Thorax, 1978, **33**, 603–607

Pulmonary manifestations of hypogammaglobulinaemia

RUSSELL J DUKES, EDWARD C ROSENOW III, AND PAUL E HERMANS

From the Division of Thoracic Diseases and Internal Medicine and the Division of Infectious Diseases and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA

Dukes, R J, Rosenow, E C III, and Hermans, P E (1978). *Thorax*, **33**, 603–607. **Pulmonary manifestations of hypogammaglobulinaemia.** Fifty-five patients with late-onset idiopathic immunoglobulin deficiency were studied and upper or lower respiratory tract infections were encountered in about 90%. Cylindrical bronchiectasis was shown in all of the 21 patients in whom bronchograms were done. A thymoma was found in four patients. Three patients had diffuse interstitial pulmonary disease—two with proved and one with presumed lymphocytic interstitial pneumonitis. Five patients had no evidence of pulmonary disease, including two patients with long-standing late-onset immunoglobulin deficiency who had essentially no serum immunoglobulins. This small subgroup of patients with immunoglobulin deficiency without severe pulmonary infections cannot be explained in the context of current understanding of immunoglobulin deficiency. Thirty-two patients were followed up for long enough for the response to treatment to be assessed.

Idiopathic late-onset immunoglobulin deficiency or variable immune deficiency was defined by an expert committee of the World Health Organisation in 1971. Patients with this disorder acquire abnormally low concentrations of serum immunoglobulins and experience recurrent infections starting several years after birth but have no underlying demonstrable disease to which the immunoglobulin deficiency can be attributed (Fundenberg *et al*, 1971). Because respiratory symptoms are the most common presenting complaint in late-onset immunoglobulin deficiency, we undertook a review of our clinical experience and chest radiographs. We studied 55 patients with this disorder to evaluate the spectrum of chest disease.

Material and methods

In this retrospective study, data on 55 patients (29 male and 26 female) were analysed. The earliest onset of symptoms was at the age of 7 years and the latest at age 67, the mean being 30 years (male 27, female 35). The mean age at which a definite diagnosis was made, however, was 41·9 years (male 38·6, female 45·7). All patients save one were white; this distribution reflects a bias introduced by our patient population. The specific criteria used in diagnosing late-onset immunoglobulin deficiency and the methods used for quantitative measurement of the serum immunoglobulins and for serum protein electrophoresis have been reported (Hermans *et al*, 1976). The lower limit of normal for γ-globulin at our institution is 0·8 g/dl. The lower limits of normal for IgA, IgG, and IgM are 0·3, 6·4, and 0·2 mg/ml respectively.

Since almost all of these patients were seen by one of us, the treatment was fairly consistent and included γ-globulin injections and antibiotics. Commercial pooled human γ-globulin was given by intramuscular injections as a loading dose of 60 ml and then either 20 or 30 ml intramuscularly, according to the patient's weight, once a month thereafter. The antibiotic regimen usually consisted of tetracycline or ampicillin, 500 mg four times a day for one week in alternating fashion with a rest period of one week in between. It must be emphasised that each patient's treatment was somewhat different, depending on the severity of his disease. Specifically, patients who had only minor respiratory infections received only antibiotics initially until the severity of the infection warranted the use of γ-globulin.

Most patients were instructed in the techniques

of postural drainage and physiotherapy to the chest. The presence of cough, sputum production, and documented episodes of pneumonia were recorded. Each symptom was described as none, mild, moderate, or severe. Cough and sputum production were called moderate if the patient complained of them spontaneously, as severe if the patient woke with them at night, and mild if they were simply elicited during the review of systems. Susceptibility to pneumonia was graded as follows: none, when there were no recurrent episodes of pneumonia in one year; mild, one episode a year; moderate, two to four episodes a year; and severe, five or more episodes a year.

Results

RESPIRATORY SYMPTOMS

The severity of cough and sputum production and the number of episodes of pneumonia a year at the time of diagnosis are summarised in table 1. Forty-one (75%) of our patients had an initial complaint of cough, 39 (71%) had sputum production, and 41 (75%) had a history of recurrent pneumonia. Other presenting symptoms included dyspnoea on exertion in 13 (24%), haemoptysis in eight (15%), and asthmatic bronchitis in one (2%). Five patients (9%) denied that they had ever had any respiratory symptoms or episodes of pneumonia; three of these patients had symptoms of chronic sinusitis.

Table 1 *Signs and symptoms at time of diagnosis in 55 patients*

	No of patients		
	Cough	*Sputum production*	*No of pneumonias/ year**
None	12 (22%)	14 (26%)	7 (13%)
Mild	17 (31%)	16 (30%)	4 (7%)
Moderate	22 (41%)	22 (40%)	14 (26%)
Severe	2 (4%)	0 (0%)	23 (43%)
Total	53	52	48

*mild=1, moderate=2–4, severe=5 or more.

Of 33 patients available for follow-up, 32 were treated according to the above regimen. The follow-up period ranged from four months to 19 years, with an average of two years. No comparison can be made between treated and untreated groups, but the effect of treatment was evaluated on the basis of complaints by comparing the severity of complaints before and during treatment. Table 2 shows that patients tended to improve with treatment. Of the 16 patients who complained of five or more episodes of pneumonia a year before treatment, only one patient had this many episodes of pneumonia during treatment.

Table 2 *Results of treatment (%) in 32 patients**

	Cough		*Sputum production*		*No of pneumonias/ year*	
	Before	*During*	*Before*	*During*	*Before*	*During*
None	9	13	6	19	13	63
Mild	38	78	38	62	6	15
Moderate	51	6	56	19	31	19
Severe	2	3	0	0	50	3

*Results are measured by evaluation of symptoms before and during treatment.

A total of 15 patients had complete pulmonary function tests. The results usually showed a pattern of airways obstruction and did not correlate well with other indicators of the severity of the disease.

CHEST RADIOGRAPHS

We reviewed all chest radiographs (table 3). Seven patients (13%) had normal and 48 (87%) had abnormal chest films. Thymoma was present in four patients (two were spindle cell, one was lymphocytic, and one was of unknown type). Diffuse interstitial pulmonary disease was noted in three patients; in two of these lymphocytic interstitial pneumonitis was proved by biopsy, and in the other this diagnosis was thought possible on the basis of radiographic findings only. Bronchograms were done on most patients who expectorated copious amounts of purulent sputum. Bronchiectasis was found in all 21 so examined. The bronchiectasis was all of the cylindrical type, and in most of these cases it affected both lower lobes. No saccular bronchiectasis was seen. Changes such as localised fibrosis, focal areas of atelectasis, or apical thickening were present on the chest films of the other patients. One patient had squamous cell carcinoma of the lung. No case of pleural effusion, lung abscess, or pneumothorax was found but four patients had a history of empyema.

Table 3 *Chest radiographic findings in 55 patients (%)*

Normal	13
Abnormal	87
Bronchiectasis	38
Thymomas	7
(2 spindle cell, 1 lymphocytic predominant, 1 unknown)	
Lymphocytic interstitial pneumonia	5
(2 proved, 1 suspected)	
Nonspecific	37

LYMPHOCYTIC INTERSTITIAL PNEUMONITIS AND HYPOGAMMAGLOBULINAEMIA

Two patients had diffuse pulmonary disease with the finding of lymphocytic interstitial pneumonitis on open lung biopsy. A third patient had similar findings on the chest radiograph, but no biopsy was performed.

Case 1

A 38-year-old white woman with a long history of sinusitis and frequent upper respiratory infections came for evaluation of lymphadenopathy; biopsy of a lymph node showed only hyperplasia. The chest film, which had been normal two years before, showed diffuse bilateral infiltration. An open lung biopsy showed interstitial pneumonitis with scattered interstitial lymphoid follicles. Results of all cultures were negative. Serum protein electrophoresis showed the following (normal range in parentheses): albumin 4·10 g/dl (3·5 to 4·7); α_1-globulin 0·37 g/dl (0·2 to 0·5); α_2-globulin 0·54 g/dl (0·5 to 0·8); β-globulin 0·71 g/dl (0·7 to 1·3); γ-globulin 0·20 g/dl (0·8 to 1·6); and total proteins 5·92 g/dl. Immunoglobulins measured: IgM 0·0 mg/ml (0·2 to 1·4); IgA 0·0 mg/ml (0·3 to 3·0); IgG 0·7 mg/ml (6·4 to 14·3); and IgE less than 5 ng/ml (6 to 780).

The patient was treated with monthly injections of 30 ml of γ-globulin, alternating courses of antibiotics, and prednisone—initially 40 mg/day and tapered over a few months to a maintenance dosage of 5 mg twice daily. When last seen 14 years later in 1977 she was still on this regimen, and the chest radiograph was normal. The frequency of respiratory infections was less. Pulmonary function is compared below (normal in parentheses).

	1964	1977
Vital capacity, litres (4·0)	3·5	3·7
Total lung capacity, litres (5·5)	4·7	4·9
Maximal midexpiratory flow, litres/sec (>1·7)	4·0	2·3
Maximal voluntary ventilation, litres/min (90)	66	117
Transfer factor, ml/min per mmHg (exercise, steady state) (18 to 29)	17	15

Case 2

A 38-year-old white woman had a long history of frequent upper respiratory infections, ear infections, and eczema. Four years before her first visit she had had her first documented attack of pneumonia and had suffered a persistent productive cough since then. On admission, her chest film showed diffuse infiltration, more pronounced on the left side (fig 1). An open lung biopsy showed chronic interstitial pneumonitis with pronounced proliferation of lymphocytes (fig 2). No granulomas were seen. Immunoglobulins were as follows (normal range in parentheses): IgM 0·14 mg/ml (0·2 to 1·4); IgA 0·5 mg/ml (0·3 to 3·0); and IgG 0·8 mg/ml (6·4 to 14·3).

She was treated with 30 ml of γ-globulin intramuscularly once a month, together with antibiotics alternated monthly, and there was pronounced improvement in pulmonary symptoms. She was not given corticosteroids. A chest film two years later showed slight improvement.

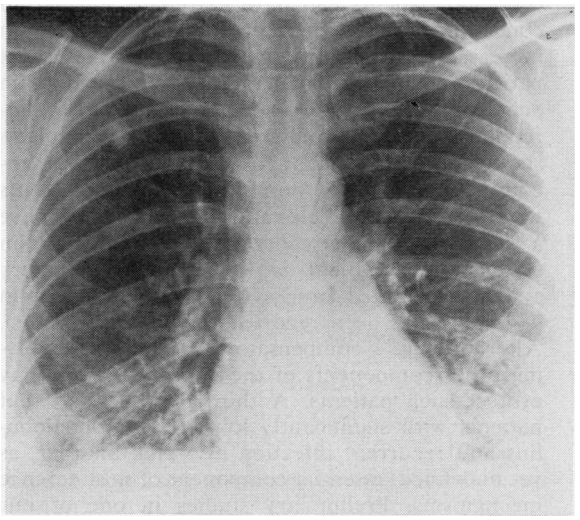

Fig 1 *Case 2. Chest radiograph showing diffuse interstitial infiltration.*

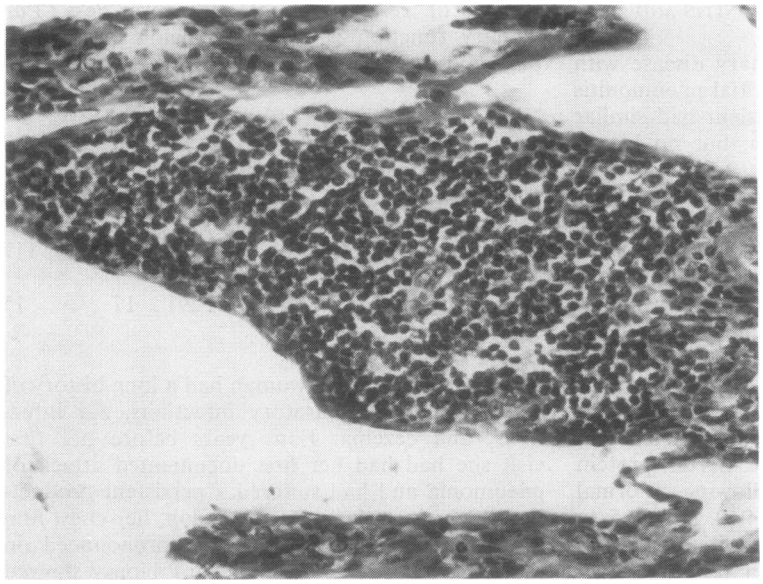

Fig 2 *Case 2. Open lung biopsy specimen showing chronic interstitial pneumonitis with pronounced lymphocytic proliferation (Haematoxylin and eosin ×400).*

Discussion

Late-onset idiopathic immunoglobulin deficiency is diagnosed after exclusion of conditions that may lead to secondarily low immunoglobulin concentrations. Lymphocytic lymphoma, chronic lymphocytic leukaemia, multiple myeloma, nephrotic syndrome, and protein-losing enteropathy (Asherson, 1975) must be ruled out.

In addition to recurrent infections, individuals with late-onset hypogammaglobulinaemia are predisposed to other diseases. These include lymphoreticular neoplasms, carcinomas, atrophic gastritis, diarrhoea with or without malabsorption, nodular lymphoid hyperplasia of the small bowel, cholelithiasis, giardiasis, lymphocytic interstitial pneumonia, thymomas, and thyroid abnormalities (Gafni *et al*, 1960; Hermans *et al*, 1976).

Of our patients with hypogammaglobulinaemia 91% had respiratory symptoms, and 87% had abnormal chest radiographs. Treatment with antibiotics and γ-globulin injections resulted in subjective improvement in respiratory symptoms in most patients. A loading dose of 60 ml of γ-globulin was injected intramuscularly over a period of three days followed by a maintenance dosage of 20 to 30 ml once a month. Since *Haemophilus influenzae*, *Streptococcus (Diplococcus) pneumoniae*, and *Streptococcus pyogenes* are the predominant pathogens in immunoglobulin-deficient patients, ampicillin is the antibiotic of first choice. Ampicillin-resistant strains of *H influenzae* require chloramphenicol.

The absence of necrotising pulmonary infections leading to abscess formation suggested that anaerobic micro-organisms and the Enterobacteria do not play an important part in the respiratory infections of patients with hypogammaglobulinaemia. Apparently, host defence mechanisms other than immunoglobulins offer adequate protection against these infectious agents. Of special interest were the five patients who had markedly low γ-globulin concentrations but no recurrent respiratory tract infections.

Immune defences of the lung have recently been reviewed (Kaltreider, 1976). Why some exceptional patients can have extremely low serum concentrations of immunoglobulins without an increased susceptibility to infection while most patients with a similar degree of immunoglobulin deficiency are severely affected by recurrent infections remains an enigma. Several mechanisms should be considered to explain the paradox encountered in two of our patients. Some patients with serum immunoglobulin deficiency may have a relatively intact secretory immunoglobulin system. One patient with an intact secretory system dissociated from systemic immunoglobulin deficiency has been reported (Spitler *et al*, 1973). Alternatively, a compensatory mechanism involving other components of the immune system may protect such patients. A third hypothesis is that patients with significantly lowered immunoglobulins and recurrent infection also lack another, as yet undefined, essential component of host defence mechanisms. Preliminary studies in one of our

two patients with severe immunoglobulin deficiency but without increased susceptibility to infection have shown that the secretory system of this patient also lacks the ability to produce IgA (by courtesy of Dr Tomasi, Department of Immunology).

Also of interest are the two patients with documented and a third with suspected lymphocytic interstitial pneumonitis. Liebow and Carrington (1973) have also noted this association. Little is known about this disorder. It would be of special interest to know whether these lymphocytes are of B-cell or T-cell origin. We are currently reviewing our experience with all lymphocytic interstitial pneumonitis unrelated to immunoglobulin deficiency. The clinical course of the interstitial pneumonitis in the two patients reported here is less progressive than that of the others we have seen. In fact, the clearing of the diffuse infiltration on the chest film in case 1 is most unusual.

Several mechanisms of pathogenesis for late-onset immune deficiency have been proposed. Most recently, Waldmann *et al* (1974) have found that some patients have a population of "suppressor" T cells that appear to interfere with the maturation of B cells into immunoglobulin-secreting plasma cells. Other reports have emphasised that the defect may reside at various stages of B-cell development, the common denominator being decreased immunoglobulin production (Choi *et al*, 1972; Geha *et al*, 1974).

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Requests for reprints to: Dr E C Rosenow III, Mayo Clinic, 200 First Street SW, Rochester, MN 55901, USA.