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Review

Granulomatosis with polyangiitis (Wegener): Clinical aspects and treatment

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ABSTRACT

Granulomatosis with polyangiitis (GPA) is a systemic necrotizing vasculitis, which affects small- and medium-sized blood vessels and is often associated with cytoplasmic ANCA. GPA occurs in patients between 45 and 60 years old of both genders, and is rarely observed in blacks. The prevalence of GPA increases along a south–north gradient in Europe (20 to 150/million). The main clinical characteristics involve the upper and/or lower respiratory tract and kidneys. Ear, nose and throat manifestations with recurrent sinusitis and crusting rhinorrhea are usually severe. Lung nodules are frequently seen, sometimes excavated. Renal involvement is characterized by rapidly progressive necrotizing glomerulonephritis with extracapillary crescents. Limited forms of GPA predominantly affect the upper respiratory tract, whereas generalized forms of GPA include renal manifestations and/or alveolar hemorrhage and/or vital organ involvement with an altered general condition. The combination of immunosuppressant drugs and corticosteroids has converted this typically fatal illness into one in which 80% of patients achieve remission. However, despite considerable therapeutic progress over the last decades, relapses remain frequent (50% at 5 years), and maintenance treatment is now the main therapeutic challenge.

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1. Introduction

Since 1937, when granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, was first described by the German pathologist Friedrich Wegener, and the 1980s when antineutrophil cytoplasmic antibodies (ANCA) were identified, considerable progress has been made with regard to the diagnosis, treatment and

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pathophysiology of this disease. It is a systemic, necrotizing vasculitis associated with the presence of ANCA with a cytoplasmic staining pattern directed against proteinase 3 (PR3). GPA is characterized by granulomatous and necrotizing inflammatory lesions located mainly in the upper and lower respiratory tracts, and is often associated with pauci-immune glomerulonephritis, which may be rapidly progressive [1,2,32].

2. Epidemiology

GPA is a rare disease with a prevalence in France estimated at 22 per million inhabitants in 2000 [3]. The incidence has been evaluated between 7 and 12 new cases per million inhabitants per year, although this has probably risen in the last few decades [4]. In Europe, GPA seems to be more frequent in the Nordic countries. The annual incidence is about 10 cases per million inhabitants in northern Europe. The age at diagnosis is between 45 and 60 years. Men and women have are affected with similar frequency. Rare cases of GPA may occur in black subjects, as well as in children.

3. Classification, diagnostic criteria and differential diagnoses

According to the 2012 revised Chapel Hill criteria [5], GPA is defined as a necrotizing granulomatous inflammation of the upper and lower respiratory tracts, with necrotizing vasculitis of small- and medium-size vessels, i.e. the capillaries, veins, arterioles and arteries. Necrotizing glomerulonephritis is common but is not essential for the classification. This classification specifies that the granulomatous inflammation does not necessarily need to be histologically proven and can be predicted by non-invasive studies. In some patients, the combination of suggestive clinical characteristics and the presence of cytoplasmic-staining ANCA and/or anti-PR3 may be sufficient for making the diagnosis of GPA and initiating treatment [6,7]. It is preferable to have histological evidence however, especially as renal histology is a prognostic factor that determines the therapeutic approach, particularly for the administration of plasma exchange.

According to the criteria of the American College of Rheumatology (ACR; 1990) [8], GPA is defined by the presence of at least 2 of the following 4 criteria: 1) sinus involvement; 2) lung X-ray showing nodules, a fixed pulmonary infiltrate or cavities; 3) urinary sediment with hematuria or red cell casts; and 4) histological granulomas within an artery or in the perivascular area of an artery or arteriole. The sensitivity and specificity of the ACR criteria are 88.2% and 92.0%.

4. Etiological factors

The exact cause of GPA has yet to be identified and is probably not unique. Environmental factors, such as dust inhalation, or exposure to silica, are most likely involved, but these are only seen in 10% of patients with GPA. It has been suggested that infectious agents may play a role in triggering the disease, particularly through a mechanism of molecular mimicry. Nasal carriage of *Staphylococcus aureus* could be a factor for flares of the disease [9]. Some familial cases reporting the occurrence of GPA cases among siblings have been published. The role of genetic factors in the occurrence of GPA was recently demonstrated in a genome-wide association study of 1683 cases of GPA and 489 of microscopic polyangiitis (MPA) [10]. The cases of vasculitis with anti-PR3 ANCA were associated with the HLA-DP, SERPINA1 (gene encoding for α1-antitrypsin) and PRTN3 (gene encoding for proteinase 3) genes, while the cases of vasculitis with anti-myeloperoxidase ANCA shared a different gene pool, in association with the HLA-DQ gene.

5. Clinical manifestations

Constitutional signs (fever, asthenia, weight loss) are frequent (50%) but non-specific.

Ear, nose and throat (ENT) signs are present in 70 to 100% of cases at diagnosis. These can include crusting rhinorrhea, sinusitis, chronic otitis media, or damage of the facial cartilage with deformities causing saddle-nose (resulting in a scooped out or depressed appearance of the nose, Fig. 1), and/or perforation of the nasal septum, the palate or the pinna of the ear [11]. Nasal-sinus involvement is the most common manifestation of GPA, the most common hallmark of the disease, and may be the only sign in the localized forms. Nasal obstruction with hyposmia or anosmia is often the first symptom.

Lung involvement affects 50 to 90% of patients. It is characterized by alveolar hemorrhage of variable severity (small quantity or more massive, leading to acute respiratory failure), and/or parenchymatous nodules, either single or multiple (rarely more than 10), which are removed in half of the cases. Tracheal and subglottic stenosis, sometimes associated with endobronchial locations, are found in ~16% of cases but are rarely hallmarks of GPA [12,13].

The most typical renal involvement is focal segmental necrotizing glomerulonephritis associated with extracapillary proliferation with pauci-immune crescent formation (i.e. without immunoglobulin or complement deposition by immunofluorescence). It is observed in 40 to 100% of cases according to the series and the specialty of the clinicians managing these patients (nephrologists, rheumatologists, internists). It usually leads to microhematuria and proteinuria. There may be involvement of the interlobular arteries, veins and peritubular capillaries. It is the renal damage that negatively impacts the prognosis of this disease. The initial glomerular filtration rate (GFR) is significantly and independently linked to mortality [14]. The kidney biopsy puncture is done for both the diagnosis and the prognosis (the number of normal glomeruli on biopsy is an important prognostic factor) [15]. Urogenital manifestations are much rarer and have only been described in men. They can be both a hallmark of the disease or occur during relapse. These manifestations can include prostatitis, orchitis, epididymitis, renal pseudotumor, ureteral stenosis or penis ulceration [16].

Involvement of the peripheral nervous system affects about one-third of patients. It is characterized by mononeuritis multiplex or, less commonly, by sensorimotor neuropathy. Involvement of the central nervous system is much rarer (6 to 13%) [17] and may be caused by granulomatous deposits, intracerebral vascular lesions, or an extension of sinus lesions. Pachymeningitis is the most suggestive manifestation. Cases of granulomatous infiltration of the pituitary stalk responsible for panhypopituitarism have also been reported.

Mucocutaneous lesions, mainly vascular purpura to the lower limbs, are reported in 10 to 50% of cases (Fig. 2); they can be ulcerating, necrotic and widespread. There may be subcutaneous nodules, pyoderma gangrenosum, raspberry-red gingivitis, and intraoral and/or genital ulcerations.

Ocular involvement occurs fairly frequently (14 to 60%), usually in the form of necrotizing nodular episcleritis. Scleritis, corneal ulcerations, and retinal vasculitis also occur [18]. Involvement of the eye socket in GPA is rarer but can be suggestive of the disease, especially when it presents as a

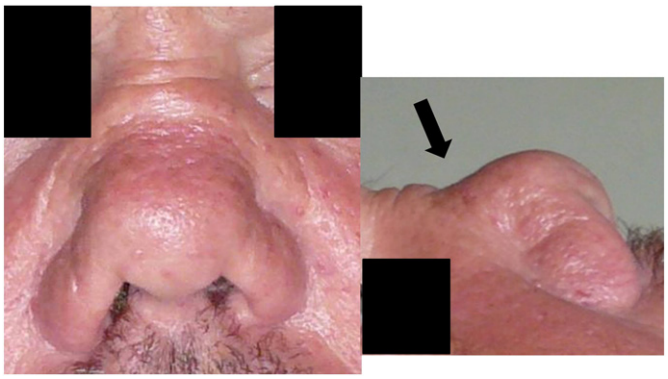

Fig. 1. Nasal deformity with a saddle-nose appearance (black arrow) in GPA.

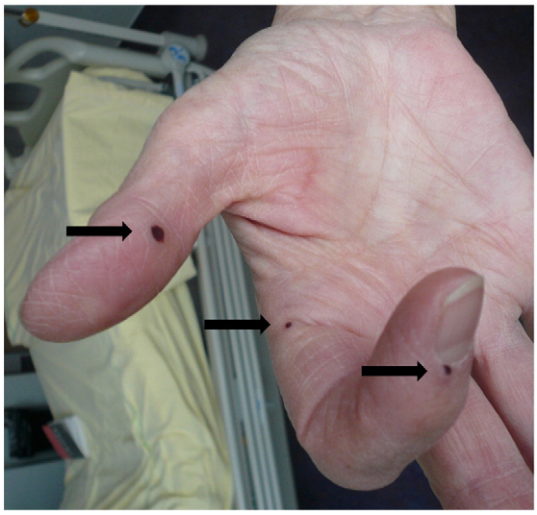

Fig. 2. Necrotic vascular purpura (black arrows) of the upper limbs in GPA.

granulomatous retro-orbital pseudotumor or as dacryoadenitis [19,20]. It can be either a primary form or occur secondary to sinus inflammation, and it typically manifests as inflammatory exophthalmia, which may or may not be associated with ophthalmoplegia.

Cardiac involvement is rare in GPA (<10%). It may be the result of the vasculitis or granulomatous effects, and can occur as pericarditis, myocarditis or conduction disorders [12,21,22]. The clinical presentation is very heterogeneous, ranging from subclinical manifestations to end-stage heart failure.

Gastrointestinal involvement is rare (5 to 11%) and is characterized by ulcerative lesions, often multiple, as well as intestinal perforation [23,24].

Several studies have highlighted a greater risk of deep vein thrombosis in patients with GPA, particularly in the active phase of the disease [25,26]. However, the available data to date do not support the recommendation of systematic preventative anticoagulation in these patients.

6. Different GPA phenotypes

At least 2 different phenotypes can be distinguished in GPA (Fig. 3), but there is no consensus as to their definition, with the two forms described as localized/limited and systemic/diffuse/severe [12].

The localized forms manifest primarily through ENT involvement, naturally limited to the upper respiratory tract, but they are recurrent and refractory (known as "grumbling disease") [27]. These localized forms appear to affect a younger and more female population [28].

The diffuse forms may manifest through renal involvement and/or intra-alveolar hemorrhage (IAH), and/or the involvement of at least one vital organ or that of a non-vital organ but in association with constitutional signs (fever, weight loss). They are often more serious initially, but relapse is less common [28]. The transition from a localized form to a diffuse form and vice-versa is possible during the course of the disease. Laboratory tests show the presence of ANCA in 90% of the systemic forms, whereas it is only present in 50 to 80% of the localized forms.

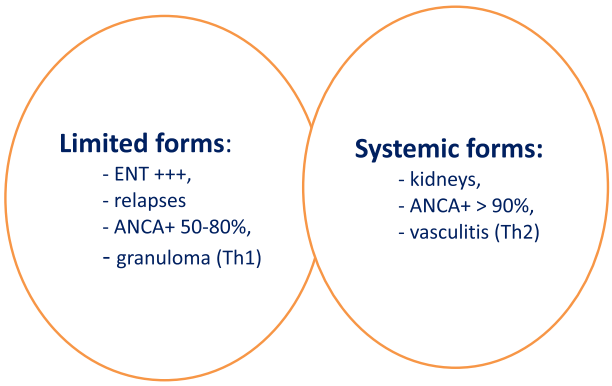

Fig. 3. The different GPA phenotypes.

Besides their clinical differences and variations with regard to their course and laboratory results, these two phenotypes probably have distinct pathophysiological processes. The localized forms are more granulomatous with greater Th1 lymphocyte polarization, as opposed to the diffuse forms that especially present with vascular inflammatory lesions with greater Th2 lymphocyte polarization [29].

7. Disease course and prognosis

Relapses during GPA occur frequently. One-quarter of patients relapse within 2 years of the diagnosis, and over half relapse within 5 years [30]. All forms of GPA can relapse. The clinical manifestations and the organs involved in relapse may differ from those present at the initial GPA diagnosis. The localized forms with an ENT presentation and/or granulomatous manifestations (orbital pseudotumor, pulmonary nodule) relapse more frequently than the systemic forms with renal involvement [28]. There is a 7-fold relative risk of relapse in chronic nasal carriers of *S. aureus* [9]. As a result, long-term use of cotrimoxazole (trimethoprim 160 mg–sulfamethoxazole 800 mg) is recommended in patients with GPA. Variations in the ANCA titre, as well as their specificity and their status, do not appear to be predictive of relapse. In contrast, a persistent positive ANCA is predictive of relapse [31]. Renal involvement in GPA is a major prognostic factor that determines both the functional renal prognosis and the life-threatening potential of the disease. The initial GFR is the best prognostic factor. The classification of glomerular damage in ANCA-associated vasculitides can be used to assess the risk of progression towards end-stage kidney failure [33]. Necrosis in a capillary tuft and the number of normal glomeruli are related to renal function at one year. In contrast, the presence of ENT involvement can be a good prognostic factor [34]. The main causes of mortality in the first year following the diagnosis of GPA were infection (32%) and kidney failure (18%) [35]. At 5 years, infections remain the main cause of mortality, while more long-term causes were not identified.

8. Treatment

GPA is a serious disease, with a nearly always fatal outcome in the absence of treatment. Fortunately, with therapeutic approaches that are increasingly standardized and the emergence of new biotherapies, 90% of patients go into remission, and the survival rate is approximately 80% at 10 years.

The current treatment for GPA follows the recommendations established by the French National Authority for Health (HAS) in November 2007 for systematic necrotizing vasculitis. Treatment is based on a first phase, known as the induction phase, which aims to quickly put the disease into remission, and lasts about 3 to 6 months according to the clinical response. A second phase, known as the maintenance phase, must then consolidate the remission and limit the risk of relapse; it lasts for 12 to 24 months [36]. The intensity of the initial therapeutic approach must be adjusted for each patient, and for the type and seriousness of the GPA in order to avoid two pitfalls: excessive treatment associated with a significant risk of side effects, or insufficient treatment with a risk of failure or early relapse.

With induction treatment, it is recommended that GPA be treated with a systemic corticosteroid and immunosuppressant combination. Oral prednisone is recommended at a daily starting dose of 1 mg/kg. For severe or refractory forms, oral corticosteroid therapy is preceded by an intravenous bolus of methylprednisolone at a dosage of 7.5 to

15 mg/kg/day for 1 to 3 consecutive days (depending on the clinical seriousness, the clinician's assessment and the patient's cardiovascular status). After a 3 to 4 week treatment of oral prednisone (1 mg/kg/day), the corticosteroids are gradually tapered, without going below 15 mg/day before the 4th month. In the absence of an internationally validated tapering regimen, the duration of the tapering in France varies from 18 to 24 months. The addition of an immunosuppressant in the induction phase is essential. For severe or refractory forms, 2 intravenous immunosuppressive agents can be offered: cyclophosphamide (CYC) or rituximab (RTX). CYC is preferred for use outside of clinical trials (rapidly progressive kidney failure with a serum creatinine >350 μmol/L, intra-alveolar hemorrhage on mechanical ventilation). CYC is used at a dose of 600 mg/m^2 (maximum dose of 1.2 g/bolus) every 2 weeks for one month (Day +1, Day +15, Day +30), then 700 mg/m^2 every 3 weeks until remission (between 6 and 9 boluses total). The dose will be adjusted for age and kidney function in order to obtain better tolerability without a decrease in efficacy: 500 mg/m^2 in the presence of kidney failure, and a 500 mg fixed dose every 3 weeks (maximum 6 boluses) if aged over 65 years (CORTAGE study, unpublished). RTX is preferred for use in women of childbearing age or in patients who have already received CYC or have had a relapse after one complete cycle of CYC. In 2010, the RAVE study showed that RTX was as effective as CYC in this indication (BVAS [Birmingham Vasculitis Activity Score] = 0 at 6 months without corticosteroid therapy, 64% in the RTX arm versus 53% in the CYC arm; $P < 0.001$ for the non-inferiority and $P = 0.09$ for the superiority), and even somewhat superior in the sub-group of patients with relapse (BVAS = 0 at 6 months without corticosteroid therapy, 67% in the RTX arm versus 42% in the CYC arm, $P = 0.01$ for the superiority) [37]. RTX is used at a dose of 375 mg/m^2 per week for 4 consecutive weeks. The 18-month follow-up of the patients included in the RAVE study shows the persistence of RTX non-inferiority compared to CYC ($P < 0.001$). In the sub-group of patients with relapse, RTX was even superior to CYC at the 6 and 12 months follow-up [38]. The role of plasma exchanges in the initial treatment is limited to the serious forms of GPA with renal involvement (serum creatinine >500 μmol/L) or alveolar hemorrhage (in analogy with the treatment of Goodpasture syndrome). They are always prescribed in combination with corticosteroids and an immunosuppressant drug (CYC or RTX), and are given over 6 to 9 sessions. Plasma exchanges at one year, compared to the methylprednisolone bolus, reduce the risk of developing end-stage kidney failure (19% versus 43%), but without significant improvement in overall survival [39]. The on-going, international PEXIVAS study is assessing the efficacy of plasma exchanges in addition to corticosteroids and immunosuppressant drugs for reducing the number of deaths and the progression to end-stage kidney failure [40]. For GPA that is not very severe or is localized/limited, methotrexate is used at a dose of 20–25 mg/week. The AGATA study reports the efficacy of abatacept (10 mg/kg IV on Day +1, Day +15, Day +29, then every month) combined with prednisone and an immunosuppressant drug (azathioprine [AZA] n = 3, methotrexate [MTX] n = 7, or mycophenolate mofetil [MMF] n = 4) for the treatment of limited and recurrent forms of GPA [41]. Remission (BVAS/WG = 0) was obtained in 16 of the 20 included patients (80%), 11 of whom without prednisone. The efficacy of abatacept appears to be very rapid (remission after a median duration of 1.9 months) and lasting (median remission duration of 14.4 months). At the end of the study, 3 (19%) patients had relapsed after going into remission, and 3 others (19%) did not have a lasting response or worsened on treatment.

The maintenance treatment of GPA lasts between 18 and 24 months after remission is achieved. It combines oral corticosteroids with azathioprine (2 mg/kg/day orally) or methotrexate (20–25 mg/week) [42]. A recent study by the French Group for the Study of Vasculitis (GFEV) shows that RTX (500 mg every 6 months: Day +1, Day +15, Month +6, Month +12, and Month +18) is more effective than AZA (2 mg/kg/day for 22 months) for maintaining patient remission after a first flare-up or relapse (results under publication). RTX has a lower risk of relapse compared to AZA at 28 and 44 months after the start of the maintenance treatment (rate of major relapses at 44 months: 18.2% in the RTX arm versus 51.9% in the AZA arm). The methods of administration of RTX for maintaining patients in remission are under evaluation (MAINRITSAN 2 study). The study compares the administration of systemic RTX given bi-annually (Day +1, Day +15, Month +6, Month +12, and Month +18) versus according to the quarterly changes in the laboratory parameters (ANCA and/or level of CD19+ lymphocytes).

Treatment with cotrimoxazole (sulfamethoxazole/trimethoprim at a dose of 400 mg/80 mg) per day is systematically given for the prevention of relapse and of *Pneumocystis jirovecii* infections. Vaccinations should follow the usual immunization schedule, with the contraindication of live vaccines.

Overall, the new therapeutic approaches significantly reduce toxicity and provide better tolerability in the long-term. The treatment regimens are increasingly adapted to the expression of the disease and to its course; relapses remain frequent however, and the maintenance treatment methods warrant better standardization.

9. Take-home messages

- GPA is a multifocal vasculitis characterized by frequent involvement of the upper and lower respiratory tract and kidneys.
- The presence of c-ANCA with anti-proteinase 3 specificity is observed in more than 90% of patients with GPA.
- Two phenotypes of GPA are recognized: systemic forms, with potentially life-threatening manifestations, and the other more limited form.
- Effective induction therapy with corticosteroids combined with cyclophosphamide or rituximab transformed the survival of patients with GPA, with 5-year survival rates >80%.
- GPA is now a chronic relapsing disorder with >50% rate of relapse within 5 years of initial remission. Maintenance therapy to prevent relapses and the occurrence of late complications remains the main therapeutic challenge in this vasculitis.

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