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Syed Mansoor Ahmed Shah

Aga Khan University, mansoor.shah@aku.edu

Malik Anas Rabbani

Aga Khan University

Ambreen Gul

Aga Khan University

Aasim Ahmad

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Case Report

Unusual Presentations of Wegener's Granulomatosis: Pitfalls in Early Diagnosis

Syed Mansoor Ahmed Shah, Malik Anas Rabbani, Ambreen Gul, Aasim Ahmad

Department of Medicine, Aga Khan University Hospital, Karachi

ABSTRACT. Wegener's Granulomatosis (WG) is a disorder characterized by necrotizing granulomatous vasculitis that primarily affects the upper and lower respiratory tracts and the kidneys. Although the cause is unknown, there is strong evidence that this is an autoimmune disease and immunosuppressive therapy with cyclophosphamide and corticosteroids efficiently relieves the symptoms and, prevents relapses. We report on four cases of WG that presented with unusual features. The first patient presented with vague joint pain, blackish discoloration of the skin and leg ulcers. The second patient presented as fever of unknown origin and gingival hyperplasia. The third patient presented with hearing loss while the fourth presented with arthritis, conjunctivitis and painful swelling of the ear. It is emphasized that WG is a complex disease and can involve multiple organ systems. Early recognition and institution of proper treatment are crucial for optimal outcome.

Key Words: Wegener's Granulomatosis, leg ulcer, glomerulonephritis, proptosis, gingival hyperplasia, sensorineural deafness, relapsing polychondritis, arthritis.

Introduction

Wegener's Granulomatosis (WG) is a disorder characterized by necrotizing granulomatous

vasculitis that primarily affects the upper and lower respiratory tracts and the kidneys.¹ Heinz Klinger first reported it in 1931, but it was not until 1936 that Wegener clearly defined the clinicopathological spectrum of the syndrome that now bears his name.^{2,3} Although the cause is unknown, there is strong evidence that this is an autoimmune disease as immunosuppressive therapy with cyclophosphamide and corticosteroids efficiently relieves the symptoms and, prevents

Reprint request and correspondence to:

Dr. Syed Mansoor Ahmed Shah
Department of Medicine
Aga Khan University Hospital
Stadium Road, PO Box 3500
Karachi – 74800
Pakistan

relapses.⁴ The presenting features of WG are variable and diagnosis is based on the criteria of the American College of Rheumatology (ACR) published in 1990: nasal or oral inflammation with painful or painless ulcers or purulent bloody discharge; abnormal chest radiography showing the presence of nodules, fixed infiltrates, or cavities; urinary sediment with microscopic hematuria (>5 RBCs per high power field) or red cell casts in urinary sediment; and granulomatous inflammation on biopsy of an artery or in the perivascular area. A patient who meets at least two of these four criteria maybe diagnosed as having “classic” WG.⁵ The sensitivity and specificity of these criteria are 88% and 92% respectively. “Limited” disease (without glomerulonephritis) and unusual presentations can lead to delay in diagnosis and, therefore, treatment. A consequence of delay in diagnosis is that severe renal failure may have developed before treatment is started.⁶ The prevalence of skin disease in WG has been reported to be between 30 and 50%, while musculoskeletal problems may accompany the symptoms in 67% and ear-nose-and-throat (ENT) problems in 92% of the patients.⁴ About 62% have oral mucosal disease and ocular manifestations may be seen in up to 50% of patients.

Wegener’s Granulomatosis is an uncommon, but not a rare disease, which affects both sexes equally. It can occur at any age, but most frequently presents in adulthood. The mean age of onset in a cohort of 158 patients reported by Hoffman et al was 40 years.¹

We present four cases of WG with unusual clinical features. The presentation is followed by discussion on the clinicopathologic features and the role of antineutrophil cytoplasmic antibody (ANCA) in the diagnosis of WG.

Case 1 - The non-healing leg ulcers

A 38-year-old seaman presented with vague joint aches and pains as well as blackish discoloration of the fingers and the toes, which were thought to be vasculitic in nature. He was treated with steroids for six months but was lost to follow-up. He presented again four years later with swollen ankle joints and was labeled as having rheumatoid arthritis without any investigations. He was again treated with steroids followed by methotrexate for about one year. Two years later, he developed blood stained nasal discharge; x-ray of the paranasal sinuses was suggestive of maxillary sinusitis and a biopsy revealed non-specific acute and chronic inflammation. A few weeks later, he developed ulcers on the lateral aspect of his left leg and on the medial aspect of the right leg. Biopsy of the ulcer revealed chronic granulomatous inflammation with extensive necrosis. A provisional diagnosis of cutaneous tuberculosis was made and he received standard four drug anti-tuberculous therapy (ATT) for nine months without any improvement in the leg ulcers. Subsequently, he developed hemoptysis, microscopic hematuria and proteinuria; the serum creatinine was 159 $\mu\text{mol/L}$ and creatinine clearance was 40 ml/min. Renal biopsy showed pauci-immune focal necrotizing glomerulonephritis as well as vasculitic changes. Correlating the pathological and clinical findings, WG was considered to be a likely possibility. The patient was started on steroids and cyclophosphamide. Following this, the leg ulcers healed, nasal discharge and proteinuria disappeared and renal function normalized. Cyclophosphamide was changed to azathioprine after three months.

Three years later, he stopped treatment and subsequently presented with proptosis of the right eye. Computerized tomographic (CT) scan revealed a soft tissue enhancing mass in

the right orbit pushing the eyeball anteriorly and surrounding the optic nerve completely. There was destruction of the medial wall with extension into the paranasal sinuses. An attempt was made to clear the mass, but was unsuccessful. Biopsy revealed only fibrocollagenous tissue. Subsequently, he lost his right eye. From renal point of view, he continues to remain in remission on steroids and azathioprine when last seen.

Case 2 - Fever of unknown origin

A 53-year-old banker presented with one week's history of swollen gums, right cervical lymphadenopathy and low grade fever. Chest X-ray showed hazy apices. Fine needle aspiration of the cervical lymph node showed chronic granulomatous inflammation without caseation. He was started on standard four drug anti-tuberculous therapy (ATT). The symptoms, however, persisted. Over the next three weeks, several other antimicrobials were also tried without any benefit. He subsequently developed generalized weakness and significant weight loss. It was around this time, about four weeks after the onset of his symptoms, that he presented to our institution.

At the time of presentation, he had a pulse of 108/min with blood pressure 100/60 mmHg and temperature of 38°C. His body weight was 30 kg. Right jugulodigastric lymph node was palpable and his gums were swollen and inflamed. Liver was palpable three cm below the right costal margin. Laboratory investigations including complete blood count, liver function tests and electrolytes were unremarkable; the blood urea nitrogen (BUN) was 6 mmol/L and creatinine was 80 µmol/L. Bone marrow examination was also normal. Bone marrow culture, smear and culture for acid fast bacilli (AFB) were negative. Echocardiogram did not show any vegetations. A CT scan of the chest and abdomen performed at this time showed no significant abnormality

except slightly bulky kidneys. Soon after, the patient developed acute oliguric renal failure with BUN, creatinine and uric acid rising to 52 mmol/L, 875 µmol/L and 660 µmol/L respectively. Repeat urinalysis showed proteinuria and microscopic hematuria. He also had an episode of hemoptysis, but the chest X-ray was normal. Bronchoscopy showed blood trickling out of the posterior segment of the upper lobe. Bronchial washings for AFB, fungal smear and culture were negative. Bronchial biopsy showed mild to moderate chronic inflammation with no specific features or evidence of malignancy. Renal biopsy showed pauci-immune crescentic nephritis with focal and segmental necrotizing inflammation along with vasculitis suggestive of WG. Thereafter, all medications were discontinued and the patient was started on pulse methylprednisolone followed by oral steroids and oral cyclophosphamide. Cyclophosphamide was switched to azathioprine after three months. He underwent few sessions of hemodialysis till his renal function normalized. Five years later, he continues to be in remission with mild proteinuria and normal renal function with serum creatinine of 115 µmol/L. His body weight, when last seen, was 77 kg.

Case 3 - The lady with deafness

A 60-year-old lady presented with one month's history of fever, red eye, decreased hearing, weight loss and vague ill health. On examination she was febrile with a temperature of 38°C. Systemic examination was unremarkable. Ophthalmologic examination revealed uveitis. The blood tests showed a mildly elevated leukocyte count of $11.1 \times 10^9/L$ with an erythrocyte sedimentation rate (ESR) of 122 mm/hr. All other investigations including urea, creatinine, electrolytes, liver function tests (LFT), immune electrophoresis and urinalysis were normal.

Audiogram showed a mixed sensorineural deafness in both ears, worse in the right ear. Considering auto-immune deafness, she was empirically started on steroids. Her deafness improved dramatically and she was able to hear perfectly well within a week of treatment. About a month following initial presentation, the patient developed loose stools associated with fever. On this occasion, the serum creatinine was found to be 230 $\mu\text{mol/L}$. Urinalysis showed trace proteins, microscopic hematuria and granular casts. Renal biopsy showed pauciimmune focal and segmental necrotizing glomerulonephritis. The cytoplasmic-ANCA (c-ANCA) was also raised to 5.42 U/ml (normal is less than 2). All these findings were consistent with WG. The patient was put on cyclophosphamide in addition to steroids. Her serum creatinine came down to 141 $\mu\text{mol/L}$ and has remained stable since then.

Case 4 - The swollen ear.

A 46-years-old male presented with two weeks history of arthritis, painful red eyes and fever. There was no history of diarrhea, dysuria or sexual contact. On examination, he was hemodynamically stable with temperature of 38°C. The metacarpophalangeal joints of both hands, both elbows, right shoulder and both ankle joints were inflamed. Eye examination revealed conjunctivitis, marginal keratitis and scleritis. Systemic examination was unremarkable. Laboratory investigations revealed hemoglobin of 128 gm/L, ESR of 80mm/hr, C-reactive protein of 10.3 mg/dl (normal 0 to 1.0); antinuclear and anti-ds DNA antibody and rheumatoid factor were negative. The anti-streptolysin titer was within normal range. The serum creatinine was 88 $\mu\text{mol/L}$, while urinalysis revealed microscopic hematuria and trace proteinuria. A provisional diagnosis of Rheumatoid arthritis or Reiter's disease was made and the patient

was started on oral steroids, non-steroidal anti-inflammatory drugs (NSAIDs), mesalazine and broad spectrum intravenous antibiotics. With NSAIDs, the arthritis improved and the patient was discharged on mesalazine and NSAIDs. Over the next three months, he had another episode of arthritis involving the large joints and was noted to have painful, swollen and reddish discoloration of his ears. At this time, a diagnosis of relapsing poly-chondritis was made; his renal function was noted to be abnormal with serum creatinine of 203 $\mu\text{mol/L}$. Urinalysis revealed 2+ proteinuria and microscopic hematuria. He was referred to the nephrology service for further evaluation. A 24-hours urine specimen revealed protein excretion of 3.4 gm and a decreased creatinine clearance of 36 ml/min. c-ANCA was found to be very high at 84 U/ml (Normal 0-2). Subsequently, a renal biopsy was performed which revealed pauci-immune, crescentic, necrotizing glomerulonephritis consistent with WG. Over the next five months, he received five cycles of pulse methylprednisolone (1 gm/day for 3 days) along with oral cyclophosphamide which was changed to azathioprine after 12 weeks. Six months after initiation of therapy he remains symptom-free with a stable serum creatinine of 106 $\mu\text{mol/L}$ and creatinine clearance of 68 ml/min. There was no proteinuria.

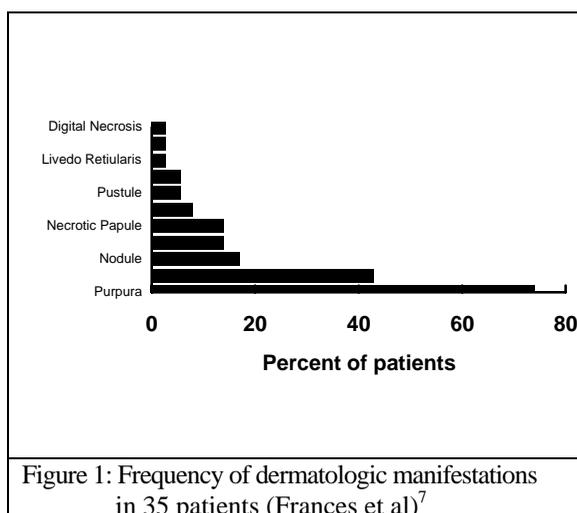
Discussion

The mean and median period from the onset of the symptoms to the diagnosis of WG were 4.7 and 15 months respectively in a study by Hoffman et al.¹ The second and third cases in our report fall in this category. However, in the first and second cases, early diagnosis was hampered by a "misdiagnosis". Other studies have shown that although accurate diagnosis was made within the first three months in

42% of the patients, the disease, especially in those without renal manifestations, followed a confusing and indolent course of up to 16 years before a definitive diagnosis was established.^{7,8} In Pakistan, because of the high prevalence of tuberculosis, a diagnosis of tuberculosis is often made in patients with signs and symptoms or histopathology of "granulomatous disease". It is imperative to mention here that it has been proposed that the clinical features of WG reflect a spectrum of immune reactivity similar to that seen in mycobacterial disease.⁹ In such a clinical/immunological spectrum, the local chronic inflammation in upper and lower airways would reflect the tuberculoid end of the disease, whereas vasculitis (in the kidney) would reflect the lepromatous end of the spectrum.⁶

The patient in Case-1 presented with cutaneous manifestations of WG. The prevalence of skin disease has been reported to be between 30% and 50%, and occasionally it may be the initial sign of the disease.^{4,9-11} It can continue for months and even years before severe multi-organ system involvement develops.¹⁰

The lower extremities are the most common location of the disease involved in 76% of the cases.¹¹ However, no single skin lesion is pathognomonic for WG. The dermatological manifestations observed by Frances et al in 35 of the 75 patients studied is shown in Figure 1.⁷ Histologically, the cutaneous lesions can cover a wide spectrum of findings. Leukocytoclastic vasculitis was the most common type in the study by Daoud et al¹¹ and necrotizing vasculitis in the study by Frances et al.⁷ Though previously described as a vasculitis of small and medium sized arteries, results have led researchers to conclude that all skin vessels could be involved in the pathologic process of WG.⁷ The prevalence of renal, ocular and central nervous system involvement is much



higher in patients with specific cutaneous involvement than in the other patients.¹¹ In the first patient, the disease manifested as joint aches and nasal problems, and it is known that musculoskeletal problems may accompany the symptoms in 67% and ENT problems in 92% of the patients.¹ As is seen in this case, it is not uncommon to label ENT problems as allergy or infection. However, it was not until hemoptysis developed that an extensive evaluation, finally leading to a renal biopsy, was performed. This correlation of clinical and pathological findings resulted in the diagnosis of WG.

In Case-2, the patient had gingival hyperplasia on presentation. In a study of 56 patients, 62% had oral mucosal disease with the commonest manifestation being oropharyngeal ulcers in 60% patients and gingival symptoms in 7%.¹³ In another study of 118 patients, the most frequent manifestation of early or late disease was buccal ulcer.¹² Well-documented reports for hyperplastic gingivitis can be found.^{6,14,15} An unusual and distinctive gingivitis is considered pathognomonic of WG in the early stages and has been reported to occur in many patients.^{16,17} It is characterized by an exophytic hyperplasia with petechial flecks and a red, friable, granular appearance.¹⁸ The

gingivitis begins focally in the inter-dental papillae and quickly spreads to produce segmental or panoral gingivitis, often accompanied by alveolar bone loss and tooth mobility.¹⁶⁻¹⁹ Pain and bleeding are common. Biopsy specimens generally show chronic, non-specific inflammation with eosinophils and histiocytes with diffuse foci of acute inflammation containing polymorphonuclear leukocytes and eosinophils, forming micro-abscesses in a few instances.¹⁴ Usually giant cells are present,^{11,19} but vasculitis does not occur.^{11,17,19} In the study by Patten et al, four of the 40 patients (10%) had oral mucosal disease but the characteristic gingivitis was present in only one of the patients. However, the presence of fever and a palpable lymph node in this case led to a search for an infection and, as already mentioned due to high prevalence of tuberculosis in this part of the world, anti-tuberculous therapy was started. Since the fever was present in conjunction with weight loss, a search was also made for occult malignancy. Retrospectively, the presence of leukocytosis was not a non-specific concomitant phenomenon. In fact, neutrophils may have a primary role in the pathogenesis, since antibody dependent activation of granulocytes is being emphasized in recent studies. Patients with leukocytosis are therefore more likely to have more aggressive and active disease.²⁰ It was not until the development of the acute renal failure and the hemoptysis, that a renal biopsy was considered and the patient was diagnosed as WG.

Case-3 presented with sensorineural deafness and uveitis, but the diagnosis was not clear till the development of glomerulonephritis. The ear is frequently involved early.¹² Common symptoms include ear ache, discharge and deafness, which is present in some 15-30% of patients and may be a presenting complaint in as many as one fifth.⁴ Hearing loss is most

commonly conductive but sensorineural impairment may also occur.²¹ Sensorineural deafness may be caused by a vasculitis affecting the vasa nervosum of the eighth nerve, the internal auditory artery or its cochlear branch.^{22,23} Fever due to WG was initially present in 23% of the patients and led in all cases to a search for secondary infection or, when there was concomitant weight loss, for an occult malignancy.¹ In this case, given the signs and symptoms, an autoimmune mechanism was suspected and steroids were started empirically with remarkable improvement. This "autoimmune sensorineural hearing loss" has been defined by otolaryngologists as "that form of progressive sensorineural deafness that responds to no treatment other than immunosuppression".²⁴ A previous report has documented the recovery of sensorineural deafness after treatment with parenteral steroids to a patient, who probably had WG although originally diagnosed as polyarteritis nodosa.²³ However, in the patient in Case-3, an episode of loose stool triggered the usual investigations and led to the discovery of a raised creatinine which was previously normal and the presence of microscopic hematuria. A subsequent renal biopsy along with a raised c-ANCA helped to make the diagnosis of WG. In case-1, during the course of the illness, the patient also developed unilateral proptosis with subsequent loss of the eye. Ophthalmological manifestations including both ocular and orbital diseases have been reported in 40-50% of cases. The main lesion is a granulomatous disease causing an inflammatory mass often with proptosis and/or optic nerve compression and small vessel vasculitis.²⁵ Orbital granulomas can be characterized as contiguous, as in this case, extending from nasal passages or paranasal sinuses or, focal i.e., arising primarily in the orbit.²⁶ The patient in case-3 had uveitis, which has been attributed to small vessel vasculitis, where as the patient in case-

4 had keratitis and scleritis. The other manifestations of vasculitis in the eye include conjunctivitis, episcleritis, optic nerve vasculitis, retinitis, central retinal artery ischemia, or cranial nerve palsies.

In case-4 the dominant feature at the time of presentation was arthritis and eye involvement. In the study by Fauci et al,⁴ joint manifestations were seen in 67% and about 42% had non-deforming polyarthritis as seen in our patient-4. Auricular chondritis has been reported less commonly.²⁷ Unilateral or bilateral external ear inflammation is the most common presenting feature of relapsing polychondritis (RPC), seen in 43% initially and in 83% eventually.²⁸ In some patients, RPC may be simultaneously present with other connective tissue diseases. Whether this association of RPC with other disorders is coincidental, or represents a possible genetic predisposition to the development of two autoimmune diseases is presently unknown.²⁹

Antineutrophil cytoplasmic antibody (ANCA), first described in 1982 in patients with systemic vasculitis and glomerulonephritis, has emerged as a new diagnostic tool and marker of disease activity for vasculitis.^{30,31} Two ANCA patterns may be seen with indirect immunofluorescence of ethanol-fixed neutrophils: a cytoplasmic pattern (c-ANCA) and the artifactual perinuclear pattern (p-ANCA).^{32,33} The major antigen for c-ANCA is proteinase 3, which is found within the azurophil granules of the neutrophils.³⁴ The major antigen for p-ANCA is myeloperoxidase, a lysosomal enzyme found in neutrophils.³²

In classic WG, defined as granulomatous inflammatory disease of the respiratory tract and active glomerulonephritis, more than 90% patients will have positive c-ANCA results. In the absence of active renal disease (so called "limited" Wegener's granulomatosis), the sensitivity of the c-ANCA test may be as low as 65% to 70%.³⁵ However, in Pakistan,

ANCA testing only became available in 1996. Therefore, c-ANCA values could not be obtained in the first and second patient. c-ANCA levels were significantly raised in case-3. For clinicians, c-ANCA serves as a useful marker of WG in some patients and of active disease in others.

Untreated, WG runs a rapidly fatal course, with a mean survival of five months: more than 90% of patients die within two years of diagnosis¹². The earlier studies showed that with the use of corticosteroids, the average time of survival improved to 12.5 months, but the disease was usually fatal despite corticosteroid therapy.³⁶ Fauci et al showed that with continuous low dose oral cyclophosphamide and prednisolone therapy, survival improved markedly, with an 80% five year survival. More than 90% of patients will experience marked improvement and 75% will achieve complete remission.⁴

Wegener's Granulomatosis is a complex disease, which can involve multiple organ systems. Early recognition and institution of appropriate treatment are critical for the optimal outcome of this disease. Diagnosis may be difficult, especially in early stages, in the absence of the complete triad or in the event of a clinical variant or unusual presentation. It must therefore be borne in mind as a differential when disease pathology is granulomatous in origin or if the disease remains unresponsive to treatment. Clinical presentation and laboratory evaluation provide adequate clues but renal biopsy is often required for a definitive diagnosis.

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