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REVIEW ARTICLE

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Proteinase-3 as an autoantigen and the development of granulomatosis with polyangiitis

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Abstract
Human proteinase 3 (hPR3) is a lysosomal enzyme of the serine protease type. In autoimmune vasculitis, autoantibodies to hPR3 appear to have a role in the inception of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV), where this protein is the main autoantigen. Indeed, patients with antibodies against hPR3 have more severe symptoms, relapses, and resistance to immunosuppressive therapies, supporting an important role for this autoantigen in the pathophysiology and severity of AAV. In this review, we describe what is known about the role of hPR3 in pathophysiology, diagnosis of AAV, and some perspectives on its treatment.

Introduction

Human proteinase 3 (hPR3) is a lysosomal enzyme of the serine protease type, with a molecular weight of 29 kD (kilodaltons), encoded by the PRTN3 gene located on a specific region on the short arm of chromosome 19 (19p13.3). This enzyme catalyzes the hydrolysis of microbial peptides, thereby maintaining homeostasis within the

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immune environment.[1,2] It is primarily expressed in the azurophilic granules of neutrophils and serves as the main autoantigen target of antineutrophil cytoplasmic antibodies (ANCAs). Antibodies against hPR3 are predominantly of the IgG (immunoglobulin G) type that specifically target the lysosomes of activated neutrophils and monocytes.[2-4] Other types of ANCAs may be directed against the enzyme myeloperoxidase (MPO) present in primary neutrophil granules and monocyte lysosomes.[5]

The binding of these ANCAs to antigens induces the release of free radicals and enzymes, leading to vascular endothelial damage and triggering vasculitis in small- and medium-sized vessels with multisystem involvement.[6-8] Small vessel vasculitides are categorized into two groups: AAV (ANCA-associated vasculitis) and immune complex vasculitides. AAV is characterized by necrotizing vasculitis with minimal or no immune complex deposition.[9-11]

Currently, AAV is classified into three categories: granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis; microscopic polyangiitis (MPA); and eosinophilic granulomatosis with polyangiitis (EGPA), previously referred to as the Churg-Strauss syndrome.[8,9,12,13] Here, in the AAV, the autoantibodies are typically directed against either hPR3 or MPO, but rarely against both. Additionally, there have been reports of patients presenting with vasculitis in the absence of detectable ANCA at the initial diagnosis, but who were subsequently tested positive for ANCAs during follow-up.[14]

In the GPA, antibodies against hPR3 are detected in approximately 80% of cases.[9] It is a form of vasculitis characterized by granulomatous inflammation that primarily affects the respiratory system, particularly the upper airways and lungs, and may occasionally involve multiple organ systems.[14]

Method and Materials

Epidemiology

GPA is a rare disease, with an estimated global incidence ranging from 0.4 to 11.9 cases per million per year.[15] In Asia, the incidence has been reported to be between 0.37 and 2.1 cases per million per year, while in the UK, it is approximately 14.3 cases.[16,17] In Europe, a prevalence of approximately 120 cases per million has been observed, with an incidence of 0.83 cases per 100,000.[16-21] In the United States, the prevalence is estimated at 21.8 cases per 100,000; however, among hospitalized patients, a prevalence of 32.6 cases per 100,000 admissions has been reported.[22] In China, a prevalence of 19.4 cases per 100,000 has been documented.[23]

GPA typically manifests between the fifth and seventh decades of life. Most studies report a mean age of symptom onset around 45 years,[24] though in China and Japan, mean ages between 60 and 65 years have been observed,[23,25-28] and in India and Tunisia, the age of presentation has been reported to range from the fourth to the sixth decade of life.[29-31] Some studies have found that African American patients tend to be younger at diagnosis, with a mean age of 35 years compared to 55 years in other populations ($p = 0.0006$).[32]

Several studies suggest that the disease has a similar frequency distribution between the sexes.[25,33,34] However, some studies have reported a higher frequency in women than in men,[33] while others have found a predominance in men.[35,36]

In Latin America, there is limited publication on the GPA, resulting in imprecise data regarding the incidence and overall prevalence of the disease. A study from Argentina reported a prevalence of 7.4 per 100,000 (95% CI [confidence interval] 2.8–12) and an incidence of nine cases per million per year (95% CI 5–13), with a higher frequency in women compared to men.[37] Similar findings regarding the higher frequency in women have been reported in studies from Brazil and Mexico.[36,38] In Colombia, two studies describing the clinical characteristics of patients with AAV found that GPA was the most common type of vasculitis, with a higher prevalence in women.[39,40]

Regarding the age of presentation—studies from Brazil reported a mean age of 45.8 ± 16.1 years, while in Chile it was 46.5.[41,42] In Colombia, two studies reported mean ages of 52 and 55 years, respectively,[39,40]while in Argentina, one study noted that the maximum age of presentation was 70.[37]

GPA has also been documented in the pediatric population, but its incidence remains unknown.[15,43-47] In 2018, Panupattanapong et al. reported that among the 5,562 GPA cases in the USA, 214 (3.8%) were pediatric patients. The incidence rate of GPA in this cohort was 1.8 cases per million person-years.[21]

A systematic review and meta-analysis of pediatric GPA by Iudici et al. in 2016 found a median age at disease onset of 11.6 years and a median age at diagnosis of 14 years (range: 4–17).[48] Numerous reports indicate a higher frequency in girls, with most cases diagnosed during adolescence. Delayed diagnosis is common, particularly in the absence of renal and pulmonary involvement,[48-50] and frequent hospitalizations due to leukopenia, neutropenia, and hypogammaglobulinemia have also been reported.[21]

Genetics and environmental factors in GPA

The consideration in the past has been that interactions between genetic predisposition and triggering factors are important for the development and pathophysiology of systemic vasculitis.[51] The European Vasculitis Genetics Consortium reported the first genome-wide association study (GWAS) in AAV, which identified associations both within the major histocompatibility complex (MHC) and in non-MHC regions.[52] This study also found that GPA and MPA are genetically distinct entities. Furthermore, subanalyses revealed that the strongest associations were not with clinical syndromes, but with the specificity of anti-MPO and anti-PR3 ANCAs. Finally, another two GWAS found associations with the non-HLA (human leukocyte antigen) genes—SERPINA1, PTPN22, and PRTN3—highlighting that a functional polymorphism in PRTN3 correlated with increased expression of PR3 in neutrophils (genetically distinct subsets within ANCA-associated vasculitis and identification of functional and expression polymorphisms associated with risk for AAV).[53,54]

A relationship was established between the development of AAV and various factors, including environmental,

inflammatory, and infectious agents. In the case of GPA, it was reported that these patients exhibited higher rates of chronic colonization by *Staphylococcus aureus*, which has been associated with an increased risk of disease relapses.[13] This finding could support the theory of molecular mimicry originally proposed by Wegener in 1936, although a study conducted by Pendergraft et al. did not show clear sequence homologies between bacterial antigens and hPR3.[55] We showed some coincidences in the aminoacid sequence from hPR3 and various bacterial proteases of important bacterial pathogens[56]; but for MPO, no clear sequence homologies have been identified in bacterial antigens.

Proteinase 3 as the centerpiece of the pathophysiological mechanism

GPA develops due to a loss of immune tolerance by T and B cells to the neutrophil protein PR3 in individuals with genetic predisposition, associated with activating factors (infection, inflammation), generating autoreactive T, and B lymphocytes that produce autoantibodies that bind PR3 in neutrophils and induce the secretion of neutrophil extracellular traps (NETs). In addition, the monocytes release tumor necrosis factor (TNF) and interleukins (ILs)—IL-1B, IL-6, and IL-17A—which stimulate the activation of neutrophils. Moreover, the dendritic cells producing IL-21 and IL-23 promote in the secondary lymphoid system the differentiation of T helper (TH) lymphocytes. These ILs stimulate the recruitment of neutrophils, which in their activated form release reactive oxygen species. They also promote the expression of proteins such as hPR3 or MPO and NETs, which are fibrillar structures composed of chromatin and granular proteins. NETs, in turn, stimulate dendritic cells to release IL-21 and IL-23, amplifying the inflammatory signal.[13]

In the secondary lymphoid tissue, T lymphocytes differentiate into TH cells, including type 1 TH cells (TH1), TH 17 lymphocytes (TH17), and TH follicular lymphocytes (TFH); differentiation into $TCD4^{+}$ and $TCD8^{+}$ lymphocytes also occurs. TFH cells produce IL-21, promoting the maturation and differentiation of B lymphocytes into plasma cells, which are the producers of ANCAs.[54]. TH17 cell produces IL-17A, which activates and recruits neutrophils located in the endothelial cells of the renal microvasculature, respiratory tract, and other tissues, contributing to tissue damage and inflammation, as there is also an overexpression of hPR3, perpetuating autoimmune activation.[13] The ANCAs produced by reactive B lymphocytes stimulate the release of cytokines TNF, IL-1B, IL-6, and IL-17A by monocytes, further perpetuating the proinflammatory cycle (Figure 1).

Activated neutrophils produce reactive oxygen species and NETs, causing direct endothelial injury. These injured

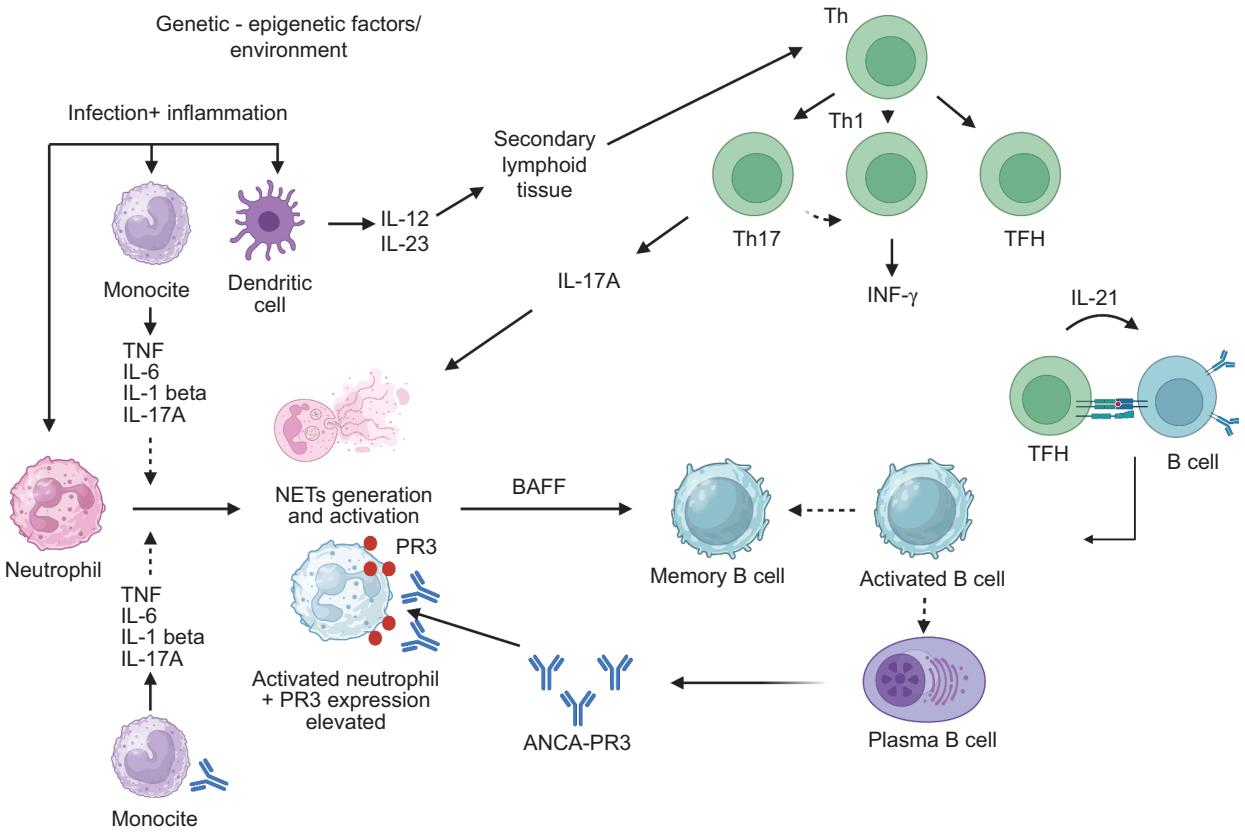

Figure 1 Loss of immune tolerance to PR3 and neutrophil activation. ANCA: Anti-Neutrophil Cytoplasmic Antibody; BAFF: B cell Activating Factor; IL: Interleukin; INFγ: Interferon gamma; MHC II: Major Complex Histocompatibility; PR3: Proteinase 3; TCR: T Cell Receptor; TH T helper: TFH T follicular helper (T follicular helper); TNF: tumor necrosis factor.

endothelial cells express the polypeptide related to the major histocompatibility complex I (MICA), which is recognized by the NKG2D receptor expressed on $CD4^+$ cytotoxic T lymphocytes, leading to a further endothelial damage. The overexpression of hPR3 on the surface of apoptotic neutrophils limits its phagocytosis by macrophages, promoting a proinflammatory state that contributes to the formation of the characteristic granulomas in this vasculitis. Macrophages release soluble CD163 (sCD163), a promising biomarker of disease activity.[13]

Neutrophils activated by ANCA adhere to endothelial cells via ß2 integrins and chemokine binding to the chemokine receptor 2 (CXCR2).[57] The extravasation of inflammatory leukocytes, such as neutrophils and T cells, from the microvasculature into the extravascular tissue is a critical process in the induction of tissue damage. B-lymphocyte aggregates form in the extravascular tissue, where they can present ANCA antigens to T lymphocytes, leading to the generation of proinflammatory cytokines and the in situ production of ANCAs.

Clinical manifestations

At the onset of the disease, symptoms are nonspecific, including fever, malaise, and weight loss, which may persist for months.[33,43,58] Localized involvement is common, particularly in the upper respiratory tract, manifesting as sinusitis, epistaxis, nasal obstruction, and otitis media that do not respond to standard treatments; however, rapid progression with generalized manifestations can occur.[15,58-60] Evidence suggests that clinical manifestations in children, similar to those in adults, may involve multiple systems. Nevertheless, certain manifestations, such as fever at disease onset and otorhinolaryngological system involvement, appear to be more frequent in children.[48,61,62]

At the time of diagnosis, a majority of patients (70–100%) presents with nasal obstruction, hyposmia, and anosmia.[63-65] Middle ear pathology is observed in 38% of cases (18–20), with serous otitis media being the most common (90%), followed by chronic otitis media (24%).[33,66-68] Otitis media may be secondary to Eustachian tube dysfunction, caused by granulomatous inflammation and nasal obstruction.[63,68] In pediatric patients, saddle nose deformity and subglottic stenosis are more frequent complications compared to adults.[69-73] Cochlear and vestibulocochlear nerve involvement manifests as tinnitus, vertigo, and in some cases, sensorineural hearing loss (43%).[63,66,74,75]

Some patients (14–60%) may present with necrotizing nodular episcleritis, scleritis, corneal ulcerations, and/or retinal vasculitis.[44,45,76] Presentations mimicking retroorbital granulomatous pseudotumor or dacryoadenitis as well as orbital involvement leading to complete visual loss and optic neuropathy have also been reported.[45,77-79] In pediatric patients, scleritis/episcleritis has been observed in 2% of cases.[48,61,62]

Pulmonary manifestations are present in 50–90% of cases and include parenchymal nodules, tracheal, and subglottic stenosis, the latter being less common (16%); additionally, patients may experience alveolar hemorrhage and acute respiratory failure.[35,63,65,81,81] In pediatric patients, Iudici et al. reported lower respiratory tract involvement in 61% (95% CI 48–74); with hemoptysis, alveolar hemorrhage in 16% (95% CI 6–29%); and pulmonary nodules in 10% of cases.[48]

Renal involvement significantly impacts the prognosis of the disease.[82] The most observed renal lesion is the focal segmental necrotizing glomerulonephritis, often associated with extracapillary proliferation and crescent formation (40–100% of cases). Clinically, this typically presents with hematuria and proteinuria. In pediatric patients, renal involvement may occur in up to 65% of cases.[48,61,62]

Additionally, patients may present with mononeuritis multiplex and sensory-motor neuropathy (30% of cases), cranial neuropathies (6–13%), and less frequently, spinal cord involvement.[83-85] Psychotic symptoms typically occur early in the disease.[86] Leukocytoclastic vasculitis, digital infarcts, purpura, skin ulcers—which may be intraoral or genital—and necrosis can occur in 10–50% of cases.[65,79,87] In pediatric patients, acne that evolves into difficult-to-heal ulcers has been reported[88-93] along with skin manifestations resembling those seen in the Henoch-Schönlein purpura.[94]

Pericarditis, myocarditis, endocarditis, arrhythmias, and heart failure may occur in less than 10% of cases.[35,95-97] Deep vein thrombosis,[98-100] aortic dissection, and coronary aneurysms have also been reported.[101,102] Vasculitis of the mesenteric vessels may occur in 5–11% of cases; therefore, patients may present with acute abdomen due to intestinal ischemia and ulcerations at different levels of the digestive tract that may progress to perforation;[103-106] also, liver and pancreatic function may be impaired.[107-109]

Pituitary involvement has been reported in case series, particularly in the early phase of the disease, leading to secondary hypogonadism and diabetes insipidus,[79,110-112] and some reports describe forms of GPA that mimic pituitary adenomas.[113]

In the urogenital and reproductive systems, involvement has been primarily observed in men, with manifestations including prostatitis, orchitis, epididymitis, ureteral stricture, or penile ulceration.[114-116] In women, involvement is less common, with reported cases of adnexitis as well as breast and placental involvement.[82,117,118]

There are cases of patients with GPA presenting with pathology suspicious for malignancy due to the appearance of bladder tumors, mediastinal and retroperitoneal masses, nodular skin lesions, and lymphomas. However, histopathological studies confirm a vasculitis etiology in these patients.[119-123] Additionally, GPA has been associated with malignant neoplasms.[124-127]

Proteinase 3 in the diagnosis of granulomatosis with polyangiitis

From a clinical perspective, diagnosing GPA is challenging due to the fact that various types of AAV share overlapping clinical features.[128] Moreover, certain clinical characteristics of GPA are not readily distinguishable from those of other systemic diseases, particularly in the early stages, thus delaying diagnosis and increasing both morbidity and mortality.[129-132]

Anti-PR3 antibodies demonstrate a sensitivity of over 90% for systemic involvement and a specificity of 98% for the diagnosis of GPA.[9,133-135] Consequently, they have been

proposed as a risk factor for relapse, as their fundamental role in the pathophysiology of the disease has been well established.[12,136,137] Some studies suggest that ANCA specificity may predict differences in long-term prognosis, with PR3-ANCA patients exhibiting a higher risk of relapse compared to those with MPO-ANCA.[138]

It has been proposed that classifying patients based on ANCA specificity (anti-PR3 vs. anti-MPO) reveals significant differences in various aspects compared to grouping them by clinical presentation, such as GPA versus MPA. These differences include relapse risk, genetic predisposition, treatment response—particularly to rituximab—cytokine profile, and overall outcomes.[14]

In 2022, the American College of Rheumatology (ACR) and the European Alliance of Rheumatology Associations (EULAR) jointly proposed new the classification criteria for AAV (ACR/EULAR 2022 criteria).[139-141] According to these criteria, patients with suspected vasculitis must meet two conditions to be eligible:

1. They must have a diagnosis of small or medium vessel vasculitis.
2. Other medical conditions that mimic vasculitis must be excluded.

The new ACR/EULAR 2022 classification criteria include items categorized into clinical, laboratory, radiological, and histological domains, each with differentiated weighting. Cut-off values are established for the classification of GPA, MPA, and EGPA. According to these criteria, a patient can be classified as having a GPA if they achieve a total score of 5 or more points. Notably, a score of 5 is awarded solely for anti-PR3 antibody positivity (PR3-cANCA), meaning that a patient with vasculitis can be classified as having GPA based purely on the presence of anti-PR3 antibodies, regardless of clinical manifestations.[14]

In a 2023 review, Yoon Pyo et al. compared their clinical experience with patients previously diagnosed with AAV according to the ACR 1990 criteria, the EMA (European Medicines Agency) 2007 algorithm, and the CHCC (Chapel Hill Consensus Conference) 2012 definition, with the ACR/EULAR 2022 criteria for GPA, MPA, and EGPA. They reported concordance rates of 96.6% for MPA, 86.3% for EGPA, and 73.8% for GPA. The authors suggested that to reduce discordance and improve the diagnostic accuracy of the EMA 2007 algorithm and the CHCC 2012 definitions, the ACR/EULAR 2022 criteria should be applied to all patients with suspected AAV.[142]

Furthermore, promising biomarkers for differentiating between AAV and non-AAV have been identified, including chemokine ligand 13 (CXCL13), matrix metalloproteinase 3 (MMP-3), and tissue inhibitor of metalloproteinase 1 (TIMP-1).[143]

Advances in the development of cell therapies and antigen-specific immunotherapies have opened new

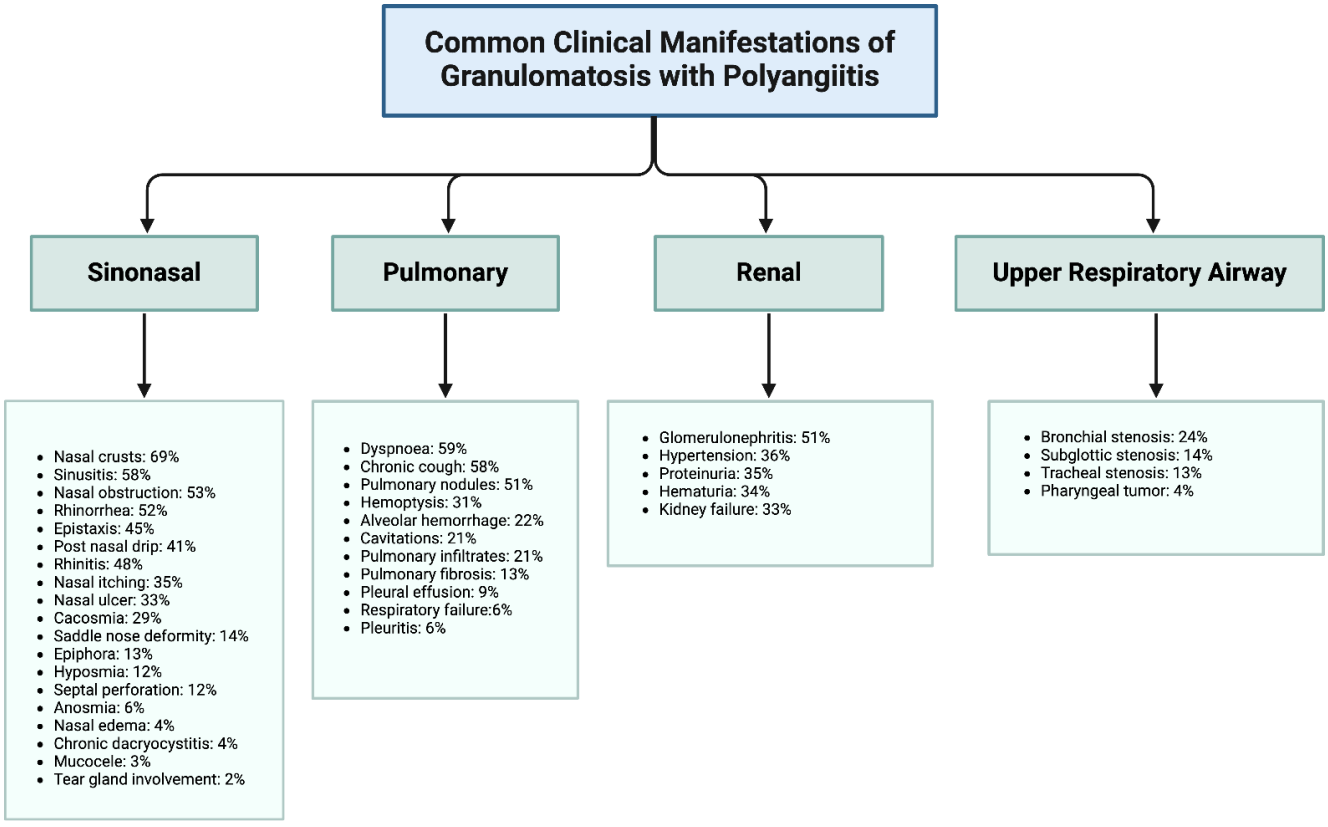

Figure 2 Most common manifestations and their average incidence. Adapted from "Clinical manifestations of granulomatosis with polyangiitis: Key considerations and major features" by Bogna Grygiel-Górniak, Nattakarn Limphaibool, Katarzyna Perkowska, and Mariusz Puszczewicz.

perspectives for the treatment of autoimmune diseases, including PR3-ANCA vasculitis. The pathogenesis of GPA is characterized by the central involvement of B lymphocytes, making them a crucial therapeutic target in the management of this disease.[5,14] For this reason, rituximab, an anti-CD20 monoclonal antibody that selectively depletes B lymphocytes, has been recognized as an effective treatment option for both induction and maintenance of remission in patients with GPA. Controlled clinical studies have demonstrated that rituximab is as effective or even superior to the conventional immunosuppressants such as cyclophosphamide and azathioprine, particularly in patients with antibodies anti-PR3.[5,14]

However, the toxicity associated with these treatments significantly contributes to persistent morbidity and mortality due to cumulative damage in patients. Therefore, the ongoing search for more effective therapies with improved safety profiles for the treatment of anti-PR3-AAV remains essential to enhance clinical outcomes and minimize treatment-related toxicity in these patients.

Future perspectives

In the next 10 years, the treatment and understanding of GPA may see significant advancements driven by progress in immunology, genetics, and biotechnology; one promising area is that of targeted therapy based on cells and monoclonal antibodies.[144] Rituximab, which has already shown effectiveness in GPA, could be succeeded by a new generation of more specific therapies based on engineered T or B cells that minimize side effects and provide greater precision in targeting pathogenic B cells.[145,146] Research in gene therapy and genetic editing, such as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), opens the possibility of modifying genes associated with susceptibility to GPA such as PRTN3, reducing or eliminating the endogenous production of hPR3 autoantigen and possibly autoimmune response, as this strategy has shown promising results in disease such as hereditary angioedema.[147] As susceptibility genes with functional impact are identified, these interventions could be personalized for patients based on their genetic profiles, enabling precision medicine to prevent disease progression or reduce its severity.

Additionally, the coming years will likely bring advances in diagnostic and monitoring biomarkers, such as those based on cell signaling molecules (e.g., CXCL13 or MMP-3), allowing for earlier and more accurate detection of disease activity. This would facilitate more proactive and personalized patient monitoring, improve long-term prognosis, and reduce the need for invasive interventions.

Furthermore, the growing understanding of the microbiome and its relationship with the immune system and autoimmunity[148] promises future treatments that include microbiota modulation as part of a comprehensive approach to treating GPA and preventing relapses.[149]

Together, these developments could transform GPA treatment, reduce side effects, and improve patients' quality of life, aiming toward a potential cure or long-term remission within the next decade.

Conclusion

hPR3 is a lysosomal enzyme primarily expressed in neutrophils and is the main ANCA autoantigen in GPA, playing a crucial role in the pathogenesis of AAV. Understanding PR3-mediated pathophysiology, along with the diverse clinical presentations of GPA, is essential for the timely diagnosis and effective management of this rare and potentially severe disease.

Author Contributions

All authors contributed equally to this article.

Conflicts of interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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