in adults than in children, in whom the disease is generally mild and resolves spontaneously. In adulthood, the necessity of a renal biopsy is implicated by the rarity of the disease, the differential diagnosis between other small-vessel vasculitides as AASV or cryoglobulinemic vasculitis or in the setting of rapid deterioration of renal function or severe renal impairment at presentation.

### 4.7. **Histology**

Histological lesions of IgAV are indistinguishable from IgAN with the diagnostic hallmark being prominent IgA deposition in the mesangium by immunofluorescence staining. Concurrent deposition of C3 and less commonly IgG and IgM may also be present. On light microscopy, the most common finding is mesangial hypercellularity and mesangial matrix

expansion. Electron microscopy examination reveals electron-dense material corresponding to the immune-complex deposition, predominantly in the mesangium. Histologic features in patients with IgAV as with IgAN have enormous variations in terms of activity and chronicity, the former including endocapillary proliferation, fibrinoid necrosis and cellular crescents and the latter comprising focal and/or segmental glomerulosclerosis, adhesions to Bowman's capsule, interstitial fibrosis and tubular atrophy, respectively [102].

In IgAN, according to the Oxford Classification, the histologic features were found to be prognostic indicators of renal outcome long term: mesangial hypercellularity, endocapillary proliferation, segmental glomerulosclerosis or adhesion and tubular atrophy and interstitial fibrosis (MEST score) [103].

In a retrospective cohort of 250 adult patients with IgAV, Pillebout et al. analyzed renal involvement and renal outcome parameters. In this study, a different classification scheme in order to determine histologic features as prognostic indicators was introduced for IgAV. This classification divides IgAV into five classes based on the severity of active as endo- and extra-capillary proliferation (classes 3a and 3b) and chronic lesions as fibrotic kidney with global sclerosis in more than 50% of glomeruli (class V), respectively [88].

This histological approach is preferable compared to the Oxford Classification adopted from IgAN, since patients with IgAV have worse initial presentation and possibly outcome compared to IgAN, while in the Oxford study, patients with severe renal impairment (eGFR <30 ml/min) and rapidly progressive glomerulonephritis (RPGN) were excluded [103].

#### 4.8. Outcome

The most relevant studies are summarized in **Table 1**. Almost all studies are retrospective and include children and adults.

A *multicenter* observational study from Italy included 95 adults and 57 children with a mean follow-up of 5 years. The authors report similar outcomes in terms of remission rates (32.5% in adults vs. 31.5% in children) and survival rates at 5 years (85 and 95%, respectively) [104]. On the other hand, a retrospective study from Spain including 116 children and 46 adults with IgAV nephritis, with a relatively short-term follow-up of 15 months, reported more frequent and severe renal involvement in adults, with high complete recovery rates at 89% in the adult and 94% in the children group, respectively [105].

Among adults, the reported rates of ESRD range from 8–16% at 5–15 years [88, 104, 106]. Proteinuria >1 g/day [88, 104, 106], impaired renal function at presentation [88, 104] and arterial hypertension [104] have been identified as negative prognostic indicators.

#### 4.9. Therapy of renal manifestations

Currently, most of the evidence for the therapy of IgAV nephritis comes from retrospective cohorts including children and adults. According to the KDIGO Guidelines of 2012, "IgAV nephritis in adults should be treated the same as in children" (weak evidence, level of recommendation 2D) [22].

Study	Number of patients	Follow-up (years)	CKD	ESRD	Death	Recovery	Prognostic indicators
Retrospective Multicenter Italy; Coppo et al. [104]	95 adults 57 children	5	This endpoint was not included in the study	16% 7%	This endpoint was not included in the study	32% 31%	↓GFR; Proteinuria >1 g/day; Arterial hypertension
Retrospective Spain; Blanco et al. [105]	116 children 46 adults	1.8	This endpoint was not included in the study	This endpoint was not included in the study	This endpoint was not included in the study	94% 89%	This endpoint was not included in the study
Retrospective Finland; Rauta et al. [106]	38 adults	6	19%	8%	This endpoint was not included in the study	This endpoint was not included in the study	Proteinuria >1 g/day
Retrospective Multicenter France; Pillebout et al. [88]	250 adults	15	38%	11%	26%	This endpoint was not included in the study	Proteinuria >1 g/day; Initial GFR < 50 ml/min

**Table 1.** Outcome of patients with IgA vasculitis.

On the other hand, almost all studies have shown more frequent and more severe renal involvement in adult IgAV nephritis with worse prognosis and outcome; therefore, it is indeed a weak suggestion to treat a disease with a different clinical picture and outcome the same as in a dissimilar patient population as children, who often have an indolent self-limiting nephritis course [88, 104–106].

The only RCT investigating treatment of IgAV nephritis in adults was a 12-month, prospective, open-label trial, the CESAR study. This study included 54 adult patients with severe, proliferative IgAV nephritis excluding those with RPGN. Patients were randomized to receive either steroid monotherapy or steroids with cyclophosphamide. The study showed that there was no additional benefit in renal outcome in the steroid and cyclophosphamide group. However, one must consider that the study was underpowered, since the number of patients was relatively low and follow-up time short [107].

With regard to the KDIGO Guidelines for the therapy of IgAV nephritis [22], as mentioned earlier, the suggestion is to treat the disease the same as in children while recommendations in children refer to the recommendations for IgAN. Taking into consideration that it is difficult to perform RCTs in adults in a rare entity as IgAV and that it is even more difficult to

extrapolate data from children into adults, the most reasonable approach is to treat renal involvement in adult IgAV based on the recommendations for adult IgAN.

Since IgAN is probably the glomerulonephritis with the broader spectrum of clinical presentations and histologic features of active and chronic lesions, therapeutic benefit must outweigh long-term toxicity, especially in a disease with chronic course and often irreversible damage at presentation.

A very pragmatic approach for the treatment of IgAN, that can be applied to IgAV nephritis, since histological features and central pathogenetic mechanisms are identical, has been published by Floege and Eitner in 2011 [108].

IgAN patients can be divided into four clinical categories and therapeutic interventions must be tailored based on these entities. Mild renal involvement.

The first patient group the so-called “silent majority” involves all patients in whom the disease is diagnosed incidentally, who present with isolated microscopic hematuria and who in fact even do not fulfill strict criteria for performing a renal biopsy. Those patients only need long-term follow-up for up to 10 years, which is indeed difficult to achieve in otherwise healthy individuals.

Moderate renal involvement.

The second category comprises the “typical IgAN patient” with micro- and macroscopic hematuria, subnephrotic proteinuria, presence or absence of arterial hypertension and preserved renal function at diagnosis. These patients should be treated with general supportive measures and if proteinuria persists above 1 g/day, they should receive a 6-month course of high-dose steroid monotherapy. This approach has shown benefit in terms of preserving renal function while mycophenolate acid has not proven efficacy, at least in Caucasian populations, and combination of steroids with other immunosuppressive agents has not shown additional benefits. In the stop-IgAN trial, addition of immunosuppression to optimized supportive treatment in patients of this category did not show a beneficial effect after a follow-up of 3 years [109].

#### *4.9.1. Severe renal involvement*

##### *4.9.1.1. Severely impaired renal function*

The third category is those patients with severely impaired renal function. The “point of no return” is defined as a creatinine level above 2.5–3.0 mg/dl or an eGFR <30 ml/min. In this patient group, optimizing supportive treatment is mandatory while immunosuppression has no indication and may be even harmful.

##### *4.9.1.2. Rapid deterioration of renal function or nephrotic syndrome*

The fourth group includes rare manifestations as rapid deterioration of renal function or nephrotic syndrome. In the case of *rapidly increased creatinine*, a repeat biopsy should be performed within 5–10 days in order to differentiate between RPGN and acute tubular injury (ATI) due to tubular obliteration by red cell casts [110].

In the case of RPGN, according to KDIGO Guidelines, treatment with steroids and cyclophosphamide as for ANCA-associated vasculitis is suggested (level 2D of recommendation) [111, 112].

In the rare cases of overt nephrotic syndrome, therapy as for minimal change disease (MCD) is indicated [113].

#### 4.10. Therapy of systemic manifestations

Corticosteroids are ineffective in shortening the course or the severity of skin lesions as well as in preventing relapses of purpura. The alkaloid drug colchicine at low doses of 1 mg/day, the antibacterial drug Dapsone and the leukotriene receptor antagonist Montelukast have been used in a small series of patients including predominantly children, with satisfactory results but with limited efficacy in terms of preventing relapses [114–116].

For gastrointestinal and joint involvement, steroids are effective and are considered first-line treatment as monotherapy [117].

#### 4.11. Summary

- IgAV in adults represents a rare entity which should always be included in the differential diagnosis of a patient presenting with nephritic features and skin rash.
- The disease differs from that in children; in adults, it has been associated with solid tumors whereas in children it is often triggered by viral or bacterial infections. In adults there is no seasonal clustering and the male predominance exists, but to a lesser degree. Most importantly, children have a more indolent, self-limiting disease course, while in adults, clinical presentation and outcomes are worse.
- Renal involvement is more frequent in adults with more severe manifestations and worse disease course which progresses to CKD/ESRD in about 30% of patients. Similarly, to IgAN and other glomerulonephritides, indicators of poor prognosis include persistent proteinuria, impaired renal function and hypertension at diagnosis. The central pathogenetic mechanism and the renal histologic features are identical to IgAN, strongly suggesting that IgAN may represent a single-organ variant of systemic IgAV. Therapeutic recommendations for IgAV are extrapolated from studies in children and, more correctly, from IgAN.
- Though our understanding of IgAV has improved over the last few years, several questions about the pathogenetic mechanisms, the genetic predisposition, the determinants of outcome and the optimal therapeutic approach still remain unanswered.

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