Indolent Wegener's granulomatosis

DIANA G. MACFARLANE, J. T. BOURNE, P. A. DIEPPE, AND D. L. EASTY*

*From the University Department of Medicine, Bristol Royal Infirmary, and the*Department of Ophthalmology, Bristol Eye Hospital*

SUMMARY Classical Wegener's granulomatosis is a relentlessly progressive and rapidly fatal disease. A pulmonary 'limited form' is associated with a much better prognosis. We report 3 cases of Wegener's granulomatosis which ran a prolonged indolent course despite major manifestations outside the lower respiratory tract and review the literature on survival.

In the mid-1930s Wegener described an illness in 3 patients which was characterised by destructive lesions in the upper air passages, disseminated vasculitis, and a rapidly progressive course, with death supervening 6–14 months from onset.^{1,2} A major clinical review of 56 cases of Wegener's granulomatosis by Walton in 1958³ confirmed the bad prognosis of the untreated disease. The course was usually rapid and full of incident with a mean survival of 5 months. In 1966 Carrington and Liebow⁴ reported 16 patients with pulmonary lesions histologically identical to those seen in Wegener's granulomatosis, with absent or minor lesions elsewhere, who did not go on to develop renal disease. This 'limited form' had a much better prognosis.

We wish to draw attention to another variant form of Wegener's granulomatosis which also has a prolonged indolent course despite major manifestations outside the lower respiratory tract.

Case reports

CASE 1

A 34-year-old woman had a 10-year history of severe recurrent sinusitis for which she had had several drainage operations and which was subsequently managed with daily douching and antibiotic therapy as necessary. In 1977 a particularly severe episode of sinusitis was accompanied by epistaxis, scleritis, arthralgia, and a raised red indurated rash over the lower limbs. She was found at this time to have developed a large perforation of the cartilaginous septum and a 'saddle nose' deformity (Fig. 1). *Staphylococcus aureus* was grown from nasal swabs. The haemoglobin was 10.8 g/dl, and white blood cell count $10.9 \times 10^9/l$, with 11% eosinophils. A Kveim test

showed an equivocal result, with a multinucleated epithelioid cellular reaction to the injected material. A presumptive diagnosis of sarcoidosis was made. The acute illness settled with antibiotic therapy. In 1979 she was reinvestigated. Multiple biopsies of the nasal space showed nonspecific inflammation, the chest x-ray was clear, and renal function normal. In November 1980 she suddenly became dramatically ill, with swinging pyrexia, synovitis of the wrists and knees, a purpuric rash over the thighs, nail-fold hyperaemia, and marked peripheral oedema. There was a right sclerouveitis, marginal corneal ulcerations, and a granulomatous mass overlying the lacrimal sacs.

Investigations. Haemoglobin 10.1 g/dl, leucocytes $16.6 \times 10^9/l$ with 25% eosinophils, plasma viscosity 2.02 cP, blood and protein in the urine, blood urea 4.8 mmol/l, creatinine clearance 81 ml per minute, 24-hour protein excretion 0.53 g/l, C3 1.4 g/l, C4 0.23 g/l, Clq binding assay 39%, anticomplementary activity assay 4, cryoglobulin 17.5% (mixed); latex test, antinuclear antibody (ANA) test, and the Wassermann reaction (WR) were negative. Renal biopsy showed a focal segmental glomerulitis with crescent formation (Fig. 2), IgM and complement in the loops, and red cell casts in the tubules. Biopsy of the skin lesion showed leucocytoclastic vasculitis. Histology of skin not exposed to light and without any lesion was normal. Chest x-ray showed transient mid and lower zone consolidation (Fig. 3), and sinus x-ray showed opacification with erosion of bone in the medial wall of the right maxillary sinus (Fig. 4).

She was started on treatment with cyclophosphamide 100 mg and prednisolone 20 mg per day orally. There was a rapid response in all aspects of her disease, and 20 months later she was completely well, maintained on 100 mg cyclophosphamide and 10 mg of prednisolone per day.

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Correspondence to Dr D. G. Macfarlane, Lewisham Hospital, London SE13 6LH.

Fig. 1 *Case 1: side view of face showing saddle-nose deformity.*

Fig. 2 *Case 1: photomicrograph from renal biopsy showing active focal glomerulonephritis. One of the 3 glomeruli illustrated shows classic segmental areas of tuft necrosis with epithelial adhesions. (H and E, $\times 220$).*

Fig. 3 Case 1: chest X-ray showing right mid and lower zone infiltration.

Fig. 4 Case 1: sinus x-ray showing opacification of the right maxillary antrum with bony erosion of the medial wall.

CASE 2

A 59-year-old woman presented to the Ear, Nose, and Throat Department in April 1980 with tinnitus and deafness in the right ear. She was noted to have an obvious collapse of the bridge of the nose (Fig. 5), which she thought had developed quite gradually 10 years before. She could recall several episodes of hay-fever with small recurrent epistaxis, usually on the right side. Examination revealed an effusion in the right middle ear, and x-ray of the sinuses showed bilateral polypoidal thickening of the mucosal lining

of the maxillary antrum. Multiple nasal biopsies were taken but showed only mild inflammatory changes. The Kveim test was negative. In April 1981 she developed a nodular sclerouveitis of such severity that the inflammatory exudation caused a retinal detachment, with loss of vision. This was associated with a fluffy exudate at the right edge of the optic disc and marginal corneal ulceration.

Investigations. Haemoglobin 14.2 g/dl, leucocytes $6.4 \times 10^9/l$ with a normal differential count. Plasma viscosity 1.62 cP, urea 3.1 mmol/l, creatinine clearance 16 ml/minute, urine negative for blood and protein, C3 1.10 g/l, C4 0.56 g/l, Clq binding assay 0, anticomplementary activity assay 0; latex, ANA, and WR tests were negative, and chest x-ray was normal.

She was treated with a bolus injection of 250 mg cyclophosphamide and 500 mg methylprednisolone intravenously, and then maintained on oral cyclophosphamide 100 mg and prednisolone 10 mg per day and local steroid eye drops. There was a dramatic response of the eye inflammation within 24 hours of the injection. One year later the retina is flat, with improvement of visual acuity to 6/36 (corrected). Hearing has returned, and there is marked reduction of the mucosal thickening of the maxillary antrum on x-ray.

CASE 3

A 63-year-old woman presented to the Bristol Eye Hospital in September 1981 requesting removal of a painful blind right eye. Her history began in 1960 when she developed a moderately severe arthritis affecting the wrists, elbows, and knees. She was anaemic, but seronegative. She took phenylbutazone regularly from 1968 to 1975, when the arthritis remitted spontaneously without residual deformity. In 1974 she developed small sores on the lower legs, which rapidly ulcerated and progressed to frank pyoderma gangrenosum. She was admitted to a dermatology ward for treatment. Shortly afterwards she developed a severe left necrotising scleritis with marginal corneal ulceration.

Investigations. Haemoglobin 11.5 g/dl, erythrocyte sedimentation rate (ESR) 77 mm in the first hour; latex, ANA, and WR tests negative; glucose tolerance test showed a diabetic curve; barium meal, barium enema, and sigmoidoscopy were normal; x-rays of the hands, knees, and chest normal. She developed sudden severe headaches and was started on systemic steroids for a presumptive diagnosis of temporal arteritis. This resulted in dramatic healing of the leg ulcers, and the scleritis also improved.

In October 1976 there was a severe recurrence of scleritis in the left eye which progressed remorselessly despite large doses of steroids, and the eye was eventually enucleated to control severe pain in June

Fig. 5 Case 2: frontal view of face showing saddle-nose deformity and resolving right sclerouveitis.

1977. Postoperatively she noticed permanently impaired hearing in the left ear. Attempts to reduce steroids caused headache, inflammation in the right eye, and renewed ulceration of the legs. By 1978 she had become frankly diabetic, and azathioprine was added as a steroid sparing agent; she eventually required stabilisation with insulin. Vision in the right eye then started to deteriorate gradually, with evidence of optic atrophy. She moved to the Bristol area in 1981. By now she had an extremely painful, protruded, disorganised red right eye, with a complete ocular palsy and was stone deaf in the right ear. Large deep scars were present on the lower leg. Although she was asymptomatic, examination of the upper airways showed massive destruction with absence of the septum and lateral walls of the sinuses and gross mucosal changes at the opening of the sphenoid sinus.

Investigations. Haemoglobin 13.9 g/dl, leucocytes $8.0 \times 10^9/l$ with a normal differential count, plasma viscosity 1.83 cP, no blood, protein, or abnormal sediment in the urine, urea 6.1 mmol/l, C1q 1.4 g/l, C4 0.67 g/l, C1q binding assay 1%, anticomplementary assay 0, latex, ANA, and WR tests negative, and chest x-ray normal. Sinus x-rays showed opacification of the right maxillary and frontal sinuses. Histology of multiple nasal biopsies showed non-specific inflammatory changes.

She was started on treatment cyclophosphamide 250 mg and methylprednisolone 500 mg intravenously as a bolus dose, followed by oral cyclophosphamide 150 mg and prednisolone 20 mg per day. There was a dramatic resolution of the eye pain within 24 hours of the injection. Unfortunately 5 weeks later she died from a massive pulmonary embolus.

Fig. 6 Case 3: Tissue from around the ciliary body taken from the enucleation specimen in 1977. The section shows extensive necrosis and accumulation of inflammatory neutrophil polymorphs together with multinucleated giant cells and marked vasculitis. (H and E, $\times 135$).

Histological material obtained from several tissue sites at necropsy showed nonspecific inflammatory changes. However, it was possible to trace the original sections taken from the biopsies of the skin and the eye in 1976 and 1977 respectively. The left eye histology showed the presence of fibrinoid necrosis of vessels, extensive granuloma formation with multinucleated giant cells in the ciliary body (Fig. 6), and pericorneal ulceration. The leg ulcer biopsy showed fibrinoid necrosis of small blood vessels with a patchy accumulation of Langerhans multinucleated giant cells.

Discussion

These cases are considered worth reporting because they make four points: (1) Wegener's granulomatosis may have a prolonged indolent course; (2) eye disease can be a dominant feature; (3) biopsy confirmation cannot always be obtained; (4) indolent disease may suddenly become virulent and life-threatening.

The concept of Wegener's granulomatosis has

been evolving since 1931, when Klinger described a variant form of polyarteritis nodosa characterised by a destructive sinusitis, nephritis, and disseminated vasculitis.⁵ Wegener's detailed study in 1939 confirmed this as a distinct disease, which he called rhinogenic granuloma to emphasise the predominance of nasal involvement, but which later came to bear his name.² By 1954 sufficient experience of this rare disease had been gained to enable pathological criteria to be established allowing clear separation from polyarteritis nodosa. The major features of Wegener's granulomatosis were extravascular necrotising granulomatous lesions in the upper and lower respiratory tract, focal necrotising vasculitis of arteries and veins, and a focal, segmental, necrotising glomerulitis. Granulomas and venous inflammation were not characteristics seen in polyarteritis nodosa.⁶ More cases were diagnosed, and a clinical stereotype of a classical case of Wegener's granulomatosis emerged. Symptoms presented in the respiratory tract either as rhinorrhoea, epistaxis, sinusitis, and

nasal obstruction in the upper air passages, or cough or haemoptysis and chest pains from the lungs, usually accompanied by fever, malaise, and weight loss. The nasal lesions progressed with destruction of cartilage and bone, causing a saddle-nose deformity and invasion of the orbit or buccal cavity. Renal involvement followed the respiratory phase and was ushered in by haematuria, albuminuria, urinary casts, and rising blood urea without hypertension. Transient episodes of arthritis, cutaneous eruptions, scleritis, neuritis, and myocarditis were frequent. The terminal phase was dominated by renal failure or occasionally disseminated vasculitis. Death from uraemia supervened on average 5 months from onset, with 80% of patients dead at one year, and 93% dead at 2 years.³ This bad reputation was redeemed a little when in 1966 Carrington and Liebow reported 16 cases of patients with isolated pulmonary lesions, histologically identical to those described in Wegener's granulomatosis, which were rarely associated with lesions elsewhere and followed a benign and prolonged course, uncomplicated by renal failure.⁴ This concept of a limited pulmonary form associated with longer survival has been confirmed by many reports and is variously termed 'limited', 'mitigated', 'decapitated', or 'forme fruste' Wegener's granulomatosis.⁷⁻¹⁶

Other isolated forms of Wegener's granulomatosis do occur but are not referred to as 'limited', since this term has through long usage come to imply pulmonary lesions. Midline granuloma is one such example which has caused considerable confusion. The term is a clinical rather than pathological description of a lesion causing local destruction of nasal structures and death from erosions of large blood vessels. Three histological types are described: a frank lymphoma,¹⁷ lymphomatoid granulomatosis,¹⁸ – polymorphic reticulosis,¹⁹ which are considered the same as each other and equivalent to Stewart's lethal midline granuloma,²⁰ and Wegener's granulomatosis. Since by definition a midline granuloma is not associated with disseminated vascular disease, those with the histological appearance of Wegener's granulomatosis must of necessity represent a limited form. A similar situation exists with pseudotumour of the orbit, which is again a clinical term for a condition which produces symptoms and signs of an orbital tumour but follows a benign course. Nine histological types are described, but granuloma formation is not a frequent feature.²¹ Nevertheless, 6 patients have been reported in whom pseudotumour preceded the onset of Wegener's granulomatosis, although the histology of the orbital tumour was classified as non-specific,²¹ and a seventh who had bilateral pseudotumours showing necrotising granulomas followed 2 years later by cavitating pulmonary

lesions, but who survived 15 years on a small dose of prednisolone.¹³

None of our 3 cases fit into any of these categories of 'limited' Wegener's granulomatosis. Pulmonary lesions were not present in cases 2 and 3 and in case 1 took the form of transient infiltrates, more in keeping with vasculitic than granulomatous lesions. All eventually, or retrospectively, had evidence of multi-system involvement as well as lesions in the upper air passages. Treatment may have modified the disease and prolonged the course in case 3. She was given steroids for a doubtful diagnosis of temporal arteritis one year after the onset of leg ulceration but did not start azathioprine for another 3 years. Certainly the use of cytotoxic agents has profoundly influenced the natural history of Wegener's granulomatosis,²² to the point of its being considered an effective cure,²³ but steroids alone may also have a suppressive effect, albeit temporary.²⁴ However, even in the pretreatment era the occasional case was reported which did surprisingly well. Five of Walton's original 56 cases, on which the statistic of 5 months' mean survival was based, lived for 21, 30, 39, 40, and 48 months respectively in spite of having a generalised form of the disease.³ Table 1 shows clinical features of a number of cases reported to have survived for 4 or more years without cytotoxic therapy. In contrast with our 3 cases the pulmonary lesions were pre-eminent, which emphasises the better prognosis this feature predicts. In two instances^{7, 15} a spontaneous remission has been observed.

The diagnosis of Wegener's granulomatosis was made more difficult in our patients because histological confirmation was not obtained on multiple nasal biopsies despite obvious involvement of this site by active disease. The renal biopsy in case 1 was compatible with, but not diagnostic of, Wegener's granulomatosis, and the biopsies which had been taken from case 3 four years previously were not immediately available. Ultimately the decision to treat was a clinical one, and the ocular involvement proved to be the most helpful feature.

Eye involvement is found in over 40% of cases of Wegener's granulomatosis^{25, 26} and is occasionally the presenting feature.^{27, 28} There is either direct spread from the sinuses into the orbit causing nasal and lacrimal duct obstruction, proptosis, ocular palsy, and ocular atrophy; or focal vasculitis causing conjunctivitis, episcleritis, scleritis, corneoscleral ulceration, uveitis, or granulomatous vasculitis of the retina and optic nerve. While the many clinical features in cases 1 and 3 made the diagnosis of Wegener's granulomatosis likely, case 2 posed more of a problem. The nasal, auricular, and ocular features could have been due to contiguous involvement with an expanding lesion such as a midline granuloma, but

Table 1 Cases of Wegener's granulomatosis surviving 4 or more years without cytotoxic drugs

Author	Age (onset)	Sex	Duration (years)	Presenting features	Respiratory tract	
					Upper	Lower
Fahey <i>et al.</i> ³¹	39	M	4	Sinusitis, cough pleurisy	Saddle nose	Basal infiltrates apical cavity
Morgan and O'Neil ³²	26	M	?18	Neck ulcer, gingivitis	Loose teeth	—
Lansdown ^{7 10}	34	M	8	Cough, chest pain	—	Multiple cavitating lesions
Fred <i>et al.</i> ³³	40	M	11	Sinusitis	Mass	Multiple cavitating lesions
Carrington and Liebow ⁴	44	F	4	Weight loss, fever	—	Multiple cavitating lesions
Carrington and Liebow ⁴	3 mths	M	7	Cough, dyspnoea, fever	—	Multiple cavitating lesions
Carrington and Liebow ⁴	22	M	13½	Paraesthesia, weight loss	—	Multiple infiltrates
Cassan <i>et al.</i> ¹¹	27	M	4	Nasal obstruction, haemoptysis	Septal perforation mass	Multiple cavitating lesions
Cassan <i>et al.</i> ¹³	39	M	16	Proptosis, headache, visual loss	Mucosal thickening	Multiple cavitating lesions
Israel and Patchefsky ¹⁴	33	M	6	Cough, dyspnoea	—	Diffuse nodular lesions
Israel and Patchefsky ¹⁴	58	M	6	Cough, dyspnoea	—	Bilateral apical cavities
Israel and Patchefsky ¹⁴	59	F	12	Pulmonary lesion on routine CXR	—	Multiple nodular lesions
Israel and Patchefsky ¹⁴	37	M	18	Cough	—	Solitary nodule
Asin <i>et al.</i> ¹⁵	14	F	6	Fever, cough, chest pain	—	Bilateral infiltrates
Lebeau <i>et al.</i> ³⁴	47	M	17	Ocular palsy	Maxillary cyst	Bilateral apical nodules
Van der Woude <i>et al.</i> ³⁵	49	F	4½	Chronic sinusitis	Saddle nose	Bilateral cavities
Macfarlane <i>et al.</i> ³⁶	49	F	10	Deafness	Saddle nose	—
Macfarlane <i>et al.</i> ³⁶	24	F	10	Sinusitis	Saddle node	Transient infiltrates
Macfarlane <i>et al.</i> ³⁶	56	F	7 (?21)	Skin ulcers, sclerouveitis (? arthritis)	Massive destruction	—

*, †, ‡, § = Treatment started 6, 8, 10, and >4 years from onset respectively.

<i>Eye</i>	<i>Ear</i>	<i>Skin</i>	<i>Joint</i>	<i>Neuro- pathy</i>	<i>Urinary changes</i>	<i>Specific treatment</i>	<i>Reported outcome</i>
-	+	-	+	-	+	-	Died (septicaemia)
-	-	+	+	-	-	-	Died (myocardial infarction)
-	-	-	-	-	-	-	Spontaneous remission
+	-	-	-	+	+	Steroids	Died (cerebral arteritis)
-	-	-	+	-	-	-	Well
-	-	-	-	-	+	Steroids	Died (respiratory failure)
-	-	+	-	+	-	Steroids, Lobectomy	Well
-	+	-	-	+	-	Steroids, Lobectomy	Died (respiratory failure)
+	-	+	-	-	+	Steroids	Well
-	-	-	-	-	-	Steroids, 6-mercaptopurine*	Died (marrow suppression)
-	-	-	-	-	-	Lobectomy	? Died
-	-	-	-	-	-	Nitrogen mustard† Azathioprine‡	Well
-	-	-	-	-	-	Pneumonectomy	Well
-	-	-	-	-	-	Sulphadiazine	Remission
+	+	+	-	+	+	Excision cyst, antituberculous chemotherapy	Died (cirrhosis)
+	+	+	-	-	+	Steroids	Died (cause unknown)
+	+	-	-	-	-	Steroids, cyclophosphamide‡	Well
+	-	+	+	-	+	Steroids, cyclophosphamide‡	Well
+	+	+	-	-	-	Steroids, azathioprine,§ cyclophosphamide‡	Died (pulmonary embolus)

the presence of one small but unmistakable retinal vasculitic lesion and a corneal ulcer revealed the multifocal nature of the underlying disease.

A unifying classification of respiratory vasculitis (ELK system) has been proposed.²⁹ Those patients with E (upper respiratory) involvement alone correspond to midline granuloma, ELK (plus lung and kidney) to classical Wegener's granulomatosis or Churg-Strauss disease, and those with either EL or L to the limited form. However, the starting point for inclusion is E or L, but since patients may present with lesions outside these anatomical areas—for example, eye or joint or skin—they can be included only retrospectively. Our third case was such as example. The arthritis she developed 20 years before her death may have marked the onset of her disease. Certainly the histological features of the biopsies taken from the pyoderma gangrenosum 7 years, and the left eye 5 years, before death were compatible with Wegener's granulomatosis. The alternative interpretation, made at the time, was that the clinical and histological features represented a severe form of rheumatoid vasculitis, but this is unlikely because the arthritis had remitted completely without residua, and she had never been seropositive for rheumatoid factor. However, the adoption of a scheme which emphasises only the respiratory and renal aspects of such a multisystem disease as Wegener's granulomatosis may perpetuate the kind of diagnostic uncertainty seen in our cases, which is even less desirable as there is now effective therapy.

Our third case had clearly been slowly progressing despite azathioprine and prednisolone, and it was a sad irony of fate that she should have died of a quite unrelated cause just at the onset of specific treatment with cyclophosphamide. The other 2 patients had static disease prior to the final flare of activity. One view of Wegener's granulomatosis is that it represents an aggressive hypersensitivity response to an allergen whose port of entry is the respiratory system.⁶ None of our patients could recall specific environmental change prior to recrudescence, except that the young woman in case 1 had become engaged shortly beforehand. It may ultimately transpire that the mechanisms controlling the balance of Wegener's granulomatosis are biological, involving perhaps the immune system. The presence of circulating immune complexes as detected by raised anticomplementary activity assay, Clq binding, and cryoglobulins in case 1, and the excellent therapeutic response to cyclophosphamide, which selectively depletes B lymphocytes,³⁰ in all 3 patients would support this idea.

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Book review

Advances in Inflammation Research. Vol. 5. Edited by Gerald Weissman. Pp. 220. US \$48.36. Raven Press: New York. 1982.

This collection of reviews deals with interleukins, factors influencing fibroblast function, crystal-induced chemotaxis, receptor specific probes for the mononuclear phagocyte system, cartilage degradation by chondrocytes, the myeloperoxidase system, complement and granulocyte

interactions in lung injury, and protease-antiprotease interactions. Some of the authors have the annoying habit of using so many abbreviations that the text becomes difficult to read. However, for the most part the book was easy to follow for a nonspecialist and the articles are well endowed with references, including some to very recent work. The reviewer has learned a lot in a short time, and relatively painlessly, from reading this little book. The quality of illustrations and the use of summarising tables in the reviews are particularly to be commended.

P. A. REVELL