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Chapter 2

Pauci-Immune Vasculitides with Kidney Involvement

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Abstract

The clinical entity of pauci-immune vasculitis encompasses a group of diseases that may involve any organ system of the body and may be fatal if left untreated. This chapter will review these diseases, with a special interest in the clinical setting of kidney involvement. Small vessel vasculitides associated with the presence of antineutrophil cytoplasmic autoantibodies in the circulation will be the main part, since the vast majority of patients with histopathological proof of pauci-immune vasculitis are positive for these antibodies. Pauci-immune glomerulonephritis often manifests with rapidly deteriorating kidney function, while it may be accompanied by systemic necrotizing small vessel vasculitis such as microscopic polyangiitis, granulomatosis with polyangiitis, or eosinophilic granulomatosis with polyangiitis. Importantly, antineutrophil cytoplasmic autoantibody specificity has been shown to be associated with distinct clinical syndromes and different prognostic profiles among patients with pauci-immune vasculitis allowing easier recognition of the disease and long-term prognosis. Each of the clinical phenotypes will be described thoroughly with respect to the criteria required for establishment of diagnosis, the specific characteristics of renal and extrarenal histopathology, the clinical picture, the therapeutic management, and prognosis in short and long terms.

Keywords: pauci-immune, vasculitis, kidney involvement, rapidly progressive glomerulonephritis

1. Introduction

The principal characteristic of pauci-immune vasculitides is the paucity of staining for immunoglobulins in immunofluorescence, while they may occur as a renal-limited disease or as a component of systemic disease, i.e., necrotizing small vessel vasculitis [1, 2]. They affect

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small- and medium-sized vessels, and they represent the most common cause of crescentic glomerulonephritis, i.e., glomerulonephritis with 50% or more glomeruli being involved with crescents. The systemic vasculitides that may be accompanied by pauci-immune crescentic glomerulonephritis include three major clinical phenotypes: microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA) [2]. An extremely big proportion (85–90%) of the patients with active untreated pauci-immune crescentic glomerulonephritis and vasculitis are positive for antineutrophil cytoplasmic antibodies (ANCA) [1], and therefore, the clinical entity is called ANCA-associated vasculitis. Distinct clinical syndromes and disease profiles have been associated with the type of ANCA. The classification of these diseases has been standardized by the Chapel Hill vasculitis nomenclature consensus conference in 1994 and revised in 2012. According to the current classification [3, 4] system for small vessel vasculitides, diagnostic definitions of ANCA-associated vasculitides include EGPA, which is characterized by the presence of asthma and eosinophilia, and necrotizing granulomatous inflammation is present [5], MPA is characterized by systemic necrotizing small vessel vasculitis with no evidence of granulomatous inflammation or asthma [5] and finally GPA if there is histopathological proof of necrotizing granulomatous inflammation or a clinical equivalent of it in any tissue. Moreover, patients with GPA are usually positive for C-ANCA (PR3-ANCA), patients with MPA are slightly more often positive for P-ANCA (MPO-ANCA), and patients with EGPA and renal-limited ANCA small vessel vasculitis have predominantly P-ANCA (MPO-ANCA) [1]. In some patients with pauci-immune vasculitis, conventional serologic assays fail to detect ANCA, although they present with the classic clinical and pathological characteristics of the disease. In this regard, recent advances in the field have shown that MPO-ANCA may react against a sole linear sequence in this group of patients [6].

This chapter will focus in pauci-immune vasculitides with kidney involvement, including the description of histopathological characteristics of renal and extrarenal lesions, epidemiology, pathogenesis, spectrum of clinical manifestations, definitions and diagnostic criteria of treatment response, and long-term outcomes. In addition, the current therapeutic options and prognostic factors resulting from recent advances in the understanding of correlations between laboratory and serological and clinical parameters will be reviewed.

2. Epidemiology

The incidence of pauci-immune glomerulonephritis has been shown to be higher in older patients, while distribution between genders appears equal [7–9]. In the United States specifically, it has been estimated in 3.1 cases/million/year, with the disease being significantly more frequent in Caucasians, males, and individuals older than 65 years, while 95% of cases were found ANCA positive at diagnosis [7, 10]. In Europe, the incidence has been reported is 1–2 cases in 100,000 [9, 11], with an increasing trend in recent years up to 2000 [12]. A potential explanation may be the increased awareness of these diseases among physicians and also the easier recognition of them after the introduction of ANCA testing. However, since the incidence has been shown relatively unchanged since the early 2000s, it is most probable that

the increased physician awareness, following the introduction of ANCA testing in routine clinical practice, is the most possible reason [13]. Additionally, the incidence of GPA is higher than that of MPA in northern Europe, while MPA is predominant among cases of ANCA-associated vasculitis in southern Europe [13–15].

Likewise, the prevalence of ANCA-associated small vessel vasculitis has been estimated in 46–184 cases/million [13], with the rate increasing during the last two decades. Patient survival has been improved significantly during this period, as the treatment options are more effective and physicians are aware of the disease.

3. Genetic background

Genetic predisposition appears to play a critical role in ANCA vasculitis, as shown from several reports. A study in a multiethnic cohort of patients from the University of North Carolina at Chapel Hill (USA) showed that GPA is quite infrequent among African Americans [16] with the HLA-DRB1*15 allele being a risk factor for PR3-ANCA disease in this population [16]. It is probable that there is a variation of the HLA-DRB1*15 allele worldwide, which is also recognized in the variation of clinical phenotypes of the disease across different geographical areas. Furthermore, the overall incidence rate of ANCA disease was similar between Japan and Europe; GPA and PR3-ANCA vasculitis were shown to be much less common in Japan [13].

4. ANCA role in pathogenesis

ANCA are antibodies which are directed against proteins in the cytoplasmic granules of neutrophils and the lysosomes of monocytes. They were first reported by Dr. D. Davies in 1982 [17] and were subsequently correlated with Wegener's granulomatosis and microscopic polyangiitis [18, 19]. However, in 1988, it was shown that most of the patients with pauci-immune crescentic glomerulonephritis have ANCA in their circulation, irrespective of the coexistence or not of systemic vasculitis [8]. ANCA have been distinguished on the basis of indirect immunofluorescence microscopy; cytoplasmic, C-ANCA, or perinuclear, P-ANCA, depending on the given pattern, and by enzyme immunoassay; and anti-myeloperoxidase (MPO-ANCA) and anti-proteinase 3 (PR3-ANCA) depending on the antigen protein. More than 95% of cytoplasmic ANCA are PR3-ANCA, and more than 95% of perinuclear ANCA are MPO-ANCA. ANCA glomerulonephritis occurs as a renal-limited disease or as a component of systemic necrotizing small vessel vasculitis [8, 19, 20].

After the discovery of ANCA, great effort has been made in understanding the etiology and pathogenesis of these diseases in order to discover new therapies. A pathogenic role of ANCA has been demonstrated by clinical observations and experimental studies, i.e., in vitro studies, which reveal that both PR3 and MPO-ANCA IgG activate neutrophils that then release mediators of acute inflammation [21–24]. Accordingly, it has been found that neutrophils activated by ANCA IgG can kill cultured endothelial cells in some occasions while activation of

neutrophils by ANCA causes integrin and cytokine receptor-mediated adherence to cultured endothelial cells and transmigration across the endothelial layer [1, 25] and conformational changes in β integrins, enhancing ligand binding. Furthermore, unregulated adhesion molecules in glomerular lesions, coming from kidney biopsy specimens of patients with ANCA-associated vasculitis, support the interaction of ANCA-activated neutrophils with vessels [26].

However, the most significant evidence that ANCA are involved in the pathogenesis of these diseases are provided by in vivo studies and specifically by a mouse model in which passive transfer of anti-MPO IgG (MPO-ANCA) or anti-MPO lymphocytes resulted in induction of glomerulonephritis. Xiao et al. developed a model in which intravenous administration of anti-MPO IgG into either immunocompetent mice, or Rag2−/− mice that have no functioning T or B cells, causes pauci-immune crescentic glomerulonephritis and small vessel vasculitis, remarkably similar to human disease. Within a period of 6 days after the injection, all mice developed glomerulonephritis identical with the human one, while some of them developed manifestations of systemic vasculitis, with leukocytoclastic angiitis, necrotizing arteritis, lung capillaritis, and necrotizing granulomatosis inflammation [1, 27–30]. Likewise, severe crescentic glomerulonephritis with systemic vasculitis can be caused by passive transfer of splenocytes from MPO−/− mice that have been immunized with murine MPO. The renal injury in this model is exacerbated by stimulation with LPS [29] and appears dependent on an intact alternative complement pathway and the presence of neutrophils [31]. Another model produced focal segmental pauci-immune glomerulonephritis and focal pulmonary capillaritis in rats by immunization with human MPO, which induced anti-MPO antibodies that cross react with human and rat MPO [32].

Importantly, there are patients who carry a clear clinical and histopathological diagnosis of pauci-immune necrotizing and crescentic glomerulonephritis and vasculitis, in whom negative tests for ANCA are coming out repetitively. This might lead to significant delays in establishing the correct diagnosis and initiating appropriate immunosuppressive treatment. Exploring this issue, a multicenter study recently reported the development of a novel assay to identify specific target epitopes for ANCA [6], a methodology, which led to the detection of MPO-ANCA in patients with ANCA-negative disease that reacted against a sole linear sequence. Autoantibodies against this specific epitope had certain pathogenic properties, as demonstrated by their capacity to activate neutrophils in vitro and to induce nephritis in mice. Interestingly, the researchers detected a fragment of ceruloplasmin in serum, which was eliminated in purified IgG, allowing detection of ANCA subsequently. Besides, patients with ANCA-negative small vessel vasculitis were found to have a restricted autoantibody response against the linear epitope on MPO (aa 447–459), which is the same one that was found to be associated with active disease in the MPO-ANCA-positive patients group and declined upon clinical remission [6]. The authors concluded that that epitope specificity defines pathogenicity [6].

5. Vasculitic manifestations and ANCA specificity

The antigen against which ANCA is directed, i.e., ANCA specificity, has been shown to be strongly associated with the clinical manifestations of the disease, including the affected organ systems and the histopathological findings, in patients with pauci-immune vasculitis. In this

regard, patients with renal-limited disease, or any form of vasculitis without any radiological or histological proof of granulomas, have been shown more likely to have MPO-ANCA, while those with necrotizing granulomatous inflammation were shown to have a higher probability to have PR3-ANCA. This was captured in a study of 523 patients with biopsy-proven ANCA small vessel vasculitis, where the vast majority of patients with renal-limited disease had MPO-ANCA (81%), while almost all patients with bone destruction or saddle nose deformity had PR3-ANCA (94%) [33]. The relationship between PR3- or MPO-ANCA and the anatomic site of the vasculitic manifestation and/or the presence of granulomatous inflammation has been shown remarkable. When vasculitis is expanding from the renal parenchyma to the gastrointestinal or respiratory tract, MPO-ANCA is found less frequent, while PR3-ANCA constantly increases. In patients with histological proof of granuloma at any site, 79% were shown to have PR3-ANCA, and 21% were shown to have MPO-ANCA. Therefore, MPO- or PR3-ANCA are associated with clinically distinct vasculitic syndromes, a principle which is proven critical for the classification of ANCA small vessel vasculitis and in clinical practice. Importantly, this relationship has been confirmed by a genome-wide association study, which showed that the pathogenesis of ANCA small vessel vasculitis has a substantial genetic component, with clear genetic distinctions greatly associated with ANCA specificity [34].

6. Diagnosis of pauci-immune glomerulonephritis

Clinical or pathologic evidence of renal disease is seen in approximately 90% of patients with MPA, 80% of patients with GPA and 45% of patients with EGPA. Pauci-immune crescentic glomerulonephritis is typically associated with ANCA, since 80–90% of pauci-immune crescentic glomerulonephritis occurs in ANCA-positive patients [1, 2, 20, 35]. The clinical presentation of patients with pauci-immune glomerulonephritis includes a range of disease activity starting from asymptomatic hematuria to rapidly progressive glomerulonephritis. In most cases however, clinical presentation is characterized by an elevated serum creatinine in combination with active urine sediment, i.e., demonstrating dysmorphic erythrocyturia with or without red blood cell casts and various degrees of proteinuria [36]. Rapidly progressing glomerulonephritis is characterized by reduced glomerular filtration rate occurring in a few days or weeks which cannot be attributed to other causes of acute kidney injury. A kidney biopsy in such occasion reveals, as said earlier, fibrinoid necrosis along with crescent formation in more than 50% of the glomeruli [1]. Yet, a significant proportion of patients present with acute renal failure requiring dialysis at the time of disease diagnosis.

7. Extrarenal manifestations

Constitutional symptoms often precede or come with the actual onset of the disease and include low-grade fever, fatigue, weight loss, myalgias, and arthralgias [5, 37]. The vast majority of patients (94%) when asked reported a prodromal “flu-like syndrome” before the overt vasculitic syndrome [40]. Beyond this there is a wide range of extrarenal manifestations

of vasculitis including involvement of any site of the body, such as the upper airways, the lungs, the gastrointestinal tract, the nerves, and the skin.

Disease of the ear, nose, and throat system, in different forms and degrees of severity, is present in 90% of patients with GPA [1, 38, 39]. Typical symptoms are nasal crusting and obstruction, bloody nasal discharge or epistaxis-related nasal mucosa ulceration, sinus pain with associated drainage, otitis media, and hearing loss. In patients with GPA, the vessels supplying the cartilage may be affected, and septal perforation may occur, while invading granulomas may cause destructive bone disease disrupting the anatomy of such patients. Saddle nose deformation due to collapse of the nasal structure and facial paralysis due to facial nerve entrapment may be seen, but the most dangerous complication of upper respiratory involvement is the inflammation of the trachea, especially in the subglottic region, because it may result in airway stenosis. Subglottic stenosis and destruction in the sinonasal anatomy represent characteristic manifestations of GPA. Lung involvement may manifest as necrotizing granulomatous inflammation or alveolar capillaritis and is typically demonstrated on radiographic studies as nodular opacities or alveolar infiltrates. Pulmonary nodules may cavitate, thus making disease management difficult; infections are superimposed. Capillaritis, arteritis, and granulomatous inflammation may cause hemoptysis or massive pulmonary hemorrhage, life-threatening conditions, which require immediate induction therapy. Among patients with biopsy-proven pauci-immune glomerulonephritis, 53% were found to have pulmonary involvement manifested as hemoptysis or massive hemorrhage which quickly became fatal in 50% of them [1, 37]. Involvement of the skin with palpable purpura and nodules occurs in as many as 25% of patients. Other skin lesions include erythematous macular lesions, papules, infarcts, and necrotic ulcers. Vasculitic lesions in the mucous membranes manifest as aphthous stomatitis or oral ulceration. Eye involvement includes conjunctivitis, episcleritis, blepharitis, keratitis, or acute visual loss or orbital mass. Approximately 30% of patients report symptoms of abdominal pain, gastritis, ischemic colitis, or pancreatitis due to involvement of the vessels in abdominal organs. Occasional infarction of the bowel with viscus perforation and polymicrobial sepsis may result in life-threatening phenomena. Cranial nerve palsy, sensory peripheral neuropathy, or mononeuritis multiplex may be seen. Peripheral neuropathy caused by vasculitis in epineurial arterioles and arteries occurs in approximately 30% of patients. Vessels in the central nervous system can also be affected leading to sudden onset of seizures, cerebrovascular events, and cognitive disorders. Besides, deep vein thrombosis may occur, more frequently among patients with ANCA-associated vasculitis than the general population or other autoimmune disorders [39–41]. Anti-plasminogen autoantibodies have been identified in patients with PR-3 ANCA glomerulonephritis, as a result of utilization of a peptide coded by the antisense RNA of the PRTN3 gene [41], and have been associated with such thrombotic phenomena.

The clinical phenotype of EGPA probably denotes a somewhat different disease, manifested by asthma, eosinophilia, and granulomatous inflammation in the lung. ANCA are positive in 70% of the patients, most commonly MPO-ANCA [36], and eosinophilia greater than 10% in the peripheral blood is found. Coronary arteritis and myocarditis are the main causes of morbidity and mortality, accounting for 50% of deaths. Renal disease is much less frequent and less severe in this disease category, while neuropathy and cardiac disease are more common.

However, recent advances in EGPA suggest that the majority of patients, who are ANCA positive, also have glomerulonephritis, while those lacking ANCA are more likely to have cardiac disease [42].

8. Histopathology

8.1. Renal histopathology

The hallmark histopathologic lesions of acute pauci-immune glomerulonephritis are crescents and fibrinoid necrosis (**Figure 1**), which are found at the same frequency, irrespective of the presence or absence of systemic vasculitis [2, 43]. A wide range of lesions in terms of activity and severity may be found, ranging from focal segmental fibrinoid necrosis affecting less than 10% of glomeruli to severe diffuse necrotizing and crescentic glomerulonephritis that may injure all glomeruli (**Figure 2**). Breaks in Bowman's capsule are frequent [44]. Another element, which may be found, although not disease specific, is periglomerular granulomatous inflammation [1]. ANCA-associated glomerulonephritis is by definition pauci-immune, which means that immunofluorescence microscopy reveals no staining or a low level of staining (less than +2, in the 0–4 scale) (**Figure 3**) [45]. In a significant number of patients, there is evidence for antecedent glomerular or tubulointerstitial injury, manifested by glomerular sclerosis, fibrocellular crescents, and interstitial fibrosis. These lesions may be found in different stages of activity or resolution depending on the status of the disease. Nearly 10% of biopsy specimens have necrotizing inflammation in small cortical arteries or vascular inflammation of the medullary vasa rectae (**Figure 4**), causing papillary necrosis if it is severe.

8.2. Extrarenal histopathology

The pathologic features of pauci-immune vasculitic lesions are identical in other organs as they are in the kidney. Consequently, leukocytoclastic angiitis affecting vasa recta is very

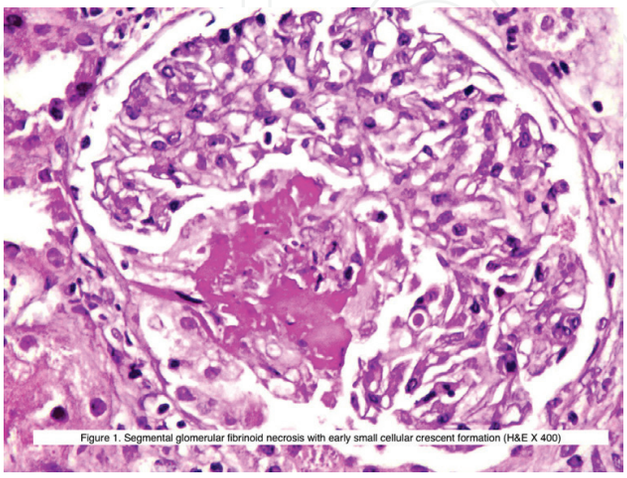


Figure 1. Segmental glomerular fibrinoid necrosis with early small cellular crescent formation (H&E 400×).

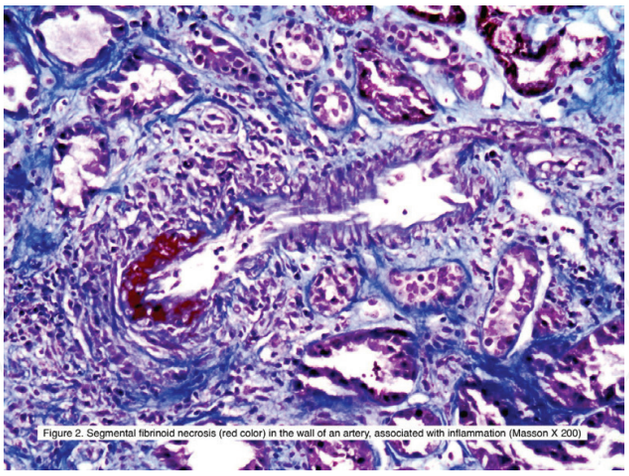


Figure 2. Segmental fibrinoid necrosis (red color) in the wall of an artery, associated with inflammation (Masson 200×).

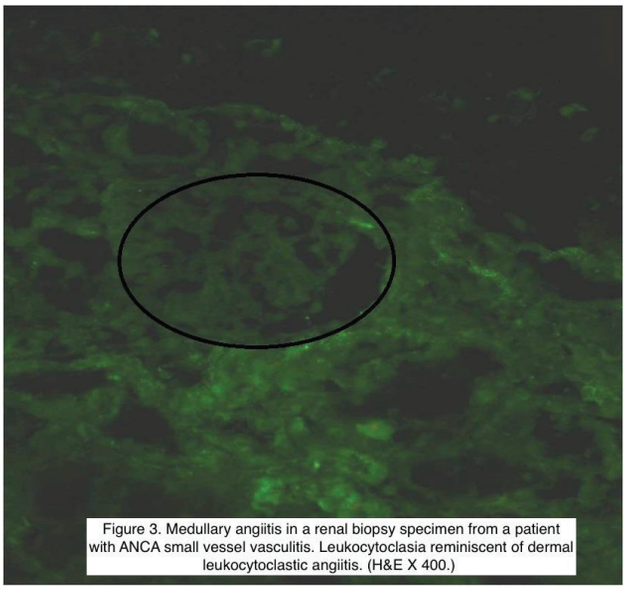


Figure 3. Medullary angiitis in a renal biopsy specimen from a patient with ANCA small vessel vasculitis. Leukocytoclasia reminiscent of dermal leukocytoclastic angiitis (H&E 400×).

similar to that in dermal venules, necrotizing capillaritis in glomeruli is identical to that in pulmonary capillaries, and necrotizing arteriolitis and arteritis in renal arteries are histologically indistinguishable from the necrotizing arteriolitis and arteritis in any site of the body, such as perineural arteritis causing peripheral neuropathy, gastrointestinal arteritis leading to focal ulceration and hemorrhage, and skeletal muscle arteritis leading to myalgias [1]. The histopathological proof of pauci-immune vasculitis prerequisites a paucity of staining for immunoglobulins [1] in order to confirm the diagnosis, and thus if glomerulonephritis is not present, a tissue biopsy at any site of active disease in any organ should be obtained.

The characteristic histological lesion in the pulmonary system in patients with MPA is capillaritis, while among patients with GPA, granulomatous inflammation may be seen as well. The necrotizing granulomatous inflammation may involve the upper and/or lower

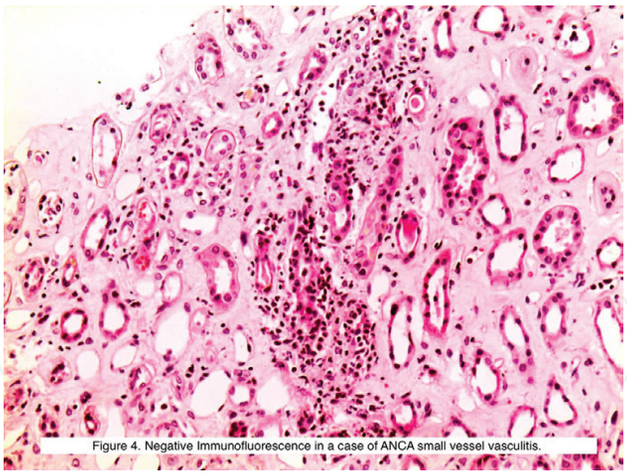


Figure 4. Negative immunofluorescence in a case of ANCA small vessel vasculitis.

respiratory system but may be found in any site, such as in the dermis and subcutaneous tissue. Granulomas are characterized histologically by an irregular central zone of necrosis that may have an amphophilic or bluish hue because of finely dispersed nuclear debris [1]. One major element of this lesion is epithelioid macrophages which may be numerous, but they do not have the compact arrangement seen in other occasions such as sarcoidosis [1]. Over time, extensive fibroblastic proliferation is usually seen, which ultimately may evolve into dense fibrotic scars. Nevertheless, for any specimen with necrotizing granulomatous inflammation, major non-vasculitic differential diagnostic considerations should be made, including myobacterial and fungal infections which need to be ruled out [1]. Conclusively, several sites of extrarenal involvement may be used to obtain a tissue biopsy, in order to have histopathological proof of the disease. A lung biopsy often requires an open or thoracoscopic lung procedure, while in a small proportion of patients, sufficient tissue for diagnosis can be obtained by transbronchial biopsy. Yet, the absence of granulomatous vasculitis on transbronchial specimens should not be considered adequate evidence to exclude the diagnosis of GPA [46]. A nasal biopsy is relatively easy and noninvasive, but its diagnostic power is limited by the high rate of false-negative results, probably related to the fact that the amount of tissue that can be removed is small. A positive lung biopsy is establishing the diagnosis in such cases and from one view precludes the need for a kidney biopsy in many cases; however, a renal biopsy is still indicated in patients who are diagnosed by lung biopsy, especially if they have severe or rapidly progressive renal involvement, in order to assess prognosis and plan immunosuppressive therapy in short and long term.

9. Definitions in relation to response to therapy

Diagnosis of active ANCA disease is followed by initiation of immunosuppressive therapy with the main goal being induction of remission, defined as stabilization or improvement of kidney function, measured by serum creatinine levels, resolution of hematuria, and all other organ-specific vasculitic symptoms [36]. However, some patients may not respond

sufficiently, a phenomenon which is called "treatment resistance" and characterized by progressive decline in kidney function with persistent active urine sediment, or persistence or new appearance of any extrarenal vasculitic manifestations despite appropriate treatment. In addition, there are patients who initially responded to therapy in a manner that let them escape life-threatening or advanced organ damage, but it was not feasible for them to achieve complete obliteration of the pathogenic process and thus maintained a low grade of persistent activity known as "grumbling disease." Yet, patients achieving remission either complete or on therapy may or may not experience one or more disease relapses afterward. These are usually manifested as vasculitic signs or symptoms in any organ system, although relapses tend to affect the same organ systems as on initial presentation, with a new organ involvement reported only in 23% of patients [36].

10. Initial treatment

The gold standard of treatment in ANCA-associated vasculitis is the combination of corticosteroids with the cytotoxic agent cyclophosphamide [37, 47–50]. Glucocorticoids are given as intravenous pulses of methyl-prednisolone (7 mg/kg for 3 consecutive days) followed by oral prednisone (1 mg/kg for the first 4 weeks), reduced in a gradual and personalized manner over the next 3–5 months [2]. The protocol of treatment with cyclophosphamide in ANCA disease includes monthly pulses, given intravenously, starting at a dose of 0.5 g/m^2, subsequently increased up to 1 g/m^2, or orally at an initial dose of 2 mg/kg/day, always adjusted on the patient's leukocyte count. The duration of therapy with cyclophosphamide is usually 6–12 months, depending on patient's initial response [38, 47–51]. Both oral and intravenous schemes of cyclophosphamide have been proven equally effective in induction of remission [49], with the cumulative dose being significantly lower in the parenteral administration. In terms of achieved remission rates, a multivariate analysis showed superior results with the intravenous regimen without significant higher relapse rates [49]. Yet, a retrospective study showed [50] that the intravenous scheme of cyclophosphamide is associated with a higher risk of relapse, but this was not associated with increased rates of end-stage renal disease (ESRD), mortality, or long-term morbidity [50].

More recently, rituximab, a chimeric monoclonal antibody which is directed against the CD20 antigen of B lymphocytes, has also been used to induce remission in patients with ANCA-associated vasculitis, either in combination with steroids or cyclophosphamide and steroids [52]. A study authored by Jones et al. [52] compared rituximab with cyclophosphamide, as inductive therapy in patients with newly diagnosed ANCA-associated vasculitis with renal involvement, to a glucocorticoid regimen plus either rituximab with two intravenous cyclophosphamide pulses, or intravenous cyclophosphamide for 3–6 months followed by azathioprine. The scheme which contained rituximab, as part of therapy, was not superior to the standard one with intravenous cyclophosphamide (76 vs. 82%), with remission rates being high in both groups, while the rituximab regimen was not associated with fewer severe adverse events in the early phase [52]. Another study, which enrolled 197 ANCA-positive patients with either GPA or MPA, compared treatment with rituximab to treatment with oral cyclophosphamide for induction of remission. The rituximab-based regimen was shown

more efficacious than the cyclophosphamide-based regimen for inducing remission of relapsing disease (67 vs. 42%, p = 0.01). Rituximab was also as effective as cyclophosphamide in the treatment of patients with renal or pulmonary involvement [52].

There are two clear indications which justify addition of plasma exchange in the inductive phase of treatment in ANCA-associated vasculitis: pulmonary hemorrhage and severe renal dysfunction at clinical presentation (serum creatinine is greater than 500 μmol/L). Pulmonary hemorrhage, either as isolated capillaritis, or as part of the pulmonary renal syndrome, may be a life-threatening condition leading to high mortality rates [1, 53, 54]. A retrospective study showed that the prompt institution of plasma exchange in addition to immunosuppressive therapy is 100% lifesaving [55] for these patients with diffuse pulmonary hemorrhage due to ANCA vasculitis, when compared to 50% historical controls. Furthermore, a randomized controlled study of 137 patients within the European Vasculitis Society (EUVAS) group with ANCA glomerulonephritis showed a clear benefit with the addition plasmapheresis to standard treatment in patients with severe renal impairments (serum creatinine >500 μmol/L). Specifically, addition of plasmapheresis was associated with a reduction in risk for progression to ESRD of 24% at 12 months and was also shown to be a positive predictor of dialysis independence at 1 year in patients with renal failure [54] (**Figure 5**).

Aggressive immunosuppressive therapy is warranted in patients with ANCA-associated small vessel vasculitis, since patient and renal survival have been shown very poor in untreated patients [38]. However, toxicity related to therapy is also problematic. For instance,

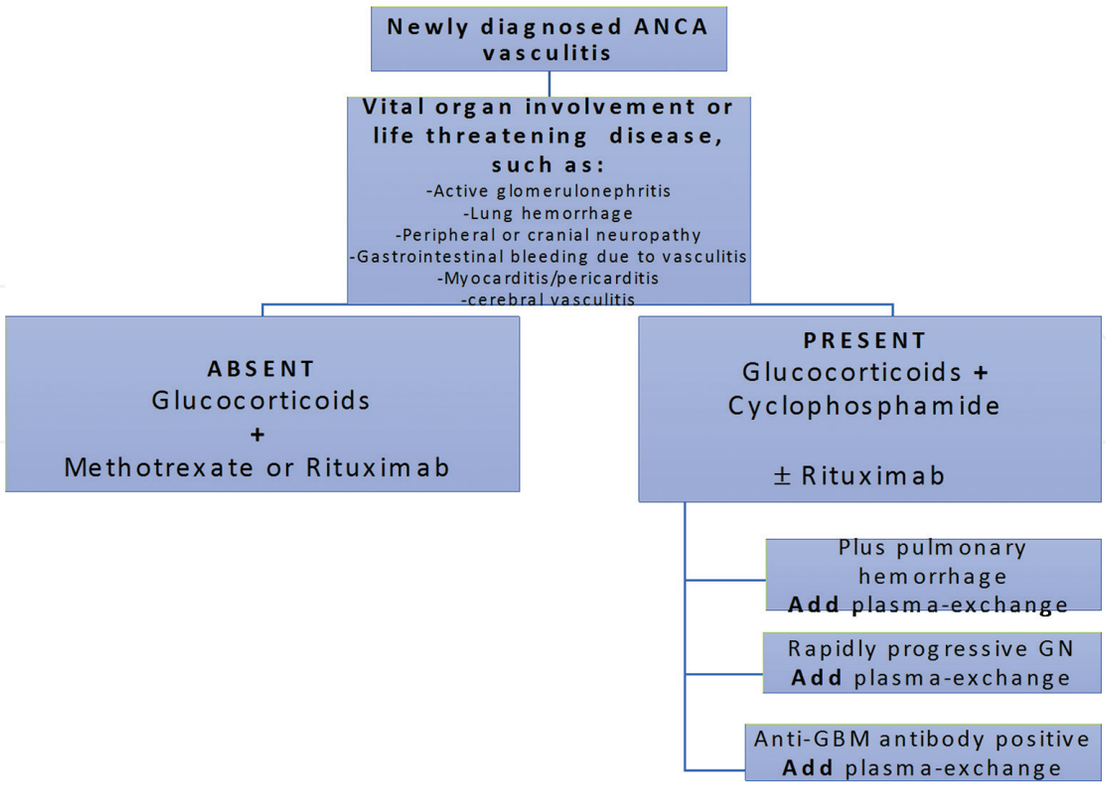


Figure 5. Algorithm to guide initial therapy for patients with newly diagnosed ANCA-associated vasculitis.

glucocorticoid therapy is associated with osteoporosis, glucose intolerance, and changes in body habitus in the long term, while life-threatening infections may occur during the acute phase. The frequency of severe infections is higher with the addition of cyclophosphamide. Moreover, therapy with cyclophosphamide has been associated with myelosuppression and hemorrhagic cystitis which occurs in 10% of patients. Bladder cancer has been estimated in 5% in 10 years and 16% in 15 years in patients treated with long-term oral cyclophosphamide. Myelodysplasia, lymphoma, skin cancer, and gonadal dysfunction are also associated with cyclophosphamide therapy [56]. Sufficient hydration and administration of 2-mercaptoethanesulfonate have been used in order to minimize urotoxicity.

Of note, although histopathological diagnosis is always desirable for patients with ANCA disease, we should underline that immunosuppressive treatment should be started empirically if the clinical suspicion for ANCA small vessel vasculitis is high and a tissue diagnosis cannot be obtained in a timely manner [18]. This is very important in order to avoid irreversible damage since these diseases often follow a rapidly progressive course with devastating consequences of the involved tissue.

11. Maintenance of remission

After achievement of remission, the disease course varies substantially among patients with ANCA small vessel vasculitis [10, 18]. Occurrence of relapse ranges from 30 to 50%. The majority of patients experience, either sustained long-term remission, or with one or more relapses occurring over time. Some patients continue having persistent, low-grade activity [10, 38]. Yet, evaluation of outcomes in patients in whom immunosuppressive therapy was discontinued after they attained remission showed similar rates of relapse compared to patients who remained on treatment for longer periods [10]. In the light of irreversible side effects related to therapy and relapse rates being comparable between long-term treated and not treated responders [10], optimal duration of immunosuppressive therapy should be decided on an individualized manner. In this regard, maintenance treatment is legitimate for patients who have a high rate of relapse, who have had a relapse already, or who maintain some disease activity despite full treatment. Undoubtedly, it is a challenge to select those patients in whom it is safe to discontinue therapy versus those who require remission maintenance therapy [10]. Recently, a prospective randomized trial, which compared two different durations of maintenance immunosuppressive therapy for the prevention of relapse in ANCA-associated vasculitis [55] showed that prolonged remission maintenance therapy with azathioprine/prednisolone, beyond 24 months after diagnosis, reduces relapse risk out to 48 months and improves renal survival. Nonetheless, the optimum duration of maintenance therapy depends on multiple factors. Another randomized controlled trial of patients with PR3-ANCA disease who remained ANCA positive at the time of stable remission, extending the duration of maintenance therapy with azathioprine from 1 year to 4 years (followed by taper), was not associated with a significant difference in relapse-free survival at 4 years [35, 57]. Finally, these results should not be extrapolated to other agents, especially since the optimal duration of maintenance therapy with rituximab has not been formally evaluated. A practical approach for clinicians is to use predictors of relapse, in order to be able to distinguish

those patients who are at increased risk to relapse. Predictors of relapse among responders in ANCA-associated vasculitis have been shown to be PR3-ANCA seropositivity [33] and pulmonary and ear, nose, and throat involvement, each associated with an approximately two-fold increase in risk for relapse.

In terms of the agents which may be used, for maintenance of remission, conversion from cyclophosphamide to azathioprine at a dose of 2 mg/kg/day has been shown to be a safe choice with less toxicity [1, 56]. Furthermore, an open-label randomized controlled trial which was conducted in 156 patients from 42 European centers found that mycophenolate mofetil was less effective than azathioprine for maintaining remission, while adverse event rates were not different [56]. Employment of rituximab for the maintenance of remission in patients with ANCA vasculitis was tested in a study of 115 patients with GPA, MPA, or renal-limited disease after achievement of complete remission with cyclophosphamide and glucocorticoid [57]. Patients received either 500 mg of rituximab on days 0 and 14 and at months 6, 12, and 18 after study entry or daily azathioprine until month 22. In the rituximab group, more patients had sustained remission at month 28 than the azathioprine group, while the frequency of severe adverse events was similar between groups [58]. The antimicrobial agent trimethoprim-sulfamethoxazole has also been proven to prevent relapse in patients with GPA, by reducing the episodes of infections, probably by eliminating *Staphylococcus aureus* in the upper airways [59].

12. Management of persistent, refractory, or relapsing disease

Despite available options of treatment, some patients experience persistent symptoms or episodes of active inflammation that come up repentantly. In this regard, there are some choices which have been explored as potential alternatives [60–64] in order to treat the disease and minimize toxicity related to cytotoxic therapy in patients with ANCA-associated vasculitis. Among them, methotrexate combined with corticosteroids has been shown to lead to remission in 60–90% [60–62], but it was associated with an elevated rate of relapse [60–62]. Besides, yet, the use of methotrexate has been limited to patients with predominantly extrarenal manifestations of vasculitis and preserved renal function (serum creatinine <2.5 mg/dl). As a result, patients with signs of kidney involvement should not be treated with methotrexate. Mycophenolate mofetil is a safe and therapeutically beneficial alternative for patients with non-life-threatening, recurrent, or resistant ANCA vasculitis according to the results of a pilot study [64]. More recently, there are several reports of refractory disease which has been managed with rituximab, combined with steroids or cyclophosphamide or both, and ended up in remarkable improvement [65–67] or even complete remission.

13. Prognosis of patient and renal survival

The most important question of both patients and physicians in the case of ANCA-associated vasculitis is the issue of long-term prognosis, especially considering the relapsing and remitting course of this disease in association with the cumulative toxicity of therapy. The relative

risk of death has been shown to be almost nine times greater in patients with MPA, who presented with lung hemorrhage, and four times greater in patients with cytoplasmic versus perinuclear ANCA [67] although the risk of lung hemorrhage was not different from ANCA pattern. The use of cyclophosphamide lowered the risk of death nearly six times, compared to steroid therapy alone [67]. Accordingly, long-term analysis of patients with GPA, who had received treatment with prednisone and cyclophosphamide, revealed that age over 50 years at diagnosis and lung or kidney involvement were associated with an almost fourfold increased risk for death [67]. The strongest predictors of long-term renal survival were found to be entry serum creatinine value, black race, and arterial sclerosis on renal biopsy [67]. Despite the certain finding that the higher the entry serum creatinine, the worse the long-term renal prognosis, no level of serum creatinine value could be determined beyond which treatment was futile, since 50% of the dialysis-dependent patients at onset recovered renal function permitting cessation of dialysis [67]. Taken all together, prompt institution of therapy remains the gold standard in these diseases. The risk for progression to ESRD after initial response to treatment in patients with ANCA glomerulonephritis was the change in GFR within 4 months of treatment. In this regard, after controlling for baseline creatinine level, type of treatment, and ANCA specificity, patients with a GFR decrease of 8 ml/min or greater were 5.6 times more likely to progress to ESRD than patients with stable GFR [10]. Relapse itself has also been shown to increase the probability of progression to ESRD by 4.7 times, with the related risk totally attributable to the recurrence of nephritis [10]. In patients with severe renal dysfunction due to ANCA glomerulonephritis, prognostic indicators of GFR after 12 months were shown to be age, the percentage of normal glomeruli, tubular atrophy, and intraepithelial infiltrates in the renal biopsy [51], while for those who were dialysis dependent at diagnosis, the probability for renal recovery was significantly increased with the addition of plasmapheresis [54].

Prediction of treatment resistance has been studied in a large cohort of patients with ANCA-associated vasculitis [67], recruited by kidney disease, which showed that 23% of the 334 treated patients became refractory to standard therapy. Most of them ended up to ESRD in median of 2 months after initiation of therapy. Female sex, black ethnicity, and severity of renal involvement were identified as predictors of treatment resistance. The risk of treatment resistance increased 1.28 times for each serum creatinine elevation of 100 μmol/L (1.13 mg/dl). Nonetheless, these rates have not been estimated with the newer agents and especially after the introduction of rituximab in the treatment of these diseases. Typically, these patients had a relapsing and remitting course not recognized by their primary care provider, leading to advanced glomerular and interstitial scarring at the time of diagnosis [67].

In conclusion, pauci-immune vasculitides, despite the substantial progress which has been achieved in the field of pathogenesis and treatment, remain a group of diseases with significant morbidity and mortality, related to the disease itself and the toxicity coming from therapy. Renal involvement is one of the most threatening aspects of this disease, especially considering the side effects related to renal insufficiency and chronic dialysis, in the case of extended irreversible damage of the renal tissue. Speed in diagnosis and prompt institution of appropriate immunosuppressive treatment endure the key of avoiding such outcome.

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Conflict of interest

The authors have nothing to declare.

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