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ANCA-Associated Vasculitis: Advancement in Pathogenesis, Clinical Features and Management

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ABSTRACT

Anti-Neutrophil Cytoplasmic Autoantibody (ANCA)-Associated Vasculitides (AAVs) are rare disorders characterized by inflammation of the small blood vessels resulting in ischemia or haemorrhage. The main phenotypes of AAVs are Granulomatosis with Polyangiitis (GPA), Microscopic Polyangiitis (MPA), and Eosinophilic Granulomatosis with Polyangiitis (EGPA). Although the pathogenesis of these disorders is still incompletely understood, distinct roles for T cells subsets and ANCA autoantibodies were underscored. AAVs present in the head, neck, lung, kidney, skin, heart, eyes, and intestine. The treatment of AAVs aims to induce and maintain remission and rapidly control of the disease activity. Rituximab, the first major alternative to cyclophosphamide plus glucocorticoids therapy, has enhanced the management of AAVs. However, continuous evaluation is constantly needed to manage the uncommon clinical features which may accompany the disease. This review summarizes the major findings of recent studies related to the three kinds of AAVs focusing on new novelties of their pathogenesis, clinical manifestations, and management.

Abbreviations: ANCA: Anti-Neutrophil Cytoplasmic Autoantibody; AAVs: ANCA-Associated Vasculitis; GPA: Granulomatosis with Polyangiitis; EGPA: Eosinophilic Granulomatosis with Polyangiitis; MPA: Microscopic Polyangiitis; CRP: C-Reactive Protein

Introduction

Vasculitides refer to a group of pathological conditions resulting from inflammation of blood vessels, with consequent adverse effects such as ischemia and hemorrhage. According to vessels size, they are usually classified into three groups; small, medium, and large vessel vasculitides. Granulomatous Polyangiitis (GPA), Microscopic Polyangiitis (MPA), and Eosinophilic Granulomatosis with Polyangiitis (EGPA) are the main AAVs types which usually affect small-vessels and characterized by the presence of ANCA autoantibodies in patient's serum [1,2]. Although they are idiopathic, their pathogenesis and management still a hot topic [3,4]. Divers factors were involved in AAVs pathogenesis including, T cells and complement system activation, and genetic and environmental factors [5]. The details of AAVs pathogenesis are incompletely unexplained. However, evidence related to patients with AAVs suggests a role for macrophage or monocyte in increasing the intensity of tissue injury. In addition, serum of AAVs patients characterized by increased levels of colony stimulating factor 1 (CSF1) [6]. Johansson ÅC et al. found that AAVs pathogenesis was amplified through phagocytes behaviors impairment [7]. ANCA-positive glomerulonephritis is may seem to be accompanied with increased C-Reactive Protein (CRP), an acute-phase protein of inflammation related to interleukin 6 (IL-6). Moreover, of primary contributors in AAVs pathogenesis are the leukocytes via damage caused by their migration and invasion. AAVs genetic background knowledge is increased by additional genome-wide association study (GWAS) results and other genomic approaches [8].

In diagnosis, the common laboratory tools in AAVs diagnosis are indirect Immunofluorescence test (IFT) for ANCA screening and then confirm positive results by enzyme-linked immunosorbent assay (ELISA) to differentiate proteinase 3 (PR3)-ANCA or c-ANCA from myeloperoxidase (MPO)-ANCA or p-ANCA (Figure 1). In treatment, therapeutic strategies have been established for AAVs associated with increasing evidence related to their pathogenesis. These strategies aim to prevent disease relapse, reduce drugs toxicity, and limit disease consequences [9]. Two phases are considered in AAVs treatment, the first is an induction of remission, and the second is for rapid control of disease activity [10]. Currently, the monoclonal antibodies, rituximab, and mepolizumab have been reported as novel drugs in AAVs treatment [11,12]. Our previous data confirmed that TNF-α blockers in rheumatic diseases e. g. rheumatoid arthritis compromised the disease activity [13] whereas, TNF-α blocker, etanercept characterized by increasing solid malignancies development [14].

The majority of patients with AAVs develop new cascades of events led to new severe symptoms. Thus, Grayson and his co-workers suggested that continuous evaluation of patients with established vasculitis remains critical [15]. AAVs research directed towards investigating the disease duration optimization and maintenance therapy frequency as well as targeted treatment development which could unravel successful treatment or cure for AAVs. In this review, we focused on the outputs of current studies related to the main three kinds of AAVs, and prospects of alternative treatments or cure.

Granulomatosis with Polyangiitis (GPA)

GPA is a rheumatic systemic small vessels inflammation that affects multiple organs and usually accompany with c-ANCA or rarely p-ANCA autoantibodies. The most predominantly affected population category is age bracket of 40 - 55 years. The disease is frequently presented in a sino-nasal cavity, kidney, and the lung (Figure 1). Klinger in the year 1931 characterized GPA for the first time, then Friedrich Wegener, hence the name Wegener's granulomatosis was introduced by Godman and Churg 1954 [16-19]. Even though the etiology of GPA is still unknown, stimulation of TLR2 and TLR9, and the priming effect of TLR ligands on PMNs contributed to GPA pathogenesis by increase proteinase 3 (mPR3) expressions of membrane origin [20]. Also, IL-32, tartrate-resistant-acid-phosphatase (TRAP), multinucleated giant cells (MNGs), programmed death receptor-1 (PD-1) and mitochondrial DNA played roles in GPA pathogenesis [21-23]. Moreover, GPA pathogenesis was augmented by upregulation of platelets neutrophils extra-cellular traps (NETs) depend on elevated myeloperoxidase-DNA complexes and platelet-neutrophil aggregates [24]. Meanwhile, α1-antitrypsin deficiency and levamisole are reported as GPA inducer [25,26].

GPA Clinical Features and Management: a new Progress

GPA clinical manifestations were summarized in Table 1. The most common sites involved in GPA are ear, nose, and throat (ENT); lungs; and kidneys (ELK) (Figure 1). Recently, hearing loss, toothache, oral ulcer, rash, otitis media, gastrointestinal complications, ischemic stroke, bilateral ulcers on the face, and fever have been observed in GPA patients [27,35]. The clinical manifestations of GPA in children and adults' patients were similar except organ involvement frequencies [29]. Skin and gastrointestinal manifestations were considered as markers for GPA severity [27,30]. Despite neurological manifestation is not uncommon with GPA, CNS clinical features in GPA could cause fatal events. Hypertrophic pachy meningitis with unchanged PR3-ANCA level was reported as a unique consequence of GPA [31,32]. Because of central and peripheral nervous system involvement, inpatients with neurologic disorders are more susceptible to GPA [33]. In rare cases, the skull base could be injured in patients with GPA [34]. Also, GPA was associated with chronic lymphocytic leukemia, dengue fever, acute onset progressive dyspnea, and Crohn's disease [3,36-39].

Table 1: GPA clinical symptoms (35).

Site	Clinical features
Skin	Hypersensitivity angiitis.
Oral cavity	Oral ulcers.
Eye and ear	Episcleritis and conductive hearing loss.
Upper airway	Stenosis.
Lower airway	Shortness of breath, musical breathing sound, and inadequate gas exchange.
Cardiovascular	Small vessel vasculitis.
Gut	Peritonitis followed by acute abdominal pain.
Urinary tract	Diffuse glomerulonephritis.
Nervous system	Meningitis, headache, and seizures
Skeleton and muscles	Inflammatory arthritis.

On the other hand, the cardiac involvement in GPA was rare and presented as coronary vasculitis, myocarditis, or pericarditis [40]. Of cardiac involvement, valvulopathy, bacterial endocarditis, and acute aortic and mitral valve perforations were reported as secondary features for GPA [41-43]. Meanwhile, GPA misdiagnosed as an infective endocarditis in adolescent male [31]. The traditional drugs for GPA treatment are cyclophosphamide and glucocorticoids. However, recent studies have shown that patients with severe AAVs were successfully managed by rituximab [11,47,48]. Abatacept also achieved good results in treating patients with GPA [44]. In the past, the management of GPA-associated peripheral ulcerative keratitis (PUK) was a burden and lacked exact treatment protocol, but now it was controlled relatively by rituximab [45]. Meanwhile, GPA case with refractory necrotizing scleritis associated with PUK was successfully treated by surgical intervention [46]. It has been described that rituximab was effective in GPA with heart involvement [47], but low immunoglobulin levels in patients on rituximab increase the risk of severe hypogammaglobulinemia [48].

As well, the first case of GPA presented as gastric ulcer was successfully treated with rituximab [49]. In addition, GPA

association with frosted branch angiitis was improved by intravenous solumedrol of high-dose therapy [50]. Also, it has been suggested that early diagnosis, immunosuppressive therapy, and facial vascularized composite allotransplantation could manage a rare association between malignant pyoderma and GPA [51]. Indeed, Subglottic Stenosis (SGS) in GPA may be relieved by subglottic dilatation, but the patient will still at recurrence risk. As well, tracheostomy is recommended to manage severe airway-limiting stenosis [52]. A recent report suggested that differential diagnosis should include hypersensitivity pneumonitis when a GPA patient in azathioprine has fresh pulmonary lesions [53]. On the other hand, receiving maintenance immunosuppressive therapy in a patient with GPA or GPA associated with systemic lupus erythematosus could provoke acute kidney injury or alveolar hemorrhage [54,55].

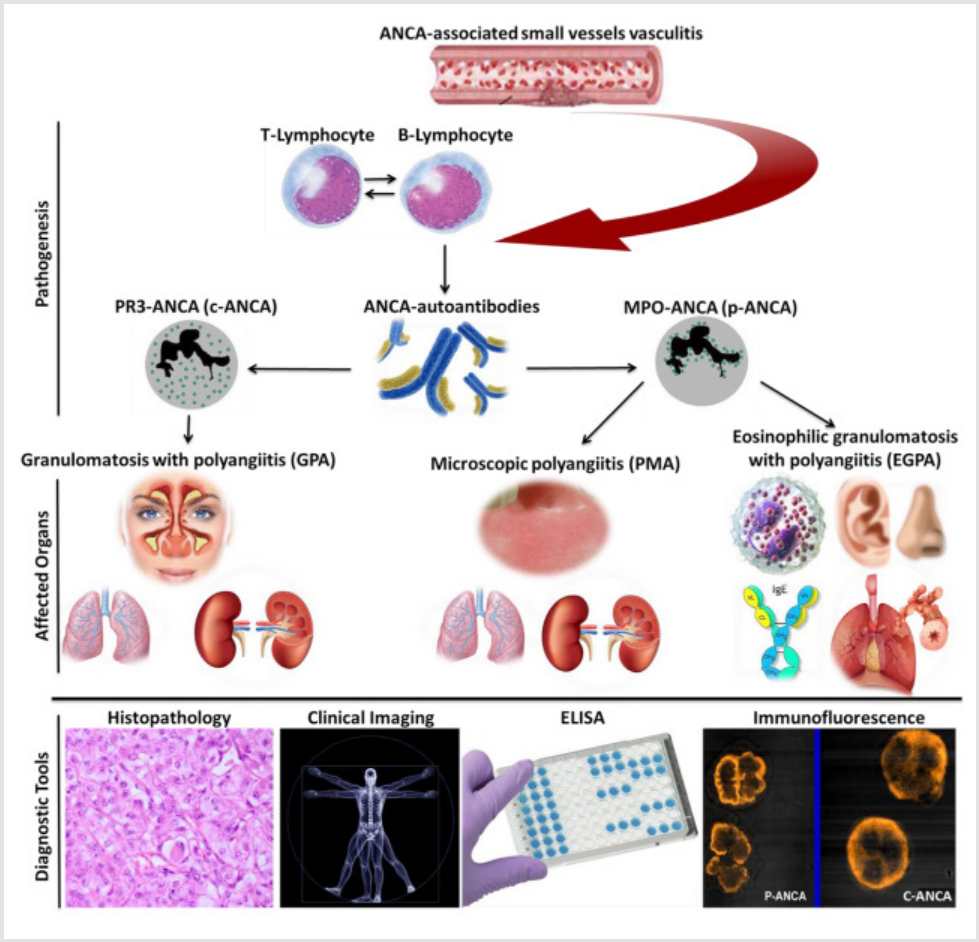

Figure 1: An overview of AAVs based on of pathogenesis, clinical features, and diagnostic tools.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

It is an autoimmune reaction of unknown cause that produces blood vessels inflammation in patients with a pulmonary allergic history. The former name for EPGA is Churg-Strauss Syndrome (CSS), sometimes referred to as allergic granulomatosis. Among AAVs it is the rarest disease described by Churg and Strauss in 1951 characterized by MPO-ANCA presence in 30-38% of patients' serum, and constant allergic reaction induced by IgE autoantibodies (Figure 1). This reaction has resulted in intensification of EGPA pathogenesis by marked infiltration of eosinophils into the affected vessels tissues. In addition, EGPA augmentation was promoted through increased production of IL-5 revealed by CD4+ cells and clonal expansion of CD8+ T cells [56]. Also, α-1-antitrypsin deficiency is observed in patient with EGPA [57].

EGPA Clinical Features and Management: A New Progress

It has been hypothesized that the ENT involvement in EGPA patients is an essential aspect. Therefore, nose and ear are the commonest sites where the clinical manifestations of EGPA are presented (Figure 1). Three stages of EPGA are recognized; (1) airway inflammation, (2) eosinophilia, and (3) cell death (vasculitis). Its prevalence is 2-22 per million persons and the annual incidence rate is 0.5-3.7 per million persons (58). Heart and cerebral lesions are considered as uncommon clinical manifestations of EPGA. However, attention should be paid whenever antiplatelet drugs recommended to such patients. Cardiac involvements in EPGA include myocarditis, heart failure, pericarditis, myocardial infarction, and constrictive pericarditis. In another topic, EGPA could

be associated with inappropriate antidiuretic hormone syndrome [59]. EGPA categorized into two different clinical phenotypes according to the type/level of autoantibodies patient serum, ANCA-negative EGPA and anti-MPO-ANCA EGPA. The patients of the first subtype are more frequently to develop complications involving the heart whereas patients of the second subtype are more likely to develops classical vasculitis symptoms usually glomerulonephritis and alveolar hemorrhage [60].

The treatment of EPGA includes glucocorticoids, azathioprine, and cyclophosphamide. The management should include continuous clinical monitoring. In EGPA patients with moderate to severe allergic asthma, rituximab and omalizumab was considered effective and safe [11,61]. It has been reported that in EGPA and refractory asthma association the treatment by mepolizumab and omalizumab is a satisfactory option [62]. Meanwhile, heart transplantation in patients with refractory EGPA was recommended [63]. Samson and his co-workers recorded two important facts, the first is, the survival rate in EGPA patients is very good when treatment is managed by the baseline Five-Factor Score (FFS), and the second is, patients with p-ANCA and <3000/mm baseline eosinophilia are more exposed to relapses [64]. On the other hand, bullous phenotypes in relapsing EGPA especially the ANCA-negative form respond rapidly to systemic corticosteroids [65,66]. In progressive cases of EPGA, intravenous immunoglobulins (IVIGs) were effective in preventing the immobilization of neuropathy [65].

Microscopic Polyangiitis (MPA)

MPA is a member of small vessel vasculitis that often has a fatal outcome, and its histology shows little or no immune deposits. In MPA almost all types of blood vessels are clinically involved. The common organs involved in MPA are kidney and lung which usually followed by of nervous and musculoskeletal systems involvement. Skin, heart, eyes, and intestine are also involved. Although ANCA in MPA is mainly directed to MPO-ANCA (Figure 1), Immunoglobulin M (IgM) autoantibodies against PR3 were reported in MPA patients [67]. MPO-ANCA autoantibodies contribute to NETs formation, which might be involved in the pathophysiology of patients with MPA [68]. Also, exposure to silica was reported as a factor which could stimulate the producing mechanisms of MPA pathogenesis [69].

MPA Clinical Features and Management: A New Progress

Clinical manifestations of MPA are so variable including the pulmonary and renal involvement, and skin manifestations (Figure 1). Also, severe co-trimoxazole-induced hypoglycaemia, crescentic glomerulonephritis, acute cervical myelitis, and acute cholecystitis have been observed in patient with MPA [70-73]. Indeed, ruptured gastric artery aneurysm, hemorrhagic stroke, pyrexia of unknown origin, lymphoma, bilateral brachial plexopathy, intraventricular hemorrhage, and pneumomediastinum are recognizesd as the uncommon manifestations and complications of MPA [66,72-75,77]. Meanwhile, patients with MPA are at risk for developing venous thromboembolic events (VTE) and eye involvement [78,79]. On the other hand, The Azathioprine hypersensitivity is presented as cardiogenic shock and weet's syndrome in a patient with MPA [80]. In addition, MPA may be associated with fibrosing interstitial lung disease (ILD), primary biliary cirrhosis, Sjogren's syndrome, and Hashimoto's thyroiditis [81,82]. In Japanese patients, kidney survival was affected in relapsed MPA associated with infectious complication [83]. Indeed, phenotypes difference in patients with MPA from Europe and Japan has been explained [84].

Despite there are no standard treatment protocols for treatment of MPA patients, the effective communication between rheumatology, pulmonary, and nephrology physicians could improve disease management. Renal survival in MPA Chinese patients was promoted by glucocorticoids and mycophenolate mofetil (MMF) therapy [85]. However, MPA Japanese patients with renal involvement couldn't get satisfactory results after treatment by cyclophosphamide and corticosteroid [86]. Other monoclonal antibodies, rituximab and Tocilizumab (TCZ) monotherapy could be a novel choice in some MPA patients [11,87]. Management protocols based on rituximab and MMF in children with MPA were achieved satisfactory outputs [88]. Meanwhile, MPA with cholecystitis elderly patient had been successfully treated using mizoribine [89]. As well, therapy directed at T cells might be an alternative treatment option for a rare MPA case with GIT involvement [90]. Unfortunately, disseminated mycetoma caused by Nocardia pseudobrasiliensis in MPA patient on long-term corticosteroid therapy was observed as a unique case in Korea [91]. Currently, gabexate by its anti-inflammatory functions could be helpful in MPA management [92].

Concluding Remarks

The exact cause of AAVs is still not fully understood and we are yet to have complete remission. Patients with AAVs develop new severe symptoms. Therefore, continuous monitoring and evaluation remains critical to avert, control, or prevent unforeseen complications that could emanate from the disease. T cells subsets differentiation and their interleukins complements pathways activation, genetic basis, auto-reactivity, and environmental factors are the main contributors to AAVs pathogenesis. Recently, an advanced understanding of AAVs pathogenesis has led to the development and use of new therapeutic alternatives such as rituximab, tocilizumab, gabexate, omalizumab, mepolizumab, and mizoribine. However, the advancement in knowledge in AAVs suggested that effective collaboration between the different internal medicine sections specialists as well as radiologist and histopathologist is strongly recommended to optimize diagnosis and enhance the management of AAVs patients. Undoubtedly, future research focusing on the optimization of duration and frequency of maintenance therapy, and development of new therapeutic agents could help in the effective treatment and cure of the disease.

Author Contributions

All authors made significant contribution to the development of this manuscript.

Competing Interest

The authors declare that they have no competing interest. None of the authors has any financial or other interest influencing the output of this review.

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