Pulmonary Wegener's Granulomatosis*
A Clinical and Imaging Study of 77 Cases
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We studied 77 patients with biopsy-proven WG and pulmonary manifestations, to characterize the nature and frequency of the clinical, imaging and endoscopic features of this condition. Pulmonary symptoms were cough, mild dyspnea, hemoptysis and chest pain. Five patients had no pulmonary symptoms. Imaging features consisted of nodules, infiltrates and pleural opacities. A CT scan proved useful by disclosing cavities in opacities or opacities which were not seen on an x-ray film. Fiberoptic bronchoscopy was performed in 74 patients, and it was macroscopically abnormal in 55 percent (showing bronchial inflammation or stenosis or both or isolated hemorrhage). Six patients presented with alveolar hemorrhagic syndrome. Four patients had a pleural exudate rich in polymorphonuclear leukocytes. The WG was limited to the lung in seven patients. Sixteen patients died because of active disease or iatrogenic complications (two). An improved knowledge of clinical and imaging features of WG could help the clinician reach an earlier diagnosis. (Chest 1990; 97:906-12)

WG = Wegener's granulomatosis

Wegener's granulomatosis is a clinicopathologic entity of unknown cause characterized by a necrotizing granulomatous vasculitis capable of affecting all organs, but especially the upper and lower respiratory tract and the kidney. Once usually fatal, the disease is now curable by combining corticosteroids and cyclophosphamide. There is a need for early diagnosis before irreversible organ damage occurs.1

The lung is the most frequent, and sometimes the only organ involved. The pulmonary features of WG are known from general studies2,3 and case reports of atypical cases. Recognizing WG clinically is necessary to indicate the appropriate biopsy (and especially open-lung biopsy), since a definite diagnosis of WG still relies on histopathologic characterization of a necrotizing granulomatous vasculitis. We present a study focused on the clinical and imaging features of pulmonary WG in order to help the clinician reach an earlier diagnosis.

METHODS
French respiratory physicians were asked to participate in the Clinicopathologic Research Group under the auspices of the Société de Pneumologie de Langue Française by referring standardized detailed clinical information on patients they diagnosed as having pulmonary WG, together with x-ray films or CT scans or both, and pathologic reports.

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RESULTS

Study Population
Seventy-seven patients with pulmonary features of WG and biopsy-proven disease were included in the study. The year of onset of disease ranged from 1967 to 1988, and was 1984 or later in 53 percent of the cases. There were 39 men and 38 women, all Caucasians, whose mean age was 46.5 years (range: 17 to 80 years). A majority of patients (43 of 77) were nonsmokers.

Histopathologic Diagnosis
Diagnosis was made on the basis of lung biopsy or necropsy in 44 patients (57 percent). Of these, 40 cases were reviewed and confirmed by the panel of pathologists (the specimens of lung tissue were obtained by open-lung biopsy or necropsy in 39 cases and by transthoracic needle biopsy in one case). In the other 33 patients, diagnosis was obtained by biopsy of the kidney (21 cases), upper respiratory tract (nine cases), skin (two cases) and of a retro-orbital mass (one case).
Table 1—Clinical Manifestations in 77 Patients with Pulmonary Wegener's Granulomatosis

<table>
<thead>
<tr>
<th>Manifestation*</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung + kidney + URT + other</td>
<td>42 (55)</td>
</tr>
<tr>
<td>Lung + kidney + other</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Lung + URT + other</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Lung only</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Lung + URT</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Lung + kidney</td>
<td>4 (5)</td>
</tr>
<tr>
<td>Lung + URT + kidney</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Lung + other</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

*URT: upper respiratory tract; other: any clinical manifestations in any organ other than the lung, kidney, or URT.

Table 2—Features of Pleuro-pulmonary Imaging in 77 Patients with Pulmonary Wegener's Granulomatosis*

<table>
<thead>
<tr>
<th>Type of Opacity</th>
<th>No. of Cases (%)</th>
<th>Cavitary Opacities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodules</td>
<td>53 (69)</td>
<td>49% of nodules (26/53)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Infiltrates</td>
<td>41 (53)</td>
<td>17% of infiltrates (7/41)</td>
</tr>
<tr>
<td>Unilateral</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Pleural opacity</td>
<td>9 (12)</td>
<td></td>
</tr>
<tr>
<td>Atelectasis</td>
<td>3 (4)</td>
<td></td>
</tr>
</tbody>
</table>

*Miscellaneous: calcification: 2; mediastinal adenopathy: 1.

General Presentation of Patients

Sixty-four patients (83 percent) presented with fever and 50 (65 percent) with weight loss. The mean weight loss (known in 48 cases) was 6.4 kg. As a result of the inclusion criteria, all patients had pulmonary features. Upper respiratory tract and ear features were present in 57 patients (74 percent), renal in 57 (74 percent), and others in 58 (75 percent). The combinations of clinical features related to WG are listed in Table 1. The onset of disease was generally progressive and multifocal, and no clear-cut chronologic sequence of manifestations could be clearly identified. Four patients had upper respiratory tract and three had renal involvement more than two years before the pulmonary manifestations became evident.

Pulmonary Clinical Presentation

Cough was present in 60 patients (78 percent), dyspnea in 43 (56 percent), hemoptysis in 30 (39 percent) and chest pain in 25 (32 percent). Cough usually was unproductive, but in seven patients purulent bronchorrhea was present (in two patients it was massive, due to necrosis of a voluminous pulmonary mass). Dyspnea was mild, except in some patients with diffuse pulmonary involvement in whom it was occasionally severe. The physical signs depended on the type of pulmonary involvement and had no specific features. Five patients (6 percent) had no pulmonary symptoms, pulmonary involvement being found on systematic chest x-ray film.

Superinfection of pulmonary lesions was documented in only one patient who had acute fever and enlargement of a thin wall cavity with an air-fluid level leading to lobar resection. Subglottic stenosis was encountered in two patients.

Pleuro-pulmonary Imaging

The imaging features identified by chest x-ray films, tomograms and CT scans are listed in Table 2. Both sides of the chest were involved in 63 cases and one side was involved in 14. There was no obvious pattern of lung zone involvement but the apices usually were spared. Nodules and infiltrates were the most common lesions and often coexisted.

Nodules

Nodules consisted of rounded lesions with well-defined margins. Their size varied from about 5 to 100 mm, the largest being usually excavated. Excavated nodules had generally medium-sized walls and fluid levels were uncommon. Some nodules which were not excavated on the chest x-ray film had a typical central necrotic content and/or small cavities as seen on the CT scan. The number of nodules varied but was generally fewer than ten. In the course of the disease, nodules tended to increase, particularly in size but also in number. Furthermore, most nodules became excavated in the course of untreated disease.

Infiltrates

Infiltrates consisted of alveolar opacities with a wide range of appearance. We distinguished three categories of infiltrates, all of which could be found in the same patient, together or at different stages of the disease.

In the first category, the infiltrates were bilateral, diffuse and of low density as shown by the x-ray film. The six patients with alveolar hemorrhage, as discussed later, had opacities which fell into this category (Fig 1). In the second category, the infiltrates were more patchy and of low density (Fig 2). When followed by sequential imaging, some spontaneously cleared, some increased in density (with or without a reduction in size) and others progressed, with coalescence of adjacent opacities.

In the third category, the infiltrates were dense and localized (consolidation) (Fig 3 and 4) with ill-defined margins. In some, an air bronchogram or foci of excavation, or both, were present.

Atelectasis

Lobar or segmental atelectasis was present in three cases. Limited atelectatic zones were more frequently
Calcifications were present in two cases (in a con-

Pleural Opacities

Pleural opacities were not documented by CT scan. Frank pleural effusion was documented in four cases, as discussed in the next section.

Miscellaneous

Calcifications were present in two cases (in a con-
solidation and in the area of a previously resected nodule, respectively). Hilar and mediastinal lymph nodes were found on the CT scan in one patient with parenchymal consolidation.

Fiberoptic Bronchoscopy

Seventy-four patients underwent fiberoptic bronchoscopy which was macroscopically abnormal in 41 (55 percent). Abnormal endobronchial aspects consisted of bronchial stenosis in 13, ulcerations or pseudo-tumor in seven, inflammatory lesions without stenosis in ten, isolated hemorrhage in ten and isolated purulent secretions in one.
Biopsy of bronchial lesions showed inflammatory cells (lymphocytes, plasma cells, polymorphonuclear leukocytes) and giant cells, but definite vasculitis was not seen.

**Bronchoalveolar Lavage**

Bronchoalveolar lavage done in 20 cases showed the following mean (range) percentages of leukocytes: lymphocytes, 12.6 percent (0-53 percent); neutrophils, 22.0 percent (0-93 percent); eosinophils, 2.6 percent (0-25 percent).

**Pleural Fluid**

Pleural fluid analysis was done in four cases and in each revealed an exudate (with 38, 42, 47 and 57 g/L of protein, respectively) with a predominance of polymorphonuclear leukocytes.

**Lung Function Tests**

These tests were done only occasionally, showing principally a restrictive defect related to space-occupying lesions in the chest. No characteristic obstructive defect was found.

**Alveolar Hemorrhage**

Six patients (8 percent) presented with the alveolar hemorrhagic syndrome, characterized by dyspnea, hemoptysis (with blood originating from distal airways as seen by fiberoptic bronchoscopy), severe anemia and diffuse bilateral alveolar infiltrates on chest imaging. All six patients had further renal and upper respiratory tract involvement, and five had involvement of other organs. One of the six patients died postoperatively after diagnostic open-lung biopsy.

**WG Limited to the Lung**

Seven patients (four women, three men) had only pulmonary involvement. Five of the seven presented at the time of the chest x-ray film with nodules (excavated in two), and two patients had pulmonary infiltrates (excavated in one). When compared with classic WG, only two of the seven cases were in any way remarkable: one patient refused treatment and remained well with persistent multiple lung nodules for four years of follow-up and the other had two lobar resections (in 1972 and 1974) before diagnosis was made by reviewing the pathologic findings of the resected lobes when she developed more lung nodules in 1982.

**Laboratory Data**

The erythrocyte sedimentation rate was greater than 40 mm in 62 patients (81 percent) and greater than 80 mm in 43 (56 percent). Anemia (hemoglobin, <130 g/L in men; <120 g/L in women) was present in 46 patients (60 percent).

The white blood cell count was greater than 11,000/cu mm in 36 patients (47 percent), with a predominance of neutrophils, and the platelet count was greater than 350,000/cu mm in 40 patients (52 percent). Circulating immune complexes were found in 12 cases (16 percent). Antineutrophil antibodies were found in ten of 12 cases.

**Clinical Features Outside the Lower Respiratory Tract**

Upper respiratory tract and ear features included sinusitis in 35 patients (45 percent), rhinitis in 32 (42 percent), otitis in 24 (31 percent), hearing loss in 17 (22 percent), epistaxis in 11 (14 percent) and osseous/ or cartilaginous destruction in nine (12 percent).

Renal features included hematuria in 50 patients (65 percent) and proteinuria in 43 (56 percent). Renal failure requiring dialysis occurred in ten patients (13 percent).

Articular features were present in 26 patients (34 percent), with arthralgia in 26 and frank arthritis in four.

Neurologic features were present in 24 patients (31 percent), consisting of peripheral nerve involvement in 12 and central nervous system involvement in 12 (cranial nerves in eight and brain in six).

Ocular features were present in 22 patients (29 percent), consisting of conjunctivitis in 16, episcleritis in two, vascular thrombosis in two, lacrimal duct obstruction in one and retro-orbital pseudotumor in one.

Muco-cutaneous features were present in 22 patients (29 percent), consisting of macules and/or papules in eight, nodules in seven, purpura in seven and oral ulcerations in six.

Cardiovascular features were present in 19 patients (25 percent), consisting of pericarditis in 13, myocarditis in three, coronary arteritis in two, systemic hypertension in two, endocarditis in one and Raynaud's syndrome in one.

Muscular features were present in ten patients (13 percent), with myalgia in ten. Myositis was present in only two patients.

Other features related to WG consisted of abdominal pain in two, hepatitis in two, hypothyroidism in one, splenomegaly in one and colonic necrosis in one.

**Course of the Disease**

A precise study of the course of the disease was not possible because of the variations in both treatment protocols and the amount of information on pulmonary follow-up (especially in patients with predominantly extrathoracic involvement). Treatment included corticosteroids and cyclophosphamide in most cases. Occasionally plasmapheresis or cotrimoxazole was
used, with surgical excision of pulmonary lesions sometimes being done for diagnostic purposes. On the whole, treatment led rapidly to the regression of the lung lesions without significant residual pulmonary impairment. The chest x-ray film generally returned to normal, with only minor fibrotic sequelae in some patients. When relapse of the disease occurred after reducing or stopping treatment, it did not involve the lung in all cases.

Sixteen patients (20.8 percent) in this series died because of active disease (14) or because of iatrogenic complications (two). Of the 14 patients who died with active disease, 13 had renal involvement. Diagnosis of WG had not been obtained before necropsy in four patients (5 percent) who died of active disease. Three patients died postoperatively after diagnostic open-lung biopsy (two) or pneumonectomy (one) with uncontrolled disease, and in all three the surgical procedure undoubtedly contributed to death. Four patients with severe widespread disease died within two months of diagnosis despite treatment. One patient died of acute respiratory failure of undetermined cause, six years after diagnosis; he had chronic obstructive pulmonary disease before the onset of WG, and active widespread WG was present at the time of death despite treatment. One patient died seven years after diagnosis of WG because of widespread active disease and associated metastatic colonic carcinoma, both diagnoses being confirmed at the time of necropsy. One patient died with extrathoracic WG without pulmonary relapse after previous excision of a pulmonary nodule. Two patients died of iatrogenic complications, one because of brain toxoplasmosis in the course of AIDS acquired through a blood transfusion, and the other because of *Pneumocystis carinii* pneumonia while undergoing immunosuppressive treatment.

**Discussion**

The aim of the present study was to precisely define the nature and frequency of the features of pulmonary WG. Cases were collected at primary specialist centers but subjected to uniform systematic analysis. This avoided the possible selection bias inherent in case collections from referral centers which may for example exclude patients who die rapidly or refuse to participate in treatment protocols. On the other hand, our study has the disadvantages of all retrospective studies, and in particular yields no useful information on treatment.

The mean age of our patients (46.5 years) is similar to that of other series. The sex ratio was about equal. The majority were nonsmokers. Smoking habits have not been characterized in previous studies, and this needs further evaluation. Most patients in this series presented with fever, weight loss and extrapulmonary clinical features. Twenty patients (26 percent) had no renal involvement, thus falling into the category of "limited WG," but only seven patients (9 percent) had WG strictly limited to the lung.

The frequency of pulmonary symptoms in our patients is higher than in other studies. This is not surprising since our case definition was based on pulmonary involvement. Only 6 percent had no pulmonary symptoms, and their pulmonary involvement was found by systematic chest x-ray films.

The most classic imaging appearance of WG is bilateral infiltrates nodules, which are highly suggestive of this condition when excavated. Nevertheless, pulmonary infiltrates are common, and we could distinguish on the chest x-ray film and CT scan three broad categories of infiltrates which easily can be recognized in the data of previously published studies. Some patients present with diffuse bilateral infiltrates of low density, characteristically associated with alveolar hemorrhagic syndrome. In others, the infiltrates are less diffuse and more patchy. In our experience, the classic spontaneous clearing of pulmonary opacities in WG involves this second category of infiltrates. In the third group, the infiltrates are dense and localized (consolidation). The CT scan was most useful for further characterizing the imaging features. First it revealed lesions which were not seen on the chest x-ray film. Furthermore, the CT scan often showed previously unsuspected necrotic cavities or necrotic content in nodules or infiltrates. In the latter, an air bronchogram was sometimes present. The varied appearance of infiltrates most probably reflects the wide spectrum of lesions seen in pathologic studies, which range from alveolar hemorrhage to pneumonialike fibrinous exudation in addition to the classic vascular necrotizing granulomatous lesions. Calcification and mediastinal adenopathy were rare in this study as in others.

Fiberoptic bronchoscopy was done in almost all patients in this series, and was abnormal in 55 percent. In most cases, endobronchial involvement consisted of nonspecific inflammatory lesions with or without stenosis. The bronchial lesions seemed to be more associated with the surrounding parenchymal involvement than isolated primary bronchial disease, and atelectasis of healthy pulmonary parenchyma as a consequence of isolated bronchial stenosis was most uncommon. Bronchial biopsies showed inflammatory and giant cells, but were not diagnostic since no frank vasculitis was seen. Nevertheless, they are suggestive of active disease in a typical clinical context. Fiberoptic bronchoscopy also helped in differentiating the origin of blood in patients with hemoptysis, ie, blood originating from focal bronchial lesions vs diffuse bleeding from distal airways suggesting alveolar hemorrhage. The only relevant finding at bronchoalveolar lavage
was the increase in polymorphonuclear leukocytes at
the time of the differential cell count, but this is not a
feature peculiar to WG, and its diagnostic value is
therefore limited.

Pleural involvement in WG rarely results in much
effusion, and no published information on pleural fluid
is available. In our four cases with pleural fluid
analysis, there was an exudate with a predominance
of polymorphonuclear leukocytes.

Lung function tests have been used in the staging
and the follow up of patients with pulmonary WG,
and the most common abnormality was airflow
obstruction. Detailed lung function tests were rarely
available in the present study, thus allowing no com-
ment on this point.

The alveolar hemorrhagic syndrome has become a
more frequently recognized pulmonary manifesta-
tion of WG, and it occurred in 8 percent of patients
in this series. Patients present with hemoptysis, and
blood originating from distal airways is seen at bron-
choscopy. The chest x-ray film shows diffuse bilateral
alveolar infiltrates. Alveolar hemorrhage is generally
acute and even fulminating in some cases. Death fre-
quently occurs in untreated patients or if treatment is
delayed. On the other hand, resolution is generally
complete with early treatment and may sometimes
occur spontaneously. Alveolar hemorrhagic WG may
be confused with Goodpasture's syndrome especially
since the latter also is usually associated with renal
disease. However, patients with WG have in addition
extrapulmonary and extrarenal disease. They also have
antineutrophil antibodies, whereas they lack the anti-
basement membrane antibodies found in Goodpas-
ture's syndrome. The pathologic diagnosis of WG at
the time of the lung biopsy is often difficult when
typical lesions are absent and capillaritis is overshad-
owed by alveolar hemorrhage.

We found no striking differences between the pul-
nary manifestations of "limited" WG and those of
"classic" WG (ie, with renal involvement). The concept
of the limited form of WG has been proposed princi-
pally to differentiate patients with and without renal
involvement, the former having the poorer prognosis.
In this series, only one of the 14 patients who
died with active disease had "limited" WG.

Usual laboratory tests are of little help in the
diagnosis of WG, since they only point to an inflam-
matory syndrome with a raised erythrocyte sedimen-
tation rate, anemia, hyperleukocytosis and hyper-
thrombocytosis. Circulating immune complexes were
present in at least 16 percent of our patients and
at least 19 percent ofaucis, and they occasionally
have been reported by others. The role of immune
complexes in WG is uncertain but may be similar to
that in other vasculitic syndromes. Several recent
studies have shown that antineutrophil antibodies are
present in the serum of patients with active WG and
could be involved in the pathogenesis of the disease.
In the present series, antineutrophil antibodies
were present in ten out of the 12 patients tested.

We shall not discuss the clinical manifestations
outside the respiratory tract other than to make the
point that the multi-organ involvement can guide the
diagnosis of the pulmonary disease. The prognosis
of WG has been transformed by therapy with corticoste-
roids and cyclophosphamide. The case fatality rate
of 7 percent reported by Fauci was especially low but
related to patients enrolled in a treatment protocol at
a referral center, thus excluding patients dying before
or just after diagnosis in other institutions. In the
present and two other series, the case fatality rate
ranged from 20.8 to 28 percent. In the present series,
seven of 77 (9 percent) patients died without treat-
ment. The fact that three patients died shortly after a
diagnostic thoracotomy underlines the risk of this
procedure in patients with severe pulmonary WG. On
the other hand, treated patients generally improve
without significant sequelae, although the hazards of
immunosuppressive drugs are a major limiting factor
for long-term survival. Cotrimoxazole has been
advocated as an alternative treatment, especially
when WG is limited to the lung.

Our study shows that patients die from WG mainly
as a result of delays in diagnosis. It is therefore
necessary to recognize the protean clinical and imag-
ning presentation of WG so that the appropriate diag-
nostic investigations are done and the patient is treated
ever.

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APPENDIX

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