Pulmonary Wegener's Granulomatosis

ARTHUR S. PATCHEFSKY, M.D. AND HAROLD L. ISRAEL, M. D.

Thomas Jefferson University Hospital, Philadelphia, Pa 19107

ABSTRACT

The clinical course, radiographic features and pathology of 18 cases of Wegener’s granulomatosis with pulmonary involvement are presented. Glomerulitis and generalized vasculitis were not features of this series.

Nodular pulmonary densities characterized the chest radiographs. Five cases showed improvement in one lung with progression in another, thus differentiating the disease from neoplasia. Vasculitis, rarely with fibrinoid necrosis, characterized the pathology. Cytotoxic drugs caused sustained clinical improvement in six patients and appear to be the treatment of choice.

Introduction

This report presents additional data on the clinical and pathological features of Wegener's granulomatosis as seen in a series of 18 patients with pulmonary involvement. Twelve patients of this group have already been described.8 The therapeutic efficacy of cytotoxic or immunosuppressive drugs is evidenced by the continued control of the disease in the majority of our patients receiving these agents.

Historical Background

Klinger,9 in 1931, first described two patients with necrotizing granulomatous inflammation and angitis which he regarded as a variant of polyarteritis nodosa. Wegener, in 1936 and 1939,12 recorded several cases and recognized the clinical and pathological features of the syndrome which now bears his name. Fahey et al4 and Godman and Churg6 further defined the disease as consisting of (1) necrotizing granulomas of the respiratory tract, (2) generalized angitis, (3) necrotizing glomerulitis and (4) disseminated granulomas. Walton's report of 56 cases illustrated the dismal outlook for most cases; the average survival in that series being five months.11 The majority of cases succumbed to progressive renal failure. Hood et al, in 1956, recorded five cases of pulmonary Wegener's granuloma, which did not develop systemic illness and whose course was relatively benign compared with the disseminated disease.7 While two or three of these cases were probably cases of eosinophilic granuloma, several appear to represent examples of the localized pulmonary form of necrotizing granulomatosis.

Carrington and Liebow, in 1966, firmly established the localized pulmonary form of Wegener's granulomatosis as a distinct entity, often separable on clinical grounds from the systemic variety by the relatively indolent evolution and absence of severe renal involvement.9
Clinical Findings

The ages of the patients ranged from 27 to 72 years, being comprised of 12 men and 6 women. No unusual environmental or occupational features could be elicited. No patients showed evidence of rheumatoid arthritis or other "collagen disease."

The onset of clinical symptoms was most often slow and insidious, but in five patients (cases 1, 3, 6, 8 and 16) the onset was explosive, one patient expiring of respiratory failure after a brief illness with the diagnosis being made only at autopsy. Six patients were asymptomatic at the time of diagnosis, their disease having been detected by routine chest X-ray examination. Cough and dyspnea were major manifestations in seven patients and three patients presented with an acute febrile illness. One patient's presenting symptom was a subcutaneous nodule; this feature was an early manifestation in another.

Pharyngitis was the presenting symptom in one patient, while upper respiratory tract involvement developed subsequent to the pulmonary lesions in three cases. No patient exhibited signs of renal disease. Hemolytic anemia with thrombocytopenia developed in one patient.

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The tuberculin test was positive in seven patients and negative in five patients. Culture of sputum specimens in six cases for acid fast and fungi were negative.

The characteristic radiological features in these cases were nodular pulmonary densities. These were unilateral in six cases and bilateral in five cases. In five patients, there was cavitation of the mass lesions; three cases showed diffuse bilateral infiltration. In five patients, the masses enlarged in one lung while improving in the other.

Pathology

The most complete account of the pathologic findings in pulmonary Wegener's granulomatosis is that of Carrington and Liebow. Material from our studies closely conforms with their description.

The gross lung specimens were personally examined in five cases: one lobectomy, two excision biopsies and two autopsies. The lesions in the lung parenchyma appeared as tan-white nodules of varying sizes, with discrete but not encapsulated margins. Cavitation and necrosis was present in two cases. Most often the lesions resembled rounded "white infarcts," or had a consistency much like that of lymphoid tissue.

Microscopically, the hallmark of the lesion was a necrotizing inflammatory process with vasculitis. In most cases, there was also superimposed infarct-like necrosis. This was especially prominent in the cavitating lesions. The dominant cell population was made up of lymphocytes and plasma cells. In several cases there was a distinctly nodular, germinal center-like configuration of the inflammatory infiltrate. However, this was only a superficial resemblance as these nodules were composed of relatively mature plasma cells and lymphocytes, without actively dividing, or phagocytic reticulum cells. In one case, plasma cells were so numerous that the initial diagnosis was erroneously thought to be plasma cell granuloma (case 4), while in another, prominence of lymphocytic cells prompted an initial pathologic diagnosis of malignant lymphoma (case 7). Eosinophils and polymorphonuclear leukocytes were present in all cases in varying amounts, with eosinophils being prominent in one case (case 2).

Young, plump fibroblasts and reticulum cells were present throughout several cases. Discrete sarcoid-like granulomas were rare, but scattered giant cells were seen in several instances. Typical caseous necrosis with prominent giant cell reaction was not seen.

The periphery of the lesions usually showed a granulation tissue-like response;
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<th>Onset Age (yr)</th>
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<td>7. L. B.</td>
<td>59 1958</td>
<td>1970</td>
<td>None</td>
<td>Solitary nodule (1958); contralateral masses (1963)</td>
<td>None</td>
<td>Chlorambucil: marked improvement</td>
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<tr>
<td>Case and Patient</td>
<td>Onset Age (yr)</td>
<td>Year of Diagnosis</td>
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<td>16. A. G.</td>
<td>37 1968</td>
<td>1972 (autopsy reviewed)</td>
<td>Cough, dyspnea, fever</td>
<td>Multiple nodules (1968)</td>
<td>None</td>
<td>Rapidly progressive course to death one month after onset of symptoms</td>
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in several cases, organizing fibrinous exudate was present. The alveolar septae in the adjacent areas showed varying degrees of thickening by inflammatory cell infiltration.

Both arteries and veins showed evidence of inflammatory infiltration. Both large and small vessels showed heavy infiltration by plasma cells, lymphocytes and occasional eosinophils. The vessel wall was thereby thickened with resultant obliteration of the vascular lumen. This was best seen with the aid of elastic stains. Fibrinoid necrosis of vessels was present in only two cases, in both of which necrosis of the nodular infiltrates was prominent (cases 15 and 16). In one of these patients, fibrinoid necrosis was widespread, and this patient had a rapidly fatal course.

In all cases where a sufficient margin of grossly uninvolved lung was examined, vasculitis was present in focal areas outside the main lesions. In several biopsy specimens, this could not be demonstrated and diagnosis was established by the characteristic inflammatory pattern and clinical findings. Large and small bronchi were occasionally the site of the inflammatory reaction and bronchiolitis obliterans was present in several cases.

The pleura showed reactive fibrosis and inflammation; however, pleural effusion was encountered in only one patient (case 15). Stains and cultures of the surgical and autopsy material for fungi and tubercle bacilli were negative.

**Diagnosis**

The diagnosis of pulmonary Wegener's granulomatosis must be made from the summation of the clinical, roentgenographic and pathological features. In these patients, special attention was given to exclusion of tuberculosis, fungal infections, and neoplasia by laboratory and histological examination. The initial roentgenographic diagnosis was often that of neoplasia because of the nodular configuration of the pulmonary lesions. One helpful distinguishing feature is the demonstration of improvement of the lesions in one lung and progression in another. This was seen in five of the cases. In one patient, biopsies of a subcutaneous nodule together with this radiographic feature resulted in the diagnosis (case 13). However, the possibility of localized Wegener's granulomatosis should be entertained in any patient with a solitary or multiple "coin lesion," with or without cavitation. The development of typical upper respiratory tract disease is strong supportive evidence. The histological diagnosis is supported by exclusion of infectious agents by appropriate cultures and staining reactions.

In our own experience, one case was originally considered to be a plasma cell granuloma before the progressive nature of the patient's illness led to re-examination of the histological material* and confirmation of Wegener's granulomatosis. The

* Undertaken by Dr. A. Liebow.
nodular and predominantly lymphocytic infiltration seen in some cases may lead to the erroneous diagnosis of malignant lymphoma. Two cases of pulmonary dirofilariasis have been observed in which the possibility of Wegener's granulomatosis was entertained until the characteristic nematodes were seen in the histologic sections.

Inflammatory reaction in the vicinity of malignant tumors may resemble that seen in Wegener's granulomatosis. Adequate amounts of biopsy material are therefore required to demonstrate the neoplasm in the deeper portions of the lesion. There is a reluctance to diagnose Wegener's granulomatosis from needle biopsy specimens.

Differentiation between Wegener's granulomatosis and rheumatoid nodules may sometimes be difficult. The clinical absence of arthritis and the absence of anthracotic pigment in the lesions of Wegener's granulomatosis are differentiating points, but one case was observed where the progressive clinical course of Wegener's granulomatosis was required to differentiate the two processes (case 18).

**Course and Treatment**

The disease exhibits a benign course with spontaneous improvement in some instances; however, 5 of 16 patients of Carrington and Liebow's series died of the disease despite corticosteroid therapy. More recently, reports of successful remission with the use of cytotoxic drugs in both the generalized and limited forms of Wegener's granulomatosis have been recorded. Sustained remissions have been observed with marked roentgenographic improvement in 6 of 11 patients in whom cytotoxic drugs were administered. In one patient (case 3), death resulted from drug toxicity, while in another (case 17), these agents failed to prevent progression and death from tracheal obstruction. One patient (case 4) died of infection despite control of disease. In two patients, these drugs have been introduced only recently. Corticosteroids have given transient improvement in only one of the cases while...
the disease continued to progress in three patients. Surgical resection in two cases has been apparently curative, while disease recurred after resection in three patients.

Discussion

The etiology of Wegener's granulomatosis is unknown. Circumstantial evidence suggests an autoimmune-mechanism or "hyper-
sensitivity." This is histologically suggested by vasculitis and granulomatous inflammation. The similarity to rheumatoid nodules and the inflammatory reaction around tumor also is suggestive of such a mechanism and there is some experimental evidence to support this view.6

The similarity of the pulmonary findings in patients with generalized Wegener's granulomatosis and with the limited form suggests that the difference between the two is one of degree. Upper respiratory tract disease has also been seen in several of the patients, the separation from the generalized form therefore being the failure to develop glomerulitis and generalized vasculitis. However, even when localized to the lungs, this disease may be rapidly fatal. In this instance (case 16), widespread fibrinoid necrosis of vessels, such as seen in the generalized variety, was a prominent feature. The degree of vascular injury may, therefore, be a clue to the intensity of the disease and its propensity to disseminate more widely.

The treatment of choice in this disease is therapy with chlorambucil, Imuran, metho-
Figure 6. Case 14. Necrotizing granulomatous inflammation with infarct-like necrosis. Pulmonary vessel shows fibrinoid necrosis and surrounding histiocytic and chronic inflammatory reaction. (Hand E X50)

trexate or cyclophosphamide. While the mechanism of action of these drugs in this disorder is not understood, their ability to suppress the immune system is probably a major factor in their action. This is suggested by the inability of corticosteroids, which are potent antinflammatory agents, to successfully control the disease.

Case Histories

Case 13
This 54-year-old white male was well until March 1972 at which time he was admitted to a hospital because of chills and fever and an abnormal chest X-ray. A diagnosis of viral pneumonia was made. He was discharged after three weeks in the hospital and was afebrile. Subsequent to his discharge, several chest X-rays showed clearing of the original lesion with new densities in the opposite lung (figures 1, 2, 3 and 4). Approximately two months prior to admission, he noticed small, subcutaneous, non-tender nodules in the left upper quadrant and right lower quadrant of the abdomen. Because of the abnormal roentgenographic findings, he was hospitalized in mid-August 1972.

The pertinent physical findings were related to the lungs and skin. There were a few fine rales at the left base. Examination of the abdominal wall showed two, 2 x cm, hard, firm, non-tender subcutaneous nodules under the left costal margin. There was also a 3 x 2 cm firm nodule in the lower abdominal wall. These were freely movable. The patient stated that he was allergic to penicillin and had lost 20 pounds since March 1972.

Laboratory examination was normal. Urinalysis showed no hematuria or proteinuria. On the day after admission, one of the abdominal nodules was
excised. Histologically, it showed granulomatous panniculitis (figure 4). Cultures of this material for acid fast and fungal organisms showed no growth, and special stains for these organisms were negative. A presumptive diagnosis of Wegener's granulomatosis was made and the patient was discharged the following day. No medications were administered and the patient was to be observed closely.

Case 14

This 57-year-old white female was admitted to Thomas Jefferson University Hospital for the first time in October 1971. During a routine chest X-ray three years prior to admission, she was found to have a solitary pulmonary nodule in the left lung. The patient was asymptomatic, but ten days prior to admission, a routine chest X-ray showed increase in the size of the lesion and a 1 cm nodule was noted in the right upper lobe (figure 5). The patient stated that she had a “chronic sinus infection” with rhinitis since childhood and had noted a decreased sense of smell over the past year. She denied epistaxis, cough, hemoptysis, hoarseness, or weight loss. She smoked one pack of cigarettes a day for four years and gave a history of food allergies and allergies to flowers since childhood.

The physical examination was essentially unremarkable except for slight watery discharge from the nose. Examination of the lungs was negative. Laboratory tests including hemogram, urinalysis and VDRL were unremarkable. The patient had an excision biopsy of the left lower lobe mass lesion and a diagnosis of Wegener’s granulomatosis was made (figure 6). Cultures of the biopsy material for acid fast and fungus showed no growth. She was discharged and no therapy was instituted. Re-examination one year later revealed a slight increase in size of the nodule in the right lung. She remained well and observation was continued.

Acknowledgments

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References