

# Interstitial Lung Disease in Patients With Ataxia-Telangiectasia

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**Summary.** Ataxia-telangiectasia (A-T) is an autosomal-recessive multiorgan disease characterized by progressive neurologic deterioration in which the most common causes of death are diseases of the respiratory system and cancers. The aim of this retrospective study was to delineate the clinical, radiographic, and pathologic manifestations of the chronic progressive interstitial lung disease seen in patients with A-T. The medical records of 97 patients with A-T and chronic lung disease were reviewed. Interstitial lung disease (ILD) was specifically diagnosed in 25 of 97 patients. None of these patients had evidence of an infectious process preceding the onset of their lung disease, and none had lasting clinical improvement after treatment with antibiotics. Although many medications were used to treat their ILD, only treatment with systemic corticosteroids early in the course of their illness was associated with clinical and radiographic improvement. Nineteen of these 25 patients with ILD died within 24 months of the onset of their ILD, and of 7 patients treated with corticosteroids, 5 are still alive. Recognition of interstitial lung disease in patients with A-T and its early treatment could reduce or eliminate pulmonary disease as a leading cause of death for these patients. *Pediatr Pulmonol.* 2005; 39:537–543. © 2005 Wiley-Liss, Inc.

**Key words:** ataxia-telangiectasia; interstitial lung disease; primary immunodeficiency; pulmonary fibrosis; corticosteroids.

## INTRODUCTION

Ataxia-telangiectasia (A-T) is an autosomal-recessive multisystem disease characterized by progressive cerebellar ataxia, oculocutaneous telangiectasia, variable defects in both humoral and cell-mediated immunity, endocrine abnormalities, progeric changes, increased cancer incidence, and a predisposition to sinopulmonary infections.<sup>1</sup> Patients with ataxia-telangiectasia experience high mortality, with an annual mortality rate for white patients of 19.5/1,000 for ages 15–19, rising to 60.1/1,000 for ages 20–24, and for older ages, 70.7/1,000. The mortality rate for African-American patients was reported to be greater than 3-fold higher.<sup>2</sup> The leading causes of death were cancer and diseases of the respiratory system, with the former noted as the underlying cause of death on 33 of 127 death certificates (26%), and the latter on 29 (23%). These are minimal estimates, since A-T itself was listed as the underlying cause of death on 46 (36%).<sup>3</sup>

It was recognized at the time that A-T was first described, and confirmed repeatedly, that some patients had frequent acute sinopulmonary infections. We now report the occurrence of a chronic interstitial inflammatory lung disease, and suggest that a specific diagnostic and therapeutic approach may help reduce morbidity and prevent premature deaths of A-T patients.

## METHODS

We reviewed the medical records of 437 patients with A-T. The records were collected through a comprehensive

search for all cases of A-T in the United States; details of case findings were published previously.<sup>2</sup> In brief, records were compiled after an extensive letter-writing effort to pediatric neurologists, pediatric immunologists, medical geneticists, cerebral palsy centers, and the Immunodeficiency Cancer Registry in the United States, in which we asked for referral of all patients with A-T. Medical records were collected from all hospitals, clinics, physicians, and other health professionals who had cared for these patients. A-T was diagnosed if the medical records stated

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that the patient had progressive cerebellar ataxia and oculocutaneous telangiectasia, and if the serum alpha-fetoprotein, if available, confirmed the diagnosis. Some patients in this study were included in previous papers and case reports. The New York Medical College Committee on the Protection of Human Subjects approved this study.

All records, from 1990 to the present, that mentioned a clinical evaluation of the patient's respiratory system were evaluated. The diagnosis of chronic interstitial lung disease (ILD) was made if the patient had histologically proven pulmonary fibrosis or signs and symptoms and chest imaging suggestive of a diffuse parenchymal disease, after excluding all patients with a known cause of pulmonary fibrosis.

## RESULTS

Of the 437 charts reviewed, a total of 97 persons had either chronic respiratory symptoms or pulmonary disease listed as cause of death. ILD was definitively diagnosed in 25 of the 97 patients. Sixteen of 25 were female, and the mean age of onset of ILD was 17.5 years, with a range from 9–28 years.

The signs and symptoms that preceded radiographic evidence of ILD were a nonproductive cough in 21/25, dyspnea in 12/25, and fever in 11/25. All 10 patients who presented with a cough of greater than 1 month's duration, dyspnea, fever, and abnormal auscultatory changes had interstitial changes on a chest radiograph. As their lung disease progressed, all patients had abnormal chest radiographs, with changes that originated predominately in the lower lobes and progressed to chronic bibasilar changes (Table 1). Of the 11 patients who had pneumothoraces, 6 developed pneumothoraces that were not correctable by either medical or surgical intervention. This inability to reexpand the lung was always associated with death within 6 months after discovery of the pneumothorax.

Five patients had computerized tomographic (CT) examinations of their thoraces, none with contrast. No hilar or mediastinal adenopathy, or pulmonary nodules, were demonstrated. All had diffuse bibasilar interstitial

and interlobular reticular opacities with interlobular septal thickening. Four had pleural thickening, but none of the scans had either honeycombing or emphysematous changes. Three had bronchiectasis in the lower lobes, and one had a pneumothorax.

Fourteen patients had swallowing evaluations for dysphagia. Five of the 14 had abnormal fluoroscopic examinations, but laryngeal penetration and aspiration into the tracheobronchial tree were observed in only one patient.

Six of 25 patients in our study had pulmonary function testing. All had severe restrictive defects (total lung capacity =  $35 \pm 8.4\%$  of predicted normal) with evidence of gas trapping (mean RV =  $180 \pm 18.3\%$  of the predicted normal of either Crapo et al.<sup>4</sup> or Polgar and Promadhat.<sup>5</sup> No characteristic obstructive defect was found, and none of the patients had  $>10\%$  improvement in their FEV<sub>1</sub> after administration of an aerosolized bronchodilator. No patient was able to adequately perform a test for diffusing capacity of carbon monoxide.

Sixteen patients were hospitalized for evaluation and treatment of their ILD when they had no improvement after a course of oral antibiotics. During hospitalizations, patients were treated with intravenous antibiotics, aerosolized bronchodilators, aerosolized mucolytics, and oxygen. There were temporary improvements in their symptoms, but their course after the appearance of interstitial lung disease was, for the most part, chronic progressive clinical deterioration with decreasing time between hospitalizations, inability to maintain or gain weight, increasing need for supplemental oxygen, and continued radiographic worsening.

Nineteen patients had microbiologic examination of their respiratory secretions. Sixteen had evaluation of their sputum, and 3 had bronchoalveolar lavage (BAL) analysis. The 13 cultures that grew bacterial pathogens are shown in Table 2. Viral cultures and serology were negative in the 6 patients tested. Stains and culture for *Pneumocystis carinii* were negative in 4 patients, and cultures for *Legionella pneumophila* were also negative in 2 patients.

In each of the 3 patients who had bronchoalveolar lavage analysis, over 70% lymphocytes, 20% macro-

**TABLE 1—Radiographic Findings of 25 Persons With Ataxia-Telangiectasia and Interstitial Lung Disease**

Radiographic finding	Number of persons
Bilateral interstitial changes	25
Pneumothorax	11
Pleural abnormalities	11
Bronchiectasis	8
Pleural effusions	3
Lung abscess	3
Hilar adenopathy	1

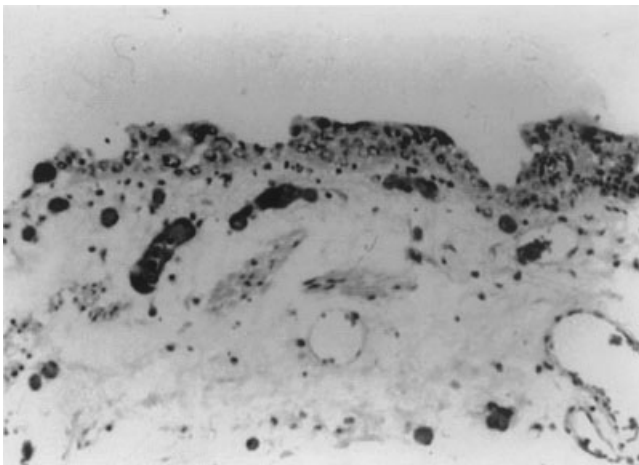
**TABLE 2—Microbiologic Evaluation of Respiratory Secretions of 19 ILD Patients**

Microorganism isolated	Number of patients
<i>Pseudomonas aeruginosa</i>	8
<i>Staphylococcus aureus</i>	7
<i>Klebsiella pneumoniae</i>	4
<i>Hemophilus influenzae</i>	2
No pathogens isolated	4
More than one pathogen isolated	5

phages, fewer than 5% neutrophils, and no eosinophils or neoplastic cells were observed.

Nineteen of the 25 patients had quantitative measurement of their serum immunoglobulins. The normative values for immunoglobulin were compared with age-matched controls according to the protocols established by Steihm and Fudenberg.<sup>6</sup> Immunoglobulin levels greater than 2 standard deviations from age-matched controls were considered abnormal. Twelve of the 19 had normal age-related IgG levels and IgG subclass levels. Six of these 12 patients had normal IgM and IgA levels, and the other 6 patients had normal IgM but decreased (<5 mg/dl) or absent levels of IgA. Six patients had decreased IgG levels (all had abnormal levels of IgG2 and/or IgG4) and decreased or absent levels of IgA. One patient had an abnormal IgG level with a normal IgA level. Cellular immune status, as determined by documentation of T-lymphocyte response to mitogens and delayed-type hypersensitivity skin testing to tetanus, was performed in 7 patients, and 3 of them had abnormal responses.

Thirteen patients had either a lung biopsy or post-mortem histologic evaluation of their lung. Figure 1 is a representative sample of the histologic changes seen in all specimens. All specimens had diffuse interstitial disease with large areas of fibrosis. Ten specimens had acute and chronic inflammatory cells scattered throughout the parenchyma. The inflammatory cells observed were either lymphocytic or lymphohistiocytic and rarely neutrophils or plasma cells. Peculiar bizarre atypical epithelial and interstitial cells with large hyperchromatic and pleomorphic nuclei were very prominent in some sections and rare in others, but present in all specimens. These unusual



**Fig. 1.** Atypical regenerative bronchial epithelium with markedly enlarged and hyperchromatic nuclei. Patient had acute lung injury with focal pneumonia superimposed on pattern of diffuse chronic interstitial lung disease with fibrosis. Bizarre gigantic cells such as this were frequently seen in epithelial and interstitial cells and were described in other organs in A-T (hematoxylin and eosin, original magnification  $\times 400$ ).

cells were also seen in other organs of 5 patients. Fibrosis was always present, and foci of honeycombing were found in two specimens. The pulmonary vessels were abnormal in regions of pulmonary fibrosis but were otherwise intact. Lymphatics were not affected in any case. No eosinophils, lipid-laden macrophages, viral inclusions, fungal hyphae, amyloid deposits, or areas of fibroblastic foci or cysts were identified in any sample. Five of 13 necropsies had microbiologic evaluation of their lung tissue, and none had positive cultures or positive staining for *Pneumocystis carinii*, *Legionella pneumophila*, fungi, parasites, or viruses.

Fourteen patients were never treated with corticosteroids; all died with a mean time of 17 months from radiographic appearance of interstitial changes until their death. Four other patients, already compromised by either bronchiectasis and/or pneumothoraces, were treated with corticosteroids during their final hospitalization. Two of these patients had a transient improvement in their arterial oxygenation and in their level of consciousness, but in neither patient was there any radiographic improvement. All four of these patients died during that final hospitalization. Figure 2 shows a computerized axial tomogram of the chest of a patient with A-T that was performed during his last hospitalization. This radiographic study shows the chronic bibasilar interstitial changes, pleural abnormalities, and acute changes that were observed on pathological examination. There were no areas of ground-glass attenuation, and there was more disease in the lower lobes than in the apices.

After a review of biopsy and autopsy material showed that some patients had chronic pulmonary inflammation, we began to recommend to physicians treating A-T patients with ILD that they consider systemic corticosteroid therapy. Not all of the physicians took our recommendations regarding the administration of corticosteroids over an extended period of time. As seen in Table 3, whether patients were placed on corticosteroids or not, they had comparable radiographic findings, were similarly immunocompromised, and for those treated, had both acute as well as chronic inflammation seen on biopsy.

All 7 patients treated with corticosteroids within 6 months after onset of their chronic pulmonary symptoms had clinical and radiographic improvement. Five of the 7 are still alive, with a mean survival of 64 months (range, 50–156 months). Figures 3 and 4 show radiographs of a patient with ILD before and 3 months after the initiation of oral corticosteroids. The radiographic improvement observed was mirrored by an improvement in the patient's clinical symptoms and overall well-being. Three patients appear to require daily oral corticosteroids to maintain their remission. For 2 other patients, it was possible to taper and then discontinue maintenance steroids without any recurrence of pulmonary symptoms. These 2 patients have been symptom-free for 24 and 28 months,

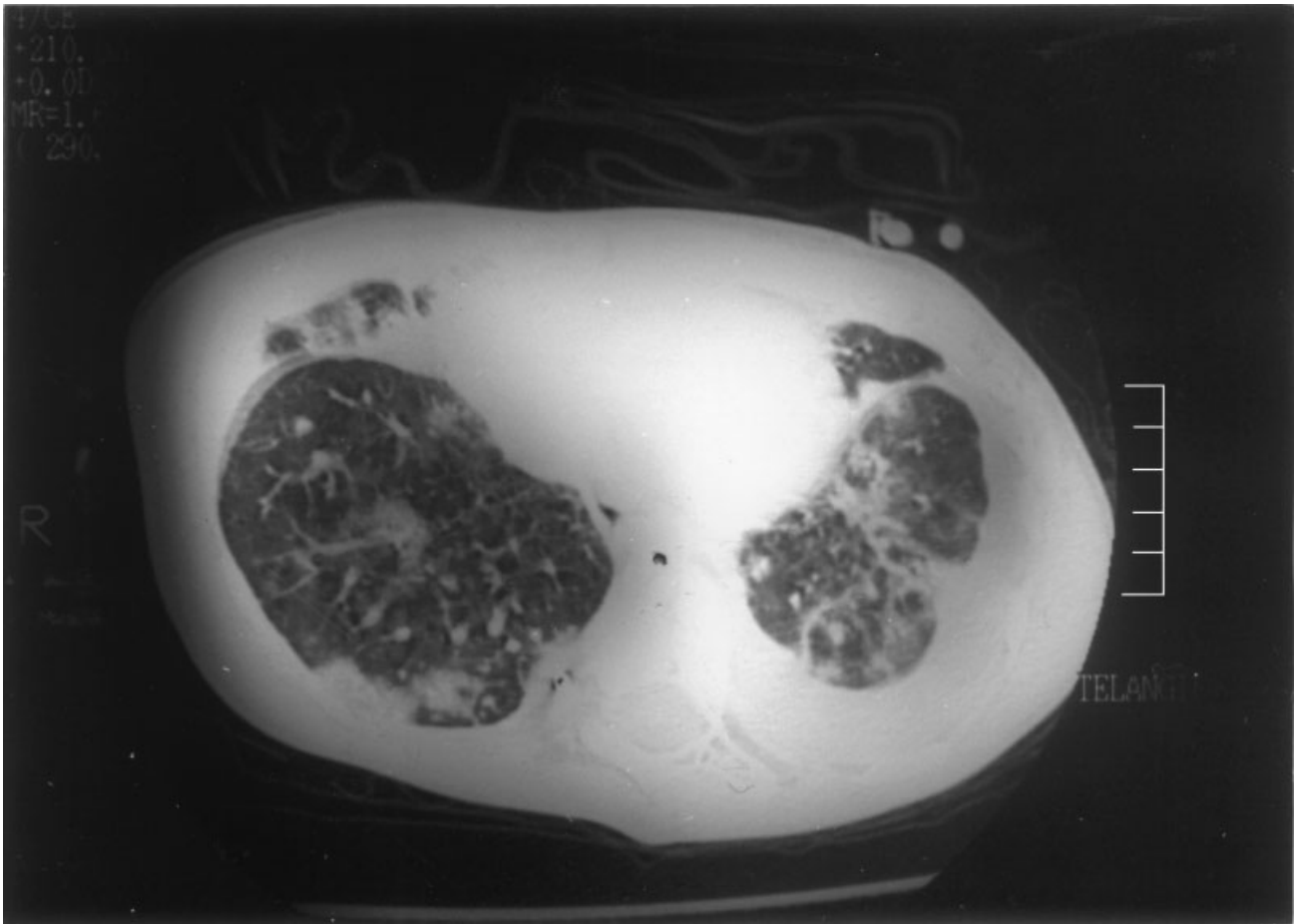


Fig. 2. Computerized axial tomogram of A-T patient, showing diffuse bibasilar chronic interstitial marking as well as acute lobar infiltrates and pleural thickening at both bases. There is pleural effusion on left with bilateral interlobular septal thickening, but no honeycombing or emphysematous changes.

TABLE 3—Demographic, Imaging, Immunological, and Pathological Features of Patients With ILD

	Patients who received corticosteroids early after diagnosis of ILD (n = 7)	Patients who did not receive corticosteroids (n = 18)
Number of females	4	10
Environmental exposure (including tobacco)	0	0
Age at diagnosis of ILD (years)	16.6	18.1
Number of patients with serum IgG deficiencies/total number of patients tested	5/7	7/12
Number of patients with humoral immune abnormalities/total number of patients tested	1/2	3/5
Number of patients who received IVIG	1	3
Radiographic evidence of interstitial lung disease	7	18
Radiographic evidence of pleural abnormalities	2	6
Diagnosis of ILD made by histological analysis	2	11
Multinucleate giant cells seen on pathology	2	11
Acute or chronic inflammatory cells seen on biopsy	2	8
Isolation of bacteria in sputum prior to diagnosis of ILD	2	3



Fig. 3. Standard P/A chest radiographs of A-T patient, showing bilateral bibasilar interstitial infiltrates in left lower lobe, right middle lobe, and right lower lobe.

respectively, after their steroids were discontinued. One patient experienced a significant remission (she survived repair of her kyphoscoliosis after this remission was induced), but went into pulmonary decline and died as her steroid dose was tapered 23 months after it was started.

## DISCUSSION

The finding of an interstitial inflammatory lung disease in 25/97 A-T patients with chronic lung disease is a minimum estimate of its prevalence, since the necessary data were not available for many other cases. This case series, and previous individual case reports,<sup>7-9</sup> establish that ILD is an important cause of morbidity and mortality for patients with A-T.<sup>10</sup> Sedgwick and Boder summarized the findings of 62 autopsies of A-T patients reported through 1991, among whom 29 (47%) had died of respiratory causes, with 8 reported to have had pulmonary fibrosis.<sup>10</sup>

All 25 patients had cough, dyspnea, and/or tachypnea and radiographic evidence of bilateral, diffuse parenchymal opacities suggestive of interstitial lung disease. All available histologic specimens showed pulmonary fibrosis and diffuse lung involvement. The inflammatory cells seen in A-T lungs were primarily lymphocytic (not neutrophils); eosinophils and neoplastic cells were never



Fig. 4. Chest radiograph of same patient 3 months after treatment with oral corticosteroids (1 mg/kg/day), showing resolution of interstitial processes in left lower and right lower lobes.

seen. There were some clinical and radiographic similarities between A-T patients and those with lymphoid interstitial pneumonitis (LIP), but neither hypergammaglobulinemia nor hepatosplenomegaly was reported in A-T patients. The histology also differed from that in LIP since, in A-T patients with interstitial lung disease, unlike LIP, plasma cells were rarely seen, and fibrosis was present in all samples. The histologic pattern of A-T interstitial lung disease does not fit a specific American Thoracic Society/European Respiratory Society (ATS/ERS) category among idiopathic interstitial pneumonias, and may represent a unique class of ILD. The interstitial lung disease of A-T is distinctive in its histology, bronchoalveolar lavage (BAL) findings, and response to corticosteroids; and the chronic inflammatory interstitial disease described here may be unique to A-T.<sup>11</sup> The large, bizarre atypical cells seen in the interstitium and epithelium of the lungs of A-T patients are unlikely to be related to the chronic lung disease, since they were observed frequently in other organs of A-T patients without lung disease.<sup>10</sup>

No specimen had evidence of an identifiable infectious agent or vascular changes that could have caused the chronic lung disease. The acute respiratory infections in persons with ataxia-telangiectasia and interstitial lung disease were almost all due to either *Staphylococcus aureus* or Gram-negative bacilli. Treatment with only antibiotics and bronchodilators did not prevent the overall,

invariable, downhill course that was fatal in all patients. Deaths usually occurred within 2 years after the appearance of chronic radiographic changes. After the initial presentation there were acute exacerbations, with cough, hypoxemia, and fever superimposed on the chronic symptoms. In our series, the inability to reinflate the lung after the development of a pneumothorax was always associated with death.

Only treatment with corticosteroids was associated with both sustained clinical and radiographic improvement. All 7 patients treated with oral corticosteroids within 6 months of the first appearance of interstitial changes had sustained clinical improvement that included weaning from supplemental oxygen, resolution of dyspnea and cough, and weight gain. Two of the 7 patients had radiographic improvement as well. The doses of corticosteroids that they received were 1–2 mg/kg for a minimum of 4 weeks, with a taper over a 2–3-month period if their dyspnea and cough resolved. A previously reported case of a person with A-T and interstitial lung disease showed similar improvement when prednisone was given at a dose of 1 mg/kg, but the patient deteriorated when the dose of corticosteroids was reduced.<sup>8</sup> A patient with A-T and lymphoid interstitial pneumonitis also responded dramatically to oral corticosteroids over a 3-month period.<sup>12</sup> The initial steroid dose we recommend and the rate of tapering are based on our uncontrolled clinical observations that lower doses and more rapid tapering led to poorer outcomes; there are no clinical trials to guide dosing decisions.

One patient developed hypertension and a Cushingoid facies, and another developed hematemesis secondary to gastritis while receiving corticosteroids. Overall, systemic corticosteroids were well-tolerated, and their beneficial effects were easily quantifiable both clinically and radiographically. Although diabetes mellitus, typically mild, is often seen in A-T patients older than 20 years, this complication of steroid therapy is not life-threatening and should not be allowed to outweigh the 100% mortality of ILD. At this point, we would not recommend the use of inhaled corticosteroids in A-T patients with interstitial lung disease. Since patients with A-T are at increased risk for osteoporosis, if oral corticosteroids are given, then patients should also receive calcium supplements, vitamin D supplementation, and perhaps even diphosphonates to prevent bone loss.

In patients with advanced disease, treatment with corticosteroids led to transient improvement in clinical symptoms, but the improvement was not sustainable and not associated with radiographic improvement. No patient whose treatment with systemic corticosteroids began more than 1 year after the onset of interstitial changes is alive. A high degree of suspicion is warranted so that those patients with interstitial lung disease can be treated early and aggressively.

The diagnosis of ILD in A-T patients must therefore be made as rapidly as possible. In considering the diagnosis, the physical examination is often not helpful. In our study, only 3 patients had crackles, and 3 had end-expiratory wheezes. A chest radiograph must be obtained immediately for any A-T patient with pulmonary symptoms that do not remit fully after vigorous antibiotic and bronchodilator therapy. The characteristic infiltrates may not be detected unless the X-ray exposure is appropriate to the build of the patient; A-T patients are often slight. The worst-case scenario is that a physician may not obtain a radiograph because of a concern that the patient may suffer tissue damage from the irradiation. While A-T patients treated for lymphoid cancer with radiation therapy have suffered severe necrosis of their normal tissues, the doses from therapy (30–60 Grays) are many orders of magnitude greater than those from radiography: 0.02 milliGrays for a standard chest radiograph to 30 milliGrays for a computerized axial tomogram of the chest.<sup>13</sup> There is no evidence that any A-T patient has ever had tissue destruction or cancer induction from repeated radiographs of the chest.

The etiology and pathogenesis of ILD and pulmonary fibrosis in A-T patients are unknown, as it is in most cases in non-A-T patients.<sup>14,15</sup> Many types of infections, including viral pneumonias<sup>16,17</sup> and *Mycoplasma pneumoniae*,<sup>18,19</sup> can mimic or initiate pulmonary fibrosis. Respiratory infections due to Epstein-Barr virus (EBV) can result in chronic interstitial infiltrates and lymphoid interstitial pneumonitis; and the presence of EBV in patients with idiopathic pulmonary fibrosis was hypothesized to amplify the progression of their respiratory decline.<sup>20,21</sup> In this series, infectious agents were isolated in respiratory secretions only after chronic radiographic changes had been noted. A prospective study that included periodic assessment of sputum for pathogens and serum collection for serial serological evaluation might clarify the possible role of viruses or bacteria in causing or accelerating the ILD seen in patients with A-T.

Although A-T patients frequently have oropharyngeal dysphagia<sup>22</sup> (in our study, 7/25 had either a history suggestive of aspiration or an abnormal swallowing evaluation), there was no histologic evidence in biopsies or autopsies in this series or in previous reports<sup>23,24</sup> to support the hypothesis that chronic aspiration causes the progressive lung disease in A-T patients. Thus no study has shown a causal relationship between the swallowing abnormalities often found in A-T patients and their interstitial lung disease.

Oxelius et al.<sup>25</sup> and McFarland et al.<sup>26</sup> reported that immunologic abnormalities, especially deficiencies in IgG2 and IgG4, are associated with a high incidence of recurrent bacterial and viral sinopulmonary infections in patients with A-T. On the other hand, Roifman and Gelfand found no consistent correlation between immune

status and respiratory status<sup>27</sup> in A-T patients. In our review of patients with A-T and ILD, patients had IgA, IgE, and IgG subclass deficiencies and increased levels of IgM, but there was no correlation between the development of interstitial lung disease and abnormalities in any of these immunoglobulin levels. Although Popa et al.<sup>29</sup> reported clinical and radiographic improvement in 8 of 20 patients with immunoglobulin subclass (IGSC) deficiency and ILD who received intravenous immunoglobulin therapy (IVIG), in our series, none of the patients who received IVIG experienced similar improvements.<sup>25</sup>

Recognition of ILD in A-T patients and its early treatment could reduce or eliminate pulmonary disease as a leading cause of death for these patients. Recent published data demonstrated that the lymphoid cancers, which predominate in A-T patients, can be effectively treated with full-dose chemotherapy.<sup>28</sup> Thus, while there is as yet no way to treat the progressive neurological disorder of A-T, a great deal can be done to reduce the excess mortality of those affected by this syndrome.

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