Pulmonary Interstitial Disease in Ig Deficiency*

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Study objectives: To determine the frequency and type of interstitial lung disease (ILD) in consecutive subjects with symptomatic Ig deficiency.

Patients: One hundred forty-eight consecutive subjects with repeated respiratory infections and Ig deficiency.

Measurements: Ig classes and IgG subclasses (IgGSCs), the response to vaccination, pulmonary function tests, chest radiography, CT scan, Ga scan and, when possible, BAL and lung biopsy.

Results: Twenty-nine of 148 subjects (19 men and 10 women aged 18 to 72 years) had evidence of ILD. In 20 subjects, no cause of ILD was apparent. The remaining nine cases were ostensibly due to identifiable causes. Twenty subjects had IgGSC deficiency, 8 subjects had common variable immunodeficiency, and 1 subject had combined IgM plus IgGSC deficiency. No isotype deficiency was consistently related to a specific ILD. After administration of IV Ig, eight subjects, all with IgGSC deficiency, improved clinically, physiologically, radiologically, and occasionally histologically, regardless of immunologic or radiologic features. In this selective sample, the prevalence of ILD in consecutive subjects with recurrent respiratory infections and Ig deficiency (29 of 148 subjects; 19.6%) was higher than in the general population (0.8%; p < 0.05).

Conclusions: ILD in Ig deficiency is frequent and usually involves IgGSC deficiency.

Key words: Ig deficiency; IgG subclass deficiency; interstitial lung disease; IV Ig; repeated respiratory infections

Abbreviations: BOOP = bronchiolitis obliterans organizing pneumonia; CVID = common variable immunodeficiency; DLCO = diffusing capacity of the lung for carbon monoxide; IgGSC = IgG subclass; ILD = interstitial lung disease; LIP = lymphocytic interstitial pneumonitis; NSIP = nonspecific interstitial pneumonitis; PCVID = partial common variable immunodeficiency; RV = residual volume; UIP = usual interstitial pneumonitis

Ig deficiencies comprise a diverse group of clinical entities that include common variable immunodeficiency (CVID), selective IgG subclass (IgGSC) deficiency, IgA or IgM deficiency, X-linked agammaglobulinemia, and other rare conditions. The diagnosis relies on laboratory demonstration of decreased serum Ig(s) and a poor response to vaccination mediated via IgG1 and/or IgG2 in a patient with manifestations consistent with Ig deficiency.1,2

The most common clinical manifestations of antibody deficiency syndromes are repeated and prolonged infections usually involving the respiratory system. Thus, rhinosinusitis, bronchitis, asthma, bronchiectasis, and pneumonia are all well recognized. Patients with Ig deficiencies may also have radiologic and/or functional evidence of interstitial lung disease (ILD), but their frequency and type are incompletely appreciated. Several histologic patterns have been reported in the lungs of patients with CVID, including lymphocytic interstitial pneumonitis (LIP),5,6 granulomatous interstitial pneumonitis,7–9 bronchiolitis obliterans organizing pneumonia (BOOP),10 and usual interstitial pneumonitis (UIP).11 For the most part, these descriptions come from small series or individual case reports10,11 that are difficult to interpret. Indeed, in individual patients, the link between Ig deficiency and repeated infections is usually argued by measuring the response to vaccination. However, the relevance of this immune deficiency for ILD calls for statistical analysis and/or IV Ig treatment since no diagnostic test can suggest this relationship.

In studying recurrent respiratory infections and Ig deficiency,12,13 one of us (V.P.) was impressed by the
frequency of radiologic\textsuperscript{3} and/or functional\textsuperscript{4} evidence of ILD. This is not a unique experience. Some authors have found a restrictive ventilatory abnormality in 20 to 30\% of adults with CVID.\textsuperscript{14} In Ig deficiencies other than IgGSC deficiency,\textsuperscript{15–19} several authors have reported many CT scan abnormalities of the large bronchi (bronchial wall thickening, bronchiectasis), small bronchi, alveoli (bullae, segmental or lobar collapse due to small airways obstruction), and interstitium. The interstitial changes were usually listed descriptively and included scattered nodules, septal and nonseptal lines, ground-glass consolidation, presumably a lesion involving both the alveolar lumen and wall\textsuperscript{18}; and occasionally honeycombing.\textsuperscript{19} Their asymmetrical localization and frequent association with bronchiectasis suggest a relation with previous infections and, for lack of a better term, we will call these lesions seen on CT scan, chronic postinfectious pneumonitis. These complex changes are much more frequent than the diffuse ILD mentioned above.

Herein we report a consecutive series of patients initially seen because of symptomatic primary Ig deficiency who also had radiologic evidence of ILD\textsuperscript{4} or BAL with physiologic findings\textsuperscript{5} consistent with ILD.

**Material and Methods**

**Materials**

The subjects included in this study were observed consecutively by V.P. either at the Veterans Administration Sacramento outpatient clinic (from 1984 to 1987) or, subsequently, in his practice of pulmonary, allergy, and internal medicine (from 1987 to 1999).

**Selection Criteria**

From 1984 to 1999, all subjects who had recurrent respiratory infections (see below), underwent a workup for Ig deficiency along with pulmonary function tests and lung imaging. Included in this series were all cases with radiologic evidence of ILD or, in its absence, with BAL and physiologic findings consistent with ILD. These findings had to be stationary or progressive over 1 month and unexplained by evolving infections or hemodynamic or lymphangitic processes.\textsuperscript{20} Since adults with CVID or IgGSC deficiency usually have bronchial respiratory infections,\textsuperscript{12–14,21} the concomitant presence of asthma, bronchitis, or bronchiectasis associated with an obstructive abnormality on physiologic testing did not constitute grounds for exclusion.

**Methods**

Recurrent respiratory infections were defined arbitrarily as five upper or lower respiratory catarrhal manifestations other than pneumonia occurring five times per year in the past 2 years and lasting each time at least 2 weeks; pneumonia was considered recurrent if it occurred once a year in the past 2 years.\textsuperscript{14,15,21} This frequency represents two to three times the number of average episodes of bronchitis, sinusitis, or otitis, and five times the average number of pneumonia cases encountered in healthy blood donors.\textsuperscript{22} The respiratory infections that did not fulfill the criteria for recurrence were considered to be occasional. Asthma, chronic bronchitis, bronchiectasis, and restrictive and obstructive ventilatory abnormalities\textsuperscript{4} were diagnosed according to current criteria.

**Studies**

**Lung Imaging:** These studies included chest radiography, CT scan of the lung (with thin sections after 1990), and Ga scan. The radiologic diagnosis of ILD was based on the presence of nodules, lines, honeycombing, and ground-glass opacity on the chest radiograph and the following abnormalities on CT scan of the chest: nodules (including centrilobular nodules), lines (thickened septa, intralobular, curvilinear, and parenchymal bands), cysts (including honeycombing), parenchymal opacification (ground-glass attenuation and consolidation), decreased lung attenuation, and mosaic pattern.\textsuperscript{3} The CT scans were interpreted by S.B.R.

**Pulmonary Function Tests:** We measured flow-volume curves, static lung volumes by He dilution, and diffusing capacity of the lung for carbon monoxide (DL(\textsubscript{CO})) with the single-breath method as indicated by Morris et al.,\textsuperscript{23} and arterial blood gases.\textsuperscript{23} The data of Morris et al.\textsuperscript{4} were used to determine the eventual type of functional abnormality. In the absence of ILD by chest imaging, restrictive impairment of ventilation\textsuperscript{5} was considered suggestive of ILD if associated with abnormal findings on BAL.

**Ig:** These studies included circulating total IgA, IgG, IgM by nephelometric method, total IgE by radioimmunoassay, and IgGSCs by radial immunodiffusion using either the commercial Immunology Laboratory of Peter Bent Brigham Hospital (from 1984 to 1987) or a commercial kit (Binding Site; ARUP Laboratory, Salt Lake City, UT). Values < 450 mg/dL for IgG, < 5 mg/dL for IgA, and < 20 mg/dL for IgM, all substantially below the 95\% confidence limit,\textsuperscript{1,24} were used to define CVID.\textsuperscript{12–13} IgA and IgM deficiency, respectively. Similar to IgA and IgM deficiency, in which the values between the lower 95\% confidence limit and the value defining arbitrarily the deficiency are called partial deficiency, the values of IgG between 650 mg/dL, the lower 95\% confidence limit,\textsuperscript{24} and 450 mg/dL\textsuperscript{12–14} the defining value of CVID, were called partial CVID (PCVID).\textsuperscript{12,23} Values of IgGSC below the 95\% confidence limits were considered abnormal: 422 mg/dL for IgG1, 117 mg/dL for IgG2, 41 mg/dL for IgG3,\textsuperscript{23} and 11 mg/dL for IgG4.\textsuperscript{28} In addition, to diagnose isolated IgGSC deficiency, we required an IgG > 450 mg/dL and planned to determine (every time it was possible) an impaired IgG response to vaccination.\textsuperscript{1,2} For IgG1-mediated pathway, we determined the change in specific IgG antibodies against tetanus toxoid in both veterans and nonveterans; for IgG2-mediated pathway, we measured IgG antibodies against Haemophilus influenzae in veterans and, in nonveterans, against Streptococcus pneumoniae antigens 3, 7A, 9, and 14. The measurements were performed in Dr. Heiner’s research laboratory at Harbor-UCLA Medical Center for veterans\textsuperscript{2} and at Specialty Laboratory (Santa Monica, CA) for nonveterans.\textsuperscript{21} Failure to double the preimmunization level of the specific antibody was considered a subnormal response.\textsuperscript{1,12,13}

**Lymphocyte Phenotyping:** These studies included lymphocyte phenotyping for B cells, and CD4 and CDS T lymphocytes. Values < 9\% for B cell, CD4 count < 500/\mu L, and a CD4/CD8 ratio < 0.8 were considered abnormal.\textsuperscript{1}

**Biopsy and BAL:** Open-lung or closed-lung biopsy and BAL were considered every time the etiologic diagnosis of ILD could not be established by CT scan. The biopsy specimens were evaluated by the same observer (T.V.C.) using standard criteria.\textsuperscript{27}
RESULTS

Of 148 patients, a total of 29 patients were included in this study: 25 patients with radiologic findings of ILD and 4 patients with neutrophil alveolitis (>25% neutrophils, >10 x 10^6 cells/mL) and restriction abnormality. Since in many cases of ILD with clear chest radiographs, as for instance in collagen vascular diseases or sarcoidosis, the presence of restrictive abnormality is taken as a sign of interstitial involvement, the four patients with neutrophil alveolitis were considered to have ILD and were combined with the 25 patients displaying radiologic findings. These 29 cases are summarized in Table 1. There were 20 male and 9 female patients (age range, 18 to 72 years); 23 patients were ≥40 years old. None of them had extrapulmonary manifestations characteristic of IgG deficiency. The onset of repeated respiratory infection, except in one patient (subject 16), was in adulthood.

The Ig deficiencies associated with ILD included 8 cases of CVID; 2 cases of IgM deficiency, combined with IgGSC deficiency or PCVID; and 21 cases representing IgGSC deficiency. To indicate the degree of IgG deficiency, the subjects with PCVID, all qualifying as CVID according to Cunningham-Rundles28 but not according to Watts et al,14 will be identified as PCVID in Table 1. In the text, for the sake of simplicity, these subjects will be included in CVID. No patient had CD4/CD8 abnormality.

The prevalence of ILD in Ig deficiency, 29 of 148 patients (19,600/100,000), is 240 times higher (p < 0.05) than the prevalence of ILD in the general population of Bernalillo County, New Mexico29 (80.9/100,000). The later study included a variety of ILD along with isolated restrictive abnormality without lung infiltrates. The 29 cases of ILD associated with Ig deficiency represented 20.7% of the total cases of ILD (n = 140) seen concurrently by V.P.

No pulmonary function tests other than arterial blood gas analysis could be performed in five subjects (two subjects with mental retardation and three subjects with acute illness). Ga scan findings, performed in 20 subjects, were positive in seven patients: three of four subjects with neutrophil alveolitis (subjects 2, 3, and 4); all three subjects with exposure to irritants (subjects 22, 23, and 24); and one subject with radiation pneumonitis (subject 25).

Except for the three patients seen exclusively in the hospital, all patients were followed up for at least 6 months; four subjects were followed up for 4 to 12 years. In these patients, the Ig measurements were repeated at 3 to 6 months, and the results confirmed the presence of the same Ig deficiency.

With the intention of preventing the recurrent respiratory infections associated with antibody deficiency, IV Ig was administered to eight subjects. The dose varied from 150 mg/kg/mo in six subjects to 400 mg/kg/mo in two subjects. All had IgGSC deficiency, IgG3, IgG4, combined IgG3 plus IgG4, and one patient had IgG3 plus IgG1. Their ILD was documented by BAL and physiologically (subjects 1 and 2), radiologically (subject 21 with bronchiectasis and chronic postinfectious pneumonitis), or histologically (subjects 5 and 6 with LIP, and subjects 7, 9, and 15 with UIP, nonspecific interstitial pneumonitis [NSIP], and—descriptive diagnosis—with interstitial pneumonitis with few scattered granulomas without vasculitis but with antiproteinase-3 antibody, homogeneous antinuclear antibody, and antiribonucleoprotein, respectively). The immune treatment lasted 4 months in subjects 6, 7, 15, and 21; 4 years in subject 9; and 10 to 12 years in subjects 1, 2, and 5. On the average, per patients’ rating, the recurrent respiratory infections decreased by 75% in frequency, duration, and severity; dyspnea on exertion (Borg scale) improved by 50 to 75%; while the rate of hospitalizations decreased by 68%. Unanimously, the subjects claimed that IV Ig increased their general well-being. All subjects improved radiologically, as illustrated in Figures 1 through 4 and, with the exception of a mentally retarded subject who could not perform pulmonary function tests reliably, physiologically as well (Fig 5). No isotype deficiency was reversed when the isotypes were measured 6 weeks after IV Ig administration. In four subjects receiving 4 months of treatment (subjects 6, 7, 15, and 21), the physiologic and radiologic improvement lasted at least 12 months (Fig 1). Subject 1 had repeated episodes of respiratory infection with clear chest radiograph, CT scan, or Ga scan, which were associated with acute, reversible restriction. These episodes (occult pneumonia?) together with the intercritical, mild restrictive abnormality improved during his many years of treatment with IV Ig (Fig 5). One of the two subjects with LIP, subject 5 (Fig 2) acquired a severe abdominal infection, followed by sepsis and ARDS after 10 years of IV Ig; a few months later, this subject died receiving mechanical ventilation. The autopsy showed chronic diffuse alveolar damage but no evidence of LIP (Fig 6). Subject 15 died during an episode of acute respiratory infection; autopsy revealed interstitial fibrosis and bronchopneumonia but no granulomas.
<table>
<thead>
<tr>
<th>Subject Age/ Smoking Status</th>
<th>BMI</th>
<th>Lung/ Systemic Disease Other Than ILD</th>
<th>Subnormal Ig(s)</th>
<th>Subnormal Response to Vaccination</th>
<th>Subnormal FEV1, FVC, TLC, RV, FRC, DLCO, PaO2, PaO2, Pathologic Features</th>
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</thead>
<tbody>
<tr>
<td><strong>Clear imaging</strong></td>
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<tr>
<td>1 37 M NS &lt; 25 A</td>
<td></td>
<td></td>
<td>IgG3, IgG4</td>
<td>TT</td>
<td>WNL 72 78 76 78 78 90 7.41 90 39 Neut. Alv.</td>
</tr>
<tr>
<td>3 44 F S &lt; 25 A</td>
<td></td>
<td></td>
<td>IgG4</td>
<td>PN</td>
<td>WNL 67 71 70 73 72 81 7.39 78 39 Neut. Alv.</td>
</tr>
<tr>
<td>4 63 M NS &lt; 25 A</td>
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<td></td>
<td>IgG4</td>
<td>WNL</td>
<td>WNL 70 78 68 76 74 59 7.39 74 38 Neut. Alv.</td>
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<td><strong>Interstitial infiltrate</strong></td>
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<td>5 40 F NS 26 A</td>
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<td></td>
<td>IgG3</td>
<td>TT and PN</td>
<td>WNL 55 92 54 52 57 10 7.46 90 39 LIP</td>
</tr>
<tr>
<td>6 64 F S &lt; 25 A</td>
<td></td>
<td></td>
<td>IgG3, IgG4</td>
<td>TT</td>
<td>WNL 50 65 76 120 78 54 7.40 74 43 LIP</td>
</tr>
<tr>
<td>7 52 F S &lt; 25 A</td>
<td></td>
<td></td>
<td>IgG4</td>
<td>PN</td>
<td>WNL 49 90 62 90 56 50 7.39 66 37 NSIP</td>
</tr>
<tr>
<td>8 36 M S 27 A</td>
<td></td>
<td></td>
<td>IgG4</td>
<td>N/D</td>
<td>WNL Died in hospital 7.34 45 46 BOOP</td>
</tr>
<tr>
<td>9 56 M S 27 A</td>
<td></td>
<td></td>
<td>IgG3, IgG4</td>
<td>TT and HIB</td>
<td>WNL 37 82 85 136 112 26 7.44 66 40 UIP</td>
</tr>
<tr>
<td>10 64 M S &lt; 25 COPD</td>
<td></td>
<td></td>
<td>CVID</td>
<td>N/D</td>
<td>WNL 68 67 72 81 84 35 7.43 57 41 UIP</td>
</tr>
<tr>
<td>11 72 M S 27 COPD and Bect</td>
<td></td>
<td></td>
<td>PCVID, IgM</td>
<td>N/D</td>
<td>WNL 29 73 115 207 150 44 7.45 61 53 BOOP</td>
</tr>
<tr>
<td>12 54 M S &lt; 25 COPD</td>
<td></td>
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<td>IgG1</td>
<td>N/D</td>
<td>WNL 70 65 87 86 96 57 7.43 64 41 Ret. nodular</td>
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<tr>
<td>13 41 F NS 28 Sarcoidosis</td>
<td></td>
<td></td>
<td>IgG3</td>
<td>N/D</td>
<td>WNL 98 80 101 91 88 99 7.41 85 39 Noncaseating granuloma in lymph node</td>
</tr>
<tr>
<td>14 42 M NS &lt; 25 Sarcoidosis</td>
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<td></td>
<td>IgG3</td>
<td>N/D</td>
<td>WNL 94 80 96 98 92 88 7.46 83 43 Noncaseating granuloma in lymph node</td>
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<tr>
<td>15 42 M NS 26 A</td>
<td></td>
<td></td>
<td>IgG3, IgG2</td>
<td>Abs, antinuclear antibody</td>
<td>WNL Mentally retarded 7.42 57 47 Fibrosis, bronchiolitis, granulomas</td>
</tr>
<tr>
<td>16 19 M NS &lt; 25 Bect</td>
<td></td>
<td></td>
<td>CVID</td>
<td>N/D</td>
<td>N/D Mentally retarded 7.39 64 44 Chronic pneumonitis</td>
</tr>
<tr>
<td>17 56 M S &lt; 25 COPD and Bect</td>
<td></td>
<td></td>
<td>IgG3, IgG4</td>
<td>PN</td>
<td>WNL 45 68 108 180 145 24 7.57 61 49 Chronic pneumonitis</td>
</tr>
<tr>
<td>18 46 M S 26 COPD and Bect</td>
<td></td>
<td></td>
<td>IgG4</td>
<td>N/D</td>
<td>WNL Seen in hospital only, lost to f/u 7.31 43 61 Chronic pneumonitis</td>
</tr>
<tr>
<td>19 50 M S &lt; 25 COPD and Bect</td>
<td></td>
<td></td>
<td>IgG4</td>
<td>TT</td>
<td>WNL 21 60 70 118 94 26 7.34 65 45 Chronic pneumonitis</td>
</tr>
<tr>
<td>20 70 M S &lt; 25 COPD and Bect</td>
<td></td>
<td></td>
<td>PCVID</td>
<td>N/D</td>
<td>WNL 29 73 115 207 150 19 7.34 67 53 Chronic pneumonitis</td>
</tr>
<tr>
<td>21 72 F S &lt; 25 COPD and Bect</td>
<td></td>
<td></td>
<td>IgG2, IgG4</td>
<td>N/D</td>
<td>WNL 34 81 73 125 90 47 7.43 53 50 Chronic pneumonitis</td>
</tr>
<tr>
<td>22 37 M NS &lt; 25 S/P exposure to respiratory irritants</td>
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<tr>
<td>23 49 F NS 26 S/P exposure to respiratory irritants</td>
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<td>24 53 M S &lt; 25 S/P exposure to respiratory irritants</td>
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<tr>
<td>25 59 F NS &lt; 25 COPD radiation pneumonitis</td>
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<tr>
<td>26 36 F S &lt; 25 Ritalin IV (with talc)</td>
<td></td>
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<tr>
<td>27 43 M S 26 Myotonia</td>
<td></td>
<td></td>
<td>IgG, IgM</td>
<td>PN</td>
<td>WNL 70 86 78 104 96 50 7.43 70 39 Patchy RUL, granulomas, birefringent crystals</td>
</tr>
<tr>
<td>28 41 M NS &lt; 25 SLE</td>
<td></td>
<td></td>
<td>PCVID, IgG1</td>
<td>N/D</td>
<td>N/D Died in hospital 7.31 48 60 BOOP</td>
</tr>
<tr>
<td>29 38 M S &lt; 25 Nonoccupational inhalation talc</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

*BMI = body mass index; M = male; F = female; S = smoker; NS = nonsmoker; FRC = functional residual capacity; TLC = total lung capacity; A = asthma; TT = tetanus toxicity; HIB = Haemophilus influenzae B; PN = pneumococcus; WNL = within normal limits; N/D = not determined; Neutr. Alv. = neutrophil alveolitis; Abs = absent; Bect = bronchiectasis; Ret. = reticular; S/P = status past; SLE = systemic lupus erythematosus; f/u = follow-up; LUL = left upper lobe; RUL = right upper lobe.
The main findings of this article are the following: (1) in Ig deficiency with repeated respiratory infections, ILD is frequent (29 of 148 subjects; 19.6%), much more prevalent than expected from general population surveys and polymorphic clinically, histologically, and immunologically; (2) the most common Ig abnormality is low IgGSC; (3) no particular histologic or radiologic aspect is consistently related to a particular immune deficiency, CVID, IgA, IgM, or IgGSC deficiency, the serum level of the deficient Ig(s), or the IgG pathway of response to vaccination; (4) regardless of the type of immune deficiency or histologic aspects, the administration of IV Ig in some cases of ILD leads to clinical, physiologic, radiologic and, when checked, histologic improvement as well.

ILD appears to be much more prevalent in patients with repeated respiratory infections and Ig deficiency than in the general population. The comparison of a selected series of patients with the general population is valid for two reasons. First, in a pulmonary and allergy practice, the separate prevalence of ILD and immune deficiency should be higher than the prevalence of these diseases in the general population. However, unless these two diseases are mechanistically interrelated, the proportion in which they are associated should be the same in the specialty practice and the general population. That the prevalence of ILD is higher in Ig-deficient patients than in the general population points to a relationship between these two diseases. Second, this series is not the product of a systematic encounter with patients harboring ILD and recurrent respira-

Figure 1. Changes in CT scan of the chest in subject 7 (NSIP) before (left and central upper panels) during (right upper panel), and after treatment with IV Ig at 6, 12, and 24 months (lower panels, in successive order). B = before IV Ig; A = after IV Ig.

Figure 2. Changes in CT scan of the chest in subject 5 (LIP). The images were obtained before beginning treatment with IV Ig (left), after 6 months (middle), and after 2 1/2 years (right). See Figure 1 legend for definition of abbreviations.
tory infections with Ig deficiency. Such an uninterrupt
ded bias during a 15-year period seems unlikely
both intuitively and factually. Indeed, the prevalence
of Ig deficiency in recurrent respiratory infections is
not higher when ILD is present (19.6%) than when
it is not (25 to 33%).

From a demographic standpoint, this report con-
firms that recurrent infections, the characteristic
manifestation of Ig deficiencies, may first appear in
adulthood. The associated ILD is usually
diagnosed several years later, after age 40 years (23
of 29 patients). Among patients with bronchiectasis
and chronic postinfectious pneumonitis, the severity
of B-cell deficiency may influence the apparent
onset: early childhood in X-linked hypogammaglobu-
linemia, late childhood or adolescence in CVID (15
to 19 years; subject 19), and in the fourth to sixth
decade in IgGSC deficiency (Table 1).

Because of respiratory infections, the chronic
symptomatology of ILD associated with Ig defi-
ciency may acquire a “bronchitic-asthmatic” charac-
ter, often with low FEV/FVC (7 of 24 subjects) or
increase in residual volume (RV) and/or functional
residual capacity with normal FEV/FVC (5 of 24
subjects).

The pathologic and radiologic spectrum of ILD
associated with Ig deficiency is remarkably wide.
This is reminiscent of collagen vascular diseases, in
which the same disease and the same immune
abnormalities can be associated with many different

![Figure 3](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21984/)

![Figure 4](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21984/)
types of ILD. With the exception of granulomatous pneumonia, which could not be confidently categorized in subject 15, all diffuse ILD and the chronic postinflammatory pneumonia previously related to CVID are now shown to coexist with IgG isotype deficiency. In addition, NSIP, apparently not reported before in CVID, may also be associated with IgGSC deficiency.

Two of the ILD cases mentioned in this article deserve special mention. Neutrophil alveolitis represents a nonspecific inflammatory reaction. It may be associated with a clear chest radiograph (e.g., systemic lupus erythematosus), radiologic ILD, or CVID with bronchiectasis in free interval. Pleading for interstitial involvement, despite a normal CT scan finding of the chest, was an occasionally positive Ga scan finding (subjects 2, 3, and 4) and mild restrictive abnormality on pulmonary function testing.

Bronchiectasis with chronic postinfectious pneumonia was described in antibody deficiency by means of high-resolution CT scan or chest radiograph and labeled interstitial disease, chronic lung disease, fibrosis, etc. As shown by CT scans (Fig. 4), the lesions are complex, involving the bronchi, alveoli, and the interstitium. In agreement with the literature, bronchiectasis with chronic interstitial pneumonia was usually diagnosed by CT scan (subjects 16 through 21) and only exceptionally by biopsy (subject 11). Radiologic and pathologic aspects (subject 11) suggest that BOOP may constitute an important part of chronic pneumonia.

In several patients (subjects 22 through 29), ILD seems to be related to a specific etiopathogenic entity, but the observed low Ig levels may still participate in the genesis of interstitial inflammation. In the patient with systemic lupus erythematosus, a low IgG1 is totally unexpected since IgG1, the isotype carrying most of the antinuclear activity, is usually increased rather than decreased. In the patient with myotonic dystrophy, a low IgG1 resulting from its increased catabolism in this disease was expected, but the bibasilar interstitial infiltrates

<table>
<thead>
<tr>
<th>Subject No.</th>
<th># 1</th>
<th># 2</th>
<th># 5</th>
<th># 6</th>
<th># 7</th>
<th># 9</th>
<th># 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months After Start of I.V. Ig</td>
<td>3</td>
<td>6</td>
<td>120</td>
<td>4</td>
<td>7</td>
<td>12</td>
<td>4</td>
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</table>

**Figure 5.** Pulmonary function changes in seven subjects administered IV Ig. The figure shows the percentage changes in lung volumes and DLCO, and the absolute changes in FEV/FVC percentage and PaO as related to the corresponding baseline values (Table 1). Triangles indicate FVC; circles indicate RV; closed symbols are measurements during the administration of IV Ig; open symbols are measurements after this treatment has ended. Note the isolated improvement in subject 3, who had only an isolated decrease in DLCO at baseline. In subject 21 with chronic pneumonitis, airway obstruction, and hyperinflation, IV Ig improved the restriction much more than the obstruction as shown by an increase in FVC and RV and decrease in FEV. The smallest physiologic improvement was seen in subject 9 with UIP, who continued to smoke. Abs = absolute.
were not. In the remaining cases, the presence of an associated IgG deficiency was never investigated. It is possible that the case of radiation pneumonitis, the two cases of granulomatous ILD associated with exposure to talc by inhalation or IV, and the case with restrictive abnormality that developed after acute exposure to respiratory irritants might have been related to Ig deficiency. Although there are insufficient data for a definitive conclusion, it is known that experimentally many environmental agents may elicit immunologic response and, apparently via transforming growth factor-β1, pulmonary fibrosis. Cigarette smoke may favor or produce immunodeficiency.

The effect of therapy with IV Ig in ILD confers practical relevance to this study. The study documents that IV Ig benefits chronic postinfectious pneumonitis when this disease is associated not only with CVID but also with a much more frequent immune deficiency, IgGSC deficiency. Second, this form of therapy also improves diffuse ILD associated with various IgGSC deficiencies. The theoretical implications of the study seem at least as important as its practical relevance. Currently, the manifestations of Ig deficiency are blamed on antibody deficiency. It is the deficiency in a class or, for IgG, subclasses, particularly IgG1 or IgG2, which shapes the clinical form of disease. This study suggests that the manifestations of ILD associated with Ig deficiency and their favorable influence by IV Ig reflect a dual process: an antibody deficiency explaining the recurrent infections, and a modulating effect of IgG on pulmonary inflammation.

Many pretreatment features of ILD associated with Ig deficiency would not be expected in a pure antibody deficiency syndrome. No specific ILD is invariably connected to a particular IgG deficiency (Table 1), and no aspect of immune deficiency, serum levels of isotype, or response to vaccination heralds the interstitial involvement. Indeed, the range of serum concentrations of IgGSC (in 85% of the subjects between 60% and 35% of predicted values) and the patterns of impaired response to vaccination were similar to those seen in subjects with recurrent respiratory infections but no ILD. Also, similar to noninfectious, autoimmune manifestations of CVID, in ILD associated with CVID, no concentration of IgG is consistently related to interstitial involvement. The effect of IV Ig in ILD is particularly suggestive of an anti-inflammatory action. First, the improvement relates to inflammatory lesions that are either pathogenically unrelated to infections or, in the case of bronchiectasis with chronic postinfectious pneumonitis, impossible

**Figure 6.** LIP (subject 8) at the time of diagnosis (left panels) and at autopsy (right panel) [hematoxylin-eosin]. Left upper panel: high-power microscopy in the area of infiltrate shows lymphocytes and plasma cells in the alveolar septa. Left lower panel: lower-power microscopy of a bronchiole shows adjacent lymphoid hyperplasia with germinal center. Right panel: high-power microscopy showing organizing diffuse alveolar damage with dilated alveolar ducts and alveolar septal thickening without significant inflammation.
to improve by simply preventing the infections. Second, the effect exceeds the half-life of IgG, persisting for many months. Third, the type of diffuse ILD improved by IgG treatment often responds to steroids, anti-inflammatory agents per excellence. The immunomodulatory, anti-inflammatory action of IV Ig in ILD is an extension of the therapeutic effect of IV Ig in various inflammatory diseases with immune mechanisms. Fourth, Fc-gamma receptors have been demonstrated on many cells participating in inflammation and IgG modulates various cytokines, including transforming growth factor-β1, a potent regulator of collagen tissue synthesis in the lung. It is not clear how Ig(s) modulate interstitial inflammation. The iso-type deficiency, as in the case of Ig deficiency without ILD, may be a marker of another immune abnormality, still unidentified, that modulates inflammation. If this factor is actually a circulating Ig, its concentration may be too low to lead to a quantitative deficiency in the corresponding IgGSC.

This report is observational in nature and analyzes a relatively small number of subjects. However, because it contains the largest number of ILD associated with low IgG(s) mentioned in the literature and collected serially from the largest pool of adults with IgGSC deficiency reported in this country, it is for now a reasonable surrogate for an epidemiologic survey of Ig deficiencies associated with ILD. It is with this caution that we advance the hypothesis that at times, there is a link between ILD and IgGSC deficiency.

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