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Clinic manifestations in granulomatosis with polyangiitis

A Greco,[1] C Marinelli,[2] M Fusconi,[1] GF Macri,[2] A Gallo,[1] A De Virgilio,[1] G Zambetti[1] and M de Vincentiis[1]

Abstract

Granulomatosis with polyangiitis (GPA), formerly Wegener's granulomatosis (WG), is an uncommon immunologically mediated systemic small-vessel vasculitis that is pathologically characterised by an inflammatory reaction pattern (necrosis, granulomatous inflammation and vasculitis) that occurs in the upper and lower respiratory tracts and kidneys. Although the aetiology of GPA remains largely unknown, it is believed to be autoimmune in origin and triggered by environmental events on a background of genetic susceptibility.

In Europe, the prevalence of GPA is five cases per 100,000 population, with greater incidence in Northern Europe. GPA can occur in all racial groups but predominantly affects Caucasians. Both sexes are affected equally. GPA affects a wide age range (age range, 8–99 years).

Granulomatosis with polyangiitis is characterised by necrotising granulomatous lesions of the respiratory tract, vasculitis and glomerulonephritis. Classically, the acronym ELK is used to describe the clinical involvement of the ear, nose and throat (ENT); lungs; and kidneys. Because the upper respiratory tract is involved in 70–100% of cases of GPA, classic otorhinolaryngologic symptoms may be the first clinical manifestation of disease. The nasal cavity and the paranasal sinuses are the most common sites of involvement in the head and neck area (85–100%), whereas otological disease is found in approximately 35% (range, 19–61%) of cases.

Diagnosis of GPA is achieved through clinical assessment, serological tests for anti-neutrophil cytoplasmic antibodies (ANCA) and histological analysis. The 10-year survival rate is estimated to be 40% when the kidneys are involved and 60–70% when there is no kidney involvement.

The standard therapy for GPA is a combination of glucocorticoids and cyclophosphamide. In young patients, cyclophosphamide should be switched to azathioprine in the maintenance phase.

A multidisciplinary approach, involving otorhinolaryngologists, oral and maxillofacial surgeons, oral physicians, rheumatologists, renal and respiratory physicians, and ophthalmologists, is necessary for the diagnosis and therapeutic treatment of GPA. ENT physicians have a determining role in recognising the early onset of the disease and starting an appropriate therapy.

Keywords

Granulomatosis with polyangiitis, Wegener's granulomatosis, autoimmunity, vasculitis, vertigo, neurological symptoms, vascular symptoms

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Introduction

Granulomatosis with polyangiitis (GPA) is an uncommon immunologically mediated systemic disease of unknown aetiology that is pathologically characterised by an inflammatory reaction pattern (necrosis, granulomatous inflammation and vasculitis) that occurs in the upper and lower respiratory tracts and kidneys. GPA is an autoimmune

[1]Policlinico "Umberto I" – Rome, Department of Organs of Sense – ENT Section, University of Rome "La Sapienza", Italy
[2]Hospital "Maggiore" – Parma, Department of Otolaryngology and Otoneurosurgery, Rome, Italy

Corresponding author:
Gian Franco Macri, Hospital "Maggiore" – Parma - Department of Otolaryngology and Otoneurosurgery, Lgo Valerio Bacigalupo 32 C, 00142 Rome, Italy.
Email: giano1979@hotmail.com

multisystemic small-vessel vasculitis[1] that is included in the group of anti-neutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitides.

The disease was initially described by Klinger in 1931 as a variant of polyarteritis nodosa and was described for the first time as a separated syndrome by Friedrich Wegener in two articles appearing in 1936 and 1939.[2,3]

In 1954, Godman and Churg introduced the term 'Wegener's granulomatosis' and further delineated the clinical and pathological features,[4] establishing the criteria to diagnose the disease: (1) granuloma in the upper airways; (2) necrotising vasculitis; and (3) glomerulonephritis.

Until recently the disease was known as Wegener's granulomatosis, but it has now been renamed 'Granulomatosis with polyangiitis (GPA)'.[5]

Although the aetiology of GPA remains largely unknown, it is believed to be autoimmune in origin, triggered by environmental events on a poorly characterised background of genetic susceptibility.[6,7]

GPA is a relatively rare condition.[8] In Europe the prevalence of GPA is five cases per 100,000 population, with greater incidence in Northern Europe. GPA can occur in all racial groups but predominantly affects Caucasians. Both sexes are affected equally. GPA affects a wide age range (age range, 8–99 years), with a mean age at diagnosis of 40 years.[9] A review of major literature in the last 10 years was performed.

Clinical manifestations

GPA is characterised by necrotising granulomatous lesions of the respiratory tract, vasculitis and glomerulonephritis. Classically, the acronym ELK is used to describe the clinical involvement of the ear, nose and throat (ENT); lungs; and kidneys (Table 1).

In 1953, Fienberg introduced the term of 'limited Wegener's granulomatosis',[10] a concept that was subsequently expanded by Carrington and Liebow[11] and supported by Cassan et al.[12] Limited GPA is a restricted form of the disease in which clinical findings are initially present only locoregionally.[13]

The current classification of GPA describes limited GPA as a disease involving only one or two of the ELK areas.[14] Progression to the systemic form of GPA is unpredictable when the disease is left untreated.[15]

Classic otorhinolaryngologic symptoms may be the initial clinical manifestation of GPA because the upper respiratory tract is involved in 70–100% of cases.[16] The nasal cavity and the paranasal sinuses are the most common sites of involvement in the head and neck area (85–100%), whereas otological disease is found in approximately 35% (range, 19–61%) of cases.[17] Isolated ear involvement preceding the respiratory and renal manifestations is uncommonly reported.[18]

Otological involvement may occasionally be the first and only sign of GPA;[19,20] mastoiditis may be the first manifestation of GPA.[21] Fauci et al.[22] reported that 25% of patients with GPA presented with serous otitis media and that 6% of patients presented with hearing loss as the initial sign of the disease. Kempf[23] reported that approximately half of patients with GPA developed otological manifestations in the early stage of the disease.

Early diagnosis is essential to prevent long-term complications. Otological involvement can be seen in up to 40% of patients who require early appropriate treatment to prevent permanent sensorineural hearing loss or permanent facial nerve paralysis. Primary otological presentation occurs in 20–25% of patients, and diagnosis can be difficult when the disease is limited to this locoregional phase.[24]

Otological involvement is divided into the following basic types: (1) serous otitis media, the most frequent manifestation,[25,26] which results from Eustachian tube obstruction and nasopharyngeal involvement;[19] (2) chronic otitis media, which is caused by primary involvement of the middle ear and mastoid cavity; (3) sensorineural hearing loss, the aetiology of which is unknown but is considered to involve either: (i) vasculitis of the cochlear vessels and deposition of the immune complexes in the cochlea; (ii) pressure on the acoustic nerve by granulomatous lesions;[26,27] or (iii) toxic effects of inflammatory by-products arising from the middle ear through the round window, which adversely affect the vasa nervorum and the cochlear vessels;[8,28,29] (4) vertigo, thought to be due to either: (i) immune complex deposition in the vestibular portion or (ii) manifestation of central nervous system involvement caused by a polyneuritis; and (5) facial nerve palsy, which is seen in 8–10% of cases and is usually associated with otitis media.[30] In the majority of cases, facial paralysis improves with cytotoxic therapy.

Table 1. Clinical manifestations in GPA.

Organ	Clinical manifestation
Generic	General malaise, myalgia, arthralgia, anorexia, weight loss and pyrexia
Skin	Leucocytoclastic vasculitis, digital infarcts, purpura, cutaneous ulcers and gangrene
Oral cavity	Oral ulcers, oral granulomatous lesions, gingival hyperplasia with strawberry-like aspect, swallow
Eye	Episcleritis, scleritis, conjunctivitis, keratitis, uveitis, retinal vasculitis, retinal arterial or venous thrombosis, retinal exudates, retinal haemorrhages, blurred vision, blindness, proptosis and orbital granulomatous masses, epiphora
Nose and paranasal sinus	Persistent-recurrent nasal discharges, blood-stained nasal discharge, epistaxis, crusting, mucosal ulceration, nasal bridge collapse, nasal granulomatous lesions, parasinus and sinus inflammation, regional tenderness
Ear	Sensorineural hearing loss and conductive hearing loss
Upper airway	Subglottic or tracheal stenosis
Lower airway	Cough, breathlessness, stridor, wheeze, small air way obstruction, pulmonary nodules, cavitating lung lesions, pleuritis, pleural effusions, pulmonary infiltrates, pulmonary haemorrhage, alveolar capillaritis and respiratory failure
Cardiovascular	Small vessel vasculitis, occlusive vascular disease, pericarditis, pericardial effusions, cardiomyopathy, valvular heart disease, ischaemic heart disease, heart failure
Gastrointestinal	Acute abdomen secondary to peritonitis or bowel ischaemia which may be secondary to mesenteric vasculitis
Kidney	Diffuse pauci-immune crescentic necrotising glomerulonephritis, haematuria, proteinuria, cellular casts on urine cytology, renal impairment manifested as acute kidney injury, chronic kidney disease or end-stage renal failure
Central and peripheral nervous system	Headache, meningitis, seizures, cerebrovascular accidents, spinal cord lesions, cranial nerve palsies, sensory or motor peripheral neuropathy, mononeuritis multiplex, sensorineural hearing loss, cerebral mass lesions
Musculoskeletal	Inflammatory arthritis, erosive or deforming, arhtralgia, myalgia, arthralgia

The typical otologic symptoms in GPA of common observation by ENT specialist is ANCA-induced otitis media. The clinical findings of this middle otitis are: (1) otitis media following sudden progressive hearing loss; (2) intractable otitis media not effected by antibiotics and tympanic tube insertion; (3) mostly PR3- and or MPO-ANCA positive; (4) occasionally clinical complications such as facial palsy or hypertrophic pachymeningitis; (5) tympanic membrane showing a dull appearance and vessel dilatation of tympanic membrane, granulationor normal appearance only with sensorineural hearing loss; (6) effectiveness of corticosteroid and immunosuppressive therapy using cyclophosphamide or methotrexate.

Conductive hearing loss, sensorineural hearing loss or mixed hearing loss can be observed at different clinical phases. Conductive hearing loss is caused by granulation and effusion in the middle ear, obstruction of the Eustachian tube, effusion in the middle ear caused by vasculitis in the middle ear mucosa.

Sensorineural or mixed hearing loss is caused by inflammation in the inner ear, often it is a reversible hearing loss and it had not progressed to complete deafness.

Nahohiro and Yukiko show, in their study, that the reversible nature of the hearing loss indicates that the hair cells remain intact. It is known that the inner ear maintains a specific ionic balance with ions pumping mechanism which ensures a high level of K+ ions in the endolymph and creates a 140–180 mV driving force by stria vascularis for positively charged K+ ions to flow through the stereocilia. Hair cells are morphologically coupled to fibrocytes and supporting cells by gap junctions and K+ ions recirculate from the endolymph to the stria vascularis through hair cells and supporting cells. The progressive reduction of capillaries microcirculation at spiral ligament and Stria vascularis, bring to reduction of Endocochlear Potential (EP) (in this phase sensorineural hearing loss is established). If the damage persists and is not treated pharmacologically this could lead to: structural dysfunction of stria vascularis, ischemia in the inner ear and permanent hair cell damage with inner ear damage and definitive hearing loss.

The temporal bone histopathology of cases of complete deafness caused by GPA showed that tympanic granulation and inflammatory substances also invade the inner ear through the round window,

the stria vascularis was slightly atrophic and spiral ganglion cells were well preserved.[31]

Biopsy specimens from the head and neck region are often small, and it is usually difficult to make a definite histologic diagnosis,[13,24,32] particularly when the biopsy is taken from the middle ear.[28,33] Kempf[23] reported that the expected typical histological picture of GPA was not found in middle ear biopsies. Devaney et al.[34] reported that only one of three mastoid biopsy specimens and none of four middle ear specimens showed evidence of GPA. In the head and neck region, biopsies from the paranasal sinuses showed higher positive rates for GPA. Therefore, it is recommended that biopsy specimens be taken from the paranasal sinus or nose.[27,35]

It has been reported that cytoplasmic (c)-ANCA is highly specific for active GPA and that c-ANCA titres are directly related to GPA disease activity.[36] At Hokkaido University Graduate School of Medicine, treatment for GPA is started when the c-ANCA titre is positive and clinical features of GPA are present, even if a histological diagnosis cannot be made.

Delays in diagnosis and initiation of therapy negatively affect the prognosis for hearing loss. Therefore, it is important to start treatment before irreversible change occurs in the middle and inner ears.

The most common anatomical site for manifestation of lesions in GPA is the upper airway. GPA can also affect the eyes, skin, joints and nervous system.[37] Renal involvement is characterised by abnormal renal function with red cell casts in urinalysis, and glomerulonephritis on renal biopsy.[38]

The most common features of nasal disease activity were crusting, blood-stained rhinorrhoea and nasal obstruction. Septal perforation was the most common feature of damage (24%). These findings agree with case studies reported in the literature. Acute pain, fever and mucopurulent discharge were reported in 10% of the patients and the area most affected was the maxillary sinus. The most common organism identified was *Staphylococcus aureus* which has previously been associated with GPA activity and relapse.[39]

The prevalence of subglottic stenosis was 23%, while in the reported series it was in the range of 6–23%.[30,40,41] Patients with subglottic stenosis were younger than those with a normal subglottis and 60% were women. As in other case studies, stridor and reduced exercise tolerance were often the presenting symptoms.[42]

Diagnosis

There are no diagnostic criteria for GPA. Diagnosis is based on a combination of clinical manifestations positive ANCA serology and histological evidence of necrotising vasculitis, necrotising glomerulonephritis or granulomatous inflammation from a relevant organ biopsy, such as skin, lung or kidney.

It should be emphasised that positive ANCA serology is not essential for the diagnosis of GPA if clinical and histological findings point to a diagnosis of GPA should be taken to exclude vasculitis mimics or other types of sistemi vasculitis.[43]

c-ANCA, first reported in 1985 by Wan der Woude et al.,[36] are highly specific for GPA, especially in the active phase. Thus, the presence of c-ANCA in GPA is a great aid to diagnosis. Difficulty in diagnosis often delays the initiation of treatment, and the disease occasionally progresses to the irreversible phase. The typical ANCA pattern associated with GPA is c-ANCA recognising the autoantigen proteinase 3 (PR3), which is a protease found in the granules of neutrophils. Fewer than 20% of patients with GPA have a perinuclear pattern recognising the autoantigen myeloperoxidase (MPO).

It was found that ANCA are highly specific for this disease, and as a result, there was great optimism about their potential for diagnosis. ANCA have two applications: (1) as a diagnostic test; and (2) as a marker of disease activity. Contrary to opinion, this serological marker has many limitations. Its sensitivity depends on: (1) the stage of the disease; and (2) the activity of the disease. Pooled ANCA sensitivity for active disease is 91% as compared to 63% for inactive disease.[44] Pooled ANCA sensitivity for active locoregional disease is 60% as compared to 93% for active generalised disease.[45] Limited manifestations of GPA have a high rate of ANCA false negatives (30%).

ANCA false positives have been reported for GPA and the false positive value is determined by the prevalence of GPA. Therefore, if the prevalence of GPA is low, a positive c-ANCA is very likely to be a false positive result.

According to the current literature, screening for ANCA begins with indirect immunofluorescence assay on fixed human neutrophils, after which is followed by methods determining the antigen specificities of the autoantibodies as proteinase 3

Table 2. The American College of Rheumatology criteria for GPA diagnosis.

Classification criteria	
Nasal or oral inflammation	Painful or painless oral ulcers or purulent or bloody nasal discharge
Abnormal chest radiograph	Pulmonary nodules, fixed pulmonary infiltrates or pulmonary cavities
Abnormal urinary sediment	Microscopic haematuria with or without red cell casts
Granulomatous inflammation	Biopsy of an artery or perivascular area shows granulomatous inflammation

(PR3) or myeloperoxidase (MPO). In order to avoid false negative results a broad spectrum of anti-PR3 detection methods has been developed to increase their sensitivity as ELISA test. ELISA using a mixture of human native (hn) PR3 combined with the human recombinant (hr) protein yield a very high sensitivity, but their specificity may vary.[46] Qualitative assays of ANCA immunofluorescence identify cytoplasmic c-ANCA, perinuclear p-ANCA and atypical ANCA, while enzyme immunosorbent assays with ELISA test give quantitative measure of PR3-ANCA and MPO-ANCA titres. The use of IF combined with ELISA gives a 96% sensitivity and 98.5% specificity for ANCA-associated vasculitides.

In 2011 the American College of Rheumatology proposed classification criteria for GPA (Table 2). The presence of two or more of these four criteria yields a sensitivity of 88%. The presence of two or more of these four criteria yields a specificity of 92%.[42]

Histologically, it is challenging to diagnose GPA from nasal biopsies, and it is rare to see a 'full house' of necrotising granulomata with giant cells and neutrophil-predominant vasculitis.[45] The majority of head and neck biopsy specimens have non-specific findings. The classical triad of vasculitis, necrosis and granulomatous inflammation can be observed in up to 16% of cases of GPA. Vasculitis and granulomas are observed together in up to 21% of cases, and in 23% of head and neck biopsy specimens one can observe vasculitic and necrotic features.[34] The technical difficulty of obtaining an appropriate biopsy specimen from the ear may be a large factor in explaining these findings. The majority of pulmonary biopsies show the classical triad of disease features.

There are no diagnostic criteria for GPA and diagnosis is based on a combination of the clinical manifestations of systemic disease which suggest a diagnosis of vasculitis; positive c-ANCA serology and histological evidence of necrotising vasculitis, necrotising glomerulonephritis or granulomatous inflammation from a relevant organ biopsy, such as the skin, lung or kidney. Oral lesions are uncommon during clinical anamnesis but when this lesions were observed is considered a distinctive diagnostic criteria for GPA and their recognition is most important for timely diagnosis.[47] Because an otologic disorder may be part of the initial clinical presentation of GPA all unilateral or bilateral chronic middle otitis not satisfying to the local or general antibiotics therapy, or in patients in whom discrepancies between otoscopic findings and severe mixed hypoacusis are noted, an autoimmune disease can be suspected.[48,49]

The prompt diagnosis of GPA is important for prognostic reasons, because immunosuppression regimes can induce quickly clinical remission and in the long term reduce disease morbidity and mortality. It should be stated that positive ANCA serology is not essential for a diagnosis of GPA if the clinical and histological evidence can support a diagnosis of GPA. Similarly, caution should be taken in interpreting positive ANCA serology when there are no clinical signs, symptoms or histological evidence suggestive of ANCA-associated vasculitides.

There are no special diagnostic tests for GPA. The otorhinolaringologist is often one of the first physicians for patients with GPA. The recognition of signs and symptoms of GPA affecting the upper respiratory tract is crucial for an effective diagnostic evaluation that allows the timely initiation of appropriate therapy.

Detection of ANCA and histological examination of biopsies are not always sufficient for the diagnosis of GPA, which also requires correct examination and recording of clinical signs and symptoms and exclusion of other causes of the clinical presentation. We aimed to identify, characterise and evaluate ENT signs and symptoms in GPA patients so that the condition could be identified at an earlier stage.[50]

Differential diagnosis

Rheumatoid vasculitis (RV) is a major differential diagnosis. RV usually occurs in seropositive rheumatoid arthritis (RA) patients with longstanding disease. GPA lesions show necrotising granulomatous vasculitis of small vessels, while the RV lesions mostly shows leukocytoclastic vasculitis (LCV).[51] Other differential diagnoses include pyoderma gangrenosum, lymphoma, tuberculosis, sarcoidosis and deep fungal infection.

Otological symptoms must be differentiated from sudden sensorineural hearing loss[46] and Meniere's syndrome.[53] In most cases, gradual hearing loss due to effusion and granulation in the middle ear is treated as an intractable otitis media. With sudden progressive hearing loss, an autoimmune disease should be suspected and require extensive serological testing.

Prognosis

Left untreated, GPA is a fatal condition, as renal failure secondary to renal involvement reduces the prognosis for recovery. Therapy for GPA has increased survival, resulting in remission in more than 90% of patients, particularly in patients who have not yet developed major renal damage.[14] If untreated, the disease usually runs a rapidly fatal course, and 82% of patients die within 1 year. Thus, accurate and early diagnosis of GPA is of paramount importance to improve the prognosis.

The 10-year survival rate is estimated to be 40% when the kidneys are involved and 60–70% when there is no kidney involvement.[54] Therefore, it is important to recognise the disease early, as the limited form of the disease is amenable to effective therapy, and effective therapy leads to longer patient survival.

Therapy

In 1983, Fauci[22] reported the efficacy of treatment using a combination of glucocorticoids and cyclophosphamide, and this treatment has become the standard for GPA.

Additionally, Gross[55] suggested that in young patients, cyclophosphamide should be switched to azathioprine in the maintenance phase.

Because it was reported that glucocorticoid treatment alone cannot achieve complete remission of an otological manifestation in patients with GPA,[35] we recommend the combined use of immunosuppressive drugs when there is middle and inner ear involvement.

The majority of GPA patients with serous otitis media resulting from Eustachian tube dysfunction could be helped by tympanostomy tube placement. Chronic otitis media and sensorineural hearing loss in GPA occur from primary involvement of the ear, and both of these symptoms fail to respond to conventional treatment such as antibiotics. However, early treatment with glucocorticoids and cyclophosphamide can resolve these symptoms.[45] Different authors emphasise that surgical intervention in cases of middle ear involvement should be minimal and performed only for diagnostic purposes, particularly during the acute stage.[25]

Progressive sensorineural hearing loss was evident in most cases and is one of the major otological symptoms. This symptom can be partially recovered by treatment with corticosteroid alone such as Prednisolone (0.8–1 mg/kg/day) is tapered slowly (20% reduced every month) and then maintained (5–10 mg/day) while monitoring the ANCA titre. However, corticosteroids alone could not achieve complete remission in many cases and progressed to definitive hearing. In this cases, therapy can be enhanced with immunosuppression drugs as cyclophosphamide or methotrexate although these drugs were questioned for possible clinical complications.[31]

When middle otitis ANCA associated was suspected but the ANCA titre was negative, histology of the mastoid granulation taken by mastoidectomy or nasal mucosa was recommended, although the biopsy from the middle ear specimen showed a lower positive rate.

Conclusions

GPA is an idiopathic necrotising systemic vasculitis involving both the upper and lower respiratory tracts and the kidneys. The pathogenesis of GPA is still unknown, although an autoimmune response appears to be involved in the development of the disease. In our opinion, for the diagnosis and therapeutic treatment of GPA, a multidisciplinary approach involving otorhinolaryngologists, oral and maxillofacial surgeons, oral physicians, rheumatologists, renal and respiratory physicians, and ophthalmologists is needed.

GPA must be considered when patients do not improve as expected despite being given adequate treatment, when they have unspecific systemic symptoms suggesting systemic disease (fever, myalgia, arthralgia) or when other organs are involved (eyes, kidneys, lungs and others). Prolonged evolution times of over 20 days to observe the regression of ear inflammation suggests a specific aetiology to support disease activity.

Therefore, ENT physicians have a determining role in recognising the early onset of the disease and starting proper therapy. Occasionally, ear conditions are the first and only symptoms to appear. We reviewed cases of GPA that presented with otological manifestations. The most frequent finding was chronic otitis media. Occasionally, otological manifestations presented as the first sign of the disease, which made diagnosis more difficult. Therefore, GPA should be included in the differential diagnosis in cases of atypical inflammation of the ear. Biopsy specimens are often small, and histologic diagnosis from the middle ear is usually difficult. c-ANCA is not helpful in making a diagnosis in these localised cases. Early diagnosis and appropriate treatment is important to prevent the progression of this disease to an irreversible phase.

In conclusion, the early diagnosis and specific treatment of GPA is important but difficult to achieve because of the multiplicity of presenting symptoms and unclear histological features. Otological symptoms may be the first clinical feature of GPA. Therefore, a high level of suspicion toward GPA is needed from the otolaryngologist, especially when confronted with ineffective prolonged antibiotic treatment for otitis media.

Declaration of Conflicting Interest

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