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Lessons learnt in the management of Wegener's Granulomatosis: long-term follow-up of 60 patients*

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SUMMARY

Objective: *To assess all patients with Wegener's Granulomatosis treated in Nottingham, with particular focus on relapse rate and the useful predictors of relapse. We evaluated how well the findings of nasal examination correlated with disease relapse compared to other parameters such as c-ANCA, ESR and CRP. Presenting features, diagnosis, adverse effects of treatment and mortality rate, were also studied.*

Design: *Retrospective examination of 60 patient notes, diagnosed and treated for Wegener's granulomatosis at Queen's Medical Centre, Nottingham. The mean follow up period was 8.7 years. Relapse was defined as per the European Vasculitis Study criteria.*

Results: *cANCA is a useful test at presentation for diagnosis but a negative result does not rule out the disease. Those presenting with ENT symptoms alone may have less raised inflammatory markers but similar cANCA titres as patients with multi-system disease. However, at relapse, patients with ENT disease alone have similar levels of inflammatory markers as those with multi-system relapse. Nasal examination was useful at monitoring the presence of disease activity where the nasal lining is affected.*

Conclusions: *Signs of intranasal disease in the form of granular tissue, erythema and bleeding to light touch and crusting over granulation tissue are good predictors of disease activity. A raised cANCA, ESR or CRP provide supporting information about disease activity but if they are negative this does not exclude active disease. cANCA levels were as elevated at relapse in patients who had isolated nasal symptoms and signs as in those with evidence of systemic disease. Low relapse rates were found possibly due to prompt and rigorous initial immunosuppression even in limited disease. This seemed to lead to less progression of patients to multi-system disease and hence a low mortality rate of 5%.*

Key words: Wegener's Granulomatosis, cANCA, ESR, CRP, presenting features, diagnosis, adverse effects of treatment, mortality rate

INTRODUCTION

In 1939 Wegener described a granulomatous disease that affected the upper and lower respiratory tracts and caused glomerulonephritis [(1)]. Wegener's granulomatosis is a chronic multisystem vasculitis that preferentially affects the respiratory tract and kidneys but can occur in any organ system. The cause of this disorder is still unknown.

Diagnosis is normally based on clinical features, typical pathological features and the presence of circulating cytoplasmic autoantibodies to neutophil cytoplasmic antigens (c-ANCA). Classical pathological features are three fold:

1. vasculitis of small arteries and veins
2. giant cells
3. epithelioid cell granulomas

It is unusual for all these features to be seen in every biopsy even if Wegener's is present [(2)]. Serum c-ANCA is said to have 92% sensitivity and 96% specificity for the disease (3).

Without treatment Wegener's Granulomatosis is a progressive disease that ultimately leads to organ failure and is often fatal. The empirical introduction of corticosteroids and cytotoxic agents increased survival from under 20% to over 60% [(4)]. The combination of corticosteriods and cyclophosphamide is widely accepted as the treatment of choice for Wegener's achieving an improvement in over 90% of patients [(5)]. Relapse is often seen during the clinical course although little data exists on typical relapse rate. Relapse is said to be poorly correlate with c-ANCA level (6), and there is limited evidence for how relapse is best predicted.

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Morbidity from treatment includes repeated infections, neutropenia, infertility and increased rates of leukaemia, lymphoma and bladder cancer. Mortality rates in recent studies cite figures between 9% and 36% [7,8].

The aim of this study was to assess all the patients with Wegener's Granulomatosis treated in Nottingham, with particular focus on relapse rate and the useful predictors of relapse. We evaluated how well the findings of nasal examination correlated with disease relapse compared to other parameters such as c-ANCA, ESR and CRP. We also looked at presenting features, how diagnosis was achieved, the adverse effects of treatment and mortality rate.

METHODS

The case notes of all patients with expected Wegener's Granulomatosis seen at Queens Medical Centre, Nottingham in the last ten years were retrospectively examined. These patients were identified from databases of patients seen in immunology and rhinology clinics. Notes of patients with a histology request querying Wegener's Granulomatosis from 1989 to September 2005 were also examined. This did include some patients who presented with renal disease. All recorded data was based on documentation in the case notes.

The clinical features, cytoplasmic autoantibodies to neutrophil cytoplasmic antigens (cANCA), erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) at presentation and at each relapse were recorded. The findings of the nasal examination were also documented at presentation and for each episode of relapse. Features consistent with Wegener's Granulomatosis were regarded as; granular mucosa, contact bleeding, crusting over granular mucosa, and septal perforation with granulation tissue that extends past its margin. The relapses were classified as major or minor using the European Vasculitis Study Group (EUVAS) [4] criteria detailed in Table 1.

The histology reports of nasal biopsies were examined to see how many of the classical features were seen. Side effects of treatments detailed in the notes and the mortality of these patients were also examined.

Table 1. Criteria for relapse in Wegener's granulomatosis, according to the European Vasculitis Study Group [4].

Major relapse

Recurrence or new appearance of major organ involvement, if they are attributable to active vasculitis. Such as:

1. An increase in serum creatinine of >30% or reduction in creatinine clearance of >25%, within a period of three months, or histological evidence of active, focal, necrotizing glomerulonephritis.
2. Clinical, radiological or bronchoscopic evidence of pulmonary haemorrhage or granulomata.
3. Threatened vision, e.g. increasing orbital granuloma or retinal vasculitis.
4. Significant subglottic or bronchial stenosis.
5. New multi-focal lesions on brain MR suggestive of cerebral vasculitis.
6. Motor mononeuritis multiplex.
7. Gastro-intestinal haemorrhage or perforation.

Minor relapse

Recurrence of disease activity of less severity, if they are attributable to active vasculitis. Such as:

1. ENT: epistaxis, crusting, pain, new deafness, active nasal ulceration or proliferative mass at nasal endoscopy.
2. Mouth ulcers.
3. Rash.
4. Myalgia, arthralgia or arthritis.
5. Episcleritis or scleritis.
6. Pulmonary symptoms with or without minor radiological changes, e.g. cough wheeze, dyspnoea.

Table 2. Organs involved at presentation.

Organs	% of patients
Nose	68%
Eye	35%
Lung	34%
Kidney	32%
Skin	22%
Ear	21%
Joints	20%
Throat	18%
Neurological	15%
General features (e.g. malaise, night sweats, weight loss)	35%

RESULTS

Of the 104 sets of case notes that were examined 60 patients had confirmed Wegener's Granulomatosis. Of the other 44 patients, 9 had other types of vasculitis, 33 had no vasculitis and 2 sets of notes had been destroyed.

The median age of patients at presentation of disease was 45 years old. The range was 18-89 years old. The sex of the patients was equally distributed; 30 men and 30 female.

Patients were followed up for 4-356 months with a mean of 104 months (8.7years) giving us a good representation of what happens to these patients long term.

At the patients first presentation 82% of patients had ENT symptoms, 59% with ENT symptoms had other organ system involvement and 23% had ENT symptoms alone. Approximately a third of patients presented with renal, pulmonary and ophthalmic symptoms. The organs involved at the time of presentation are detailed in Table 2.

The nasal symptoms that predominated at presentation were epistaxis, nasal discharge and obstruction with a small minority having a collapse of the septal cartilage and a nasal deformity at presentation. Otological symptoms were primarily due to a conductive deafness but one patient presented with a sensorineural hearing loss. Facial pain was distinctive by its progressive nature. Six patients had subglottic involvement between presentation and diagnosis with symptoms of breathlessness and coughing up crusts and 3 of them had subglottic stenosis (see Table 3).

Serum cANCA at presentation was positive in 77% of patients and negative in 10%. Unfortunately, 13% of cANCA results were not recorded in the notes or available on the hospital result reporting database. The values of the positive results are

detailed in Table 4. Some of the older reports simply recorded a weakly positive, positive or negative result.

ESR at presentation was < 30 in 23%, 30-80 in 37%, and > 80 in 27% (see Table 4).

CRP was normal (< 5) in 1.5% of patients, between 5 and 20 in 16.5%, between 20 and 100 in 10%, between 100 and 200 in 12% and > 200 in 20% (see Table 4).

Thirty nine patients had a nasal septal or turbinate biopsy around the time of diagnosis. Of these only 6 reports confirmed all three classical features of Wegener's Granulomatosis (vasculitis, granulomas and giant cells). Nine patients had one of these features and 7 had two.

Nasal examination was documented in 85% of patients (51), 39 having features consistent with Wegener's granulomatosis.

Table 3. ENT symptoms at presentation.

Symptoms	No. of patients
Conductive hearing loss	10
Sensorineural hearing loss	1
Otorrhoea	1
Subglottic involvement	6
Of which subglottic stenosis	3
Odynophagia	4
Epistaxis/ bloody nasal discharge/crusting	20
Nasal discharge	10
Nasal obstruction	17
Epiphoria	2
Nasal deformity	6
Facial pain	13
Facial swelling	1
Facial nerve palsy	1

Treatment

Thorough initial immunosuppression was used for the majority of presenting patients to achieve remission, even for those with isolated nasal symptoms. Pulse intravenous cyclophosphamide (15 mg/kg) and methylprednisolone (1 g bolus) was used in 41 patients. This was given weekly initially and then at 2-3 week intervals dependant on response. Mean cumulative dose of cyclophosphamide given during this regime was 13.6 grams (median 11, range 1-39.5 grams) and 6.1 grams (median 5, range 1-19 grams) of methylprednisolone. Eight patients were started on oral cyclophosmamide initially rather than pulse therapy. The length of treatment was usually planned for a six month course, extended if the patient was not in remission.

Maintenance therapy was achieved with a selection of agents. The first choice was either oral cyclophosphamide or azathioprine. Twenty-three patients had oral cyclophosphamide after pulse therapy and 45 patients had azathioprine. Other agents were used if the patient could not tolerate these or relapsed on this treatment (see Table 5). Etoposide was often successful at inducing remission in patients with multiple relapses on other treatment.

Relapse

Using the EUVAS criteria for relapse (see Table 1) 64 minor relapses and 20 major relapses were identified in this population. Patients had from 0-6 relapses during their follow up (mean 1.4 relapses per patient). The mean time to a patient's first relapse was 18 months although the range was large from 4 months to 113 months. The organ systems involved in each relapse can be seen in Figure 1. Thirty nine percent of relapses were confined to ENT symptoms and 57% of relapses included ENT symptoms. In those who were symptomatic examination of the nasal mucosa was a very good predictor of disease activity.

The cANCA at the time of each relapse was positive in 68%, negative in 12% and not recorded or not done in 20% of patients. The values can be seen in Table 4.

Table 4. Laboratory values at diagnosis and relapse.

Values at diagnosis						
c-ANCA						
Positive results		Negative results		Not recorded / available		
46 (77%)		6 (10%)		8 (13%)		
Recorded Positive	Recorded Weakly Positive	<160	160-320	320-640	540-1280	>1280
7	3	8	12	7	7	2
ESR						
<30	30-80	>80		None recorded/available		
14 (23%)	22 (37%)	16 (27%)		8 (13%)		
CRP						
<5	5-20	20-100	100-200	>200	No record	
1 (1.5%)	10 (16.5%)	6 (10%)	7 (12%)	12 (20%)	24 (40%)	
Values at relapse						
c-ANCA						
Negative	Recorded Positive	<160	160	320	640-1280	>1280	Not done
10(12%)	2(2%)	12(14%)	11(13%)	10(12%)	19(23%)	3(4%)	17(20%)
ESR						
<30	30-60	60-80	>80	Not done		
33 (40%)	17 (20%)	6 (7%)	12 (14%)	16 (19%)		
CRP						
<20	20-100	100-200	>200	Not done		
34 (41%)	16 (19%)	6 (7%)	1 (1%)	27 (32%)		

Table 5. Treatment given to keep patients in remission.

Treatment	No. of patients given
Methotrexate	20
Cyclosporin A	6
Etoposide	8
Mycophenolate	6
Prednisolone	50

The ESR was < 30 in 40%, 30-80 in 26%, > 80 in 14% of relapses and not recorded in 20% (see Table 4). The CRP was < 20 in 41%, 20-100 in 18%, 100- 200 in 7% and > 200 in 1% of relapses (see Table 4). CRP was not recorded in 33% of relapses.

Five nasal biopsies were done at the time of relapse, 3 had features consistent with Wegener's Granulomatosis.

Side effects of treatment

The immunosuppressive therapy used to treat these patients has recognised side effects that mainly consisted of infection. There were 33 episodes of lower respiratory tract infections and 15 episodes of upper tract infection recorded. Urinary tract infections were the next frequent with 16 recorded. Other infections include laryngitis (3 episodes), gastroenteritis (4), meningitis (1), shingles (2), varicella (2), skin infections (3), and conjunctivitis (1). Three patients were admitted with neutropenia and serious sepsis.

Cyclophosphamide induced neutropenia occurred in 29 patients and pancytopenia in 1 patient. Side effects of cyclophosphamide excluding infections were severe nausea 2, early menopause 1, hair loss 2, diarrhoea 3 and haemorrhagic cystitis 1. Mesna was used as bladder protection in the majority of these patients.

Azathioprine was used in 45 patients. Recorded side effects were deranged liver function tests in 3 patients, hypersensitivity in 2 patients, right upper quadrant pain in 1 patient, 8 patients had diarrhoea and/or vomiting and 1 patient had a rash attributed to treatment.

Methotrexate was used in 20 patients. Of these deranged liver function occurred in 1 patient. Methotrexate induced pneumonitis was seen in 2 patients.

Only 2 patients were recorded as having osteopenia secondary to prolonged steroid use but regular DEXA scanning of this population was not carried out. One patient had late onset diabetes attributed to steroid use.

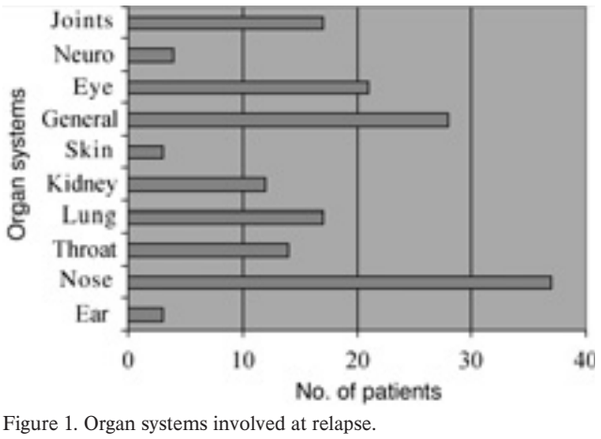

Figure 1. Organ systems involved at relapse.

Mortality and renal disease

Of this population renal failure requiring dialysis was seen in 8 patients. Five renal transplants were done in 3 patients.

The mortality rate was 5% with three deaths. The cause of death was lower respiratory tract infection in two of these and disseminated oesophageal carcinoma in the other.

DISCUSSION

The age and sex distribution of the patients in this series was very similar to those previously published, from all age groups although rare in childhood [3,5,8].

The disease most commonly presented with nasal symptoms and this is comparable to previous series [5,8]. What differed was the frequency in which other organs were involved. Pulmonary and renal diseases were seen at presentation in 34% and 32% of patients respectively. This contrasts to the Takwoingi et al. series, which had 18.2% of patients with pulmonary symptoms but 69.7% with renal disease. Hoffman et al. showed a higher proportion with pulmonary disease (45%) but less renal disease (18%). The reasons for these differences are unclear. One possibility is that in series when patients are diagnosed at a later stage they are more likely to have renal involvement.

Diagnosis was made by a combination of clinical features, cANCA results and nasal biopsy results. The cANCA in our population of patients was positive in 77% of patients. This is lower than both Hoffman et al. (> 90%) and Takwoingi et al. (79%) cite. Nasal biopsy showed classical (all three) features in only 10% of patients despite adequate biopsy specimens and thirty-seven percent of biopsies had some consistent features. This is comparable to other published data that supports nasal biopsy only if nasal features are seen and states that a negative biopsy is by no way indicative that the disease is not present [2,7]. The most important factors in making a diagnosis were the clinical features and/or a positive cANCA. Some patients with negative cANCA and nasal biopsy but suggestive features went on months later to become cANCA positive so where there is clinical suspicion it is worth repeating.

Inflammatory markers can be used to support a diagnosis of Wegener's but the ESR of patients at presentation was very varied, only 58% had a value over 80. The CRP often said to be a more useful marker was only > 20 in 42%, although 32% of those were over 100.

It has been suggested that patients presenting with just disease confined to the nose or ears are less likely to present with high inflammatory markers or cANCA titres. Of our patients, 23% had only ENT symptoms at diagnosis and their cANCA was positive in an almost identical percentage of patients (77% in all patients, 78% in those with ENT symptoms only). There was a larger proportion with a high ESR and CRP result in the patients with multi-system disease compared to those with only ENT disease (ESR > 80 25% all patients and 14% in ENT patients; CRP > 100 32% all patients and 14% of ENT patients).

Nasal examination was shown to be consistent with Wegener's Granulomatosis in 65% of patients at presentation. This is comparable to the 68% of patients that were recorded as presenting with nasal symptoms. Nasal examination should be a routine part of examining a potential Wegener's patient.

The relapse rate of these patients was lower than expected with 64 minor relapses and 20 major in our 60 patients. Other series do not use the same definitions of relapse and so comparison of rate is difficult. Hoffman et al. comment that 49% of patients experienced at least one relapse and this compares to 67% of our patients. However, relapses in the initial treatment period to first remission were not included as they were in our analysis. Of the relapses we studied 39% presented with ENT symptoms alone and 57% presented with other features as well as ENT symptoms.

We attempted to evaluate the factors that help diagnose relapse by analysing the cANCA, ESR, CRP and nasal examination at relapse. cANCA was positive in 68% of all relapses in our patients suggesting a raised level may well help in diagnosing relapse. Kerr et al., who looked at serial cANCA in a group of patients, also found that a positive cANCA was a sensitive test for active Wegener's. However, they observed a cANCA increase preceding a clinical exacerbation occurred in only 24% patients. The ESR was $>$ 80 in only 14% of relapses and this suggest it is not a particularly useful marker. CRP was only $>$ 20 in 26% of patients at relapse although a third had no CRP measured. Again this suggests limited value of this marker as a one off measurement.

The observation that those patients with solitary ENT symptoms at relapse are less likely for cANCA and inflammatory markers to be raised was not supported by our data. The proportion of patients who relapsed with a raised result were similar in those with ENT symptoms alone and those with evidence of systemic disease.

Nasal examination at relapse was consistent with Wegener's in 43%. This again was comparable to the number of patients with nasal symptoms (44%). This suggests that nasal examination could be very useful in diagnosing relapse.

Hoffman used a treatment regime of oral cyclophosphamide and prednisolone rather than high dose pulsed therapy. Other series treatment regimes are not as clear but appear to be less rigorous, often not treating isolated nasal symptoms with full immunosuppression.

The mortality rate in our group of patients was 5%, far lower than those previously published (Takwoingi et al. 39%, Hoffman et al. 20%). Of the 3 deaths only 1 could be attributed to disease. This patient died of a lower respiratory tract infection when immunosuppressed on etoposide. The other patient died of a lower respiratory tract infection but was not immunosuppressed at the time. The other patient died of oesophageal carcinoma with liver metastasis. It was suggested by Takwoingi et al. that the higher mortality seen in their series was due to an increased incidence of renal disease. It could be hypothesized that their patients went on to develop renal disease secondary to less rigorous immunosuppression. However, only a prospective study of this hypothesis could confirm this.

CONCLUSIONS

- cANCA is a useful test at presentation for diagnosis but a negative result does not rule out the disease.
- Nasal examination should always be carried out in patients with potential Wegener's granulomatosis even if they do not present with nasal symptoms. Nasal examination by an ENT specialist with experience of these changes can be a useful adjunct when deciding how active disease may be.
- Low relapse rates seen could be secondary to prompt and rigorous initial immunosuppression even in limited disease. This also could lead to less progression of patients to multisystem disease and hence a lower mortality rate. However, these hypotheses need to be tested in a prospective trial.

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