

Brief communications

Usual interstitial pneumonitis in a patient with common variable immunodeficiency

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Common variable immunodeficiency (CVID) is a disease characterized by recurrent sinopulmonary infections, hypogammaglobulinemia, and diminished specific antibody response to immunization. Patients also have an increased incidence of autoimmune disease and lymphoproliferative disorders, as well as a host of other complicating conditions. The clinical manifestations and potential molecular mechanisms causing CVID have been recently reviewed.¹⁻²

The pulmonary manifestations that accompany CVID are variable. Pulmonary function tests (PFTs) may reveal restrictive disease or obstructive disease or may be normal.³ The most common radiologic abnormality when patients are not acutely infected is bronchiectasis caused by recurrent bronchitic infections.⁴ Bronchiolitis obliterans with organizing pneumonia has been described in one patient with CVID.⁵ Sarcoid-like granulomas have been found in pulmonary biopsy specimens and in tissue samples of other organs from patients with CVID.⁶⁻¹⁰ Also, lymphocytic interstitial pneumonitis (LIP) is a complication of CVID.^{4, 11-14} Cases of LIP in association with autoimmune hypergammaglobulinemic states, which progressed to end-stage fibrosis, have been described.^{11, 12} However, CVID has not previously been described in association with usual interstitial pneumonitis (UIP). In this report we present a patient with UIP in association with CVID.

CASE REPORT

A 35-year-old nonsmoking woman was first seen with a history of recurrent sinus infections between 1984 and 1989. In 1989 she had thrombocytopenia with a platelet count of 7000 platelets/mm³. The remainder of the results of her complete blood count were normal. Extensive evaluation including tests for antinuclear antibodies, rheumatoid factor, HIV, and antiplatelet antibodies; bone marrow aspirate and biopsy; hepatitis B panel; Monospot (Orion Diagnostics); and blood cultures failed to identify a cause for her thrombocytopenia. Her symptoms and idiopathic thrombocytopenia resolved within 2 weeks with steroid therapy.

She was seen again in May 1990 with a clinical pneumonia, and chest x-ray film demonstrated bilateral, basilar, reticulonodular infiltrates. Spirometry demonstrated a restrictive pattern. Transbronchial biopsy demonstrated chronic intersti-

Abbreviations used

CVID:	Common variable immunodeficiency
EBV:	Epstein-Barr virus
IPF:	Idiopathic pulmonary fibrosis
LIP:	Lymphocytic interstitial pneumonitis
PBMCs:	Peripheral blood mononuclear cells
PCR:	Polymerase chain reaction
PFT:	Pulmonary function test
UIP:	Usual interstitial pneumonitis

tial inflammation without granulomas. Results of cultures for fungi and acid-fast bacilli were negative. She was provisionally diagnosed with sarcoidosis, despite the lack of granulomas, and her spirometry results normalized with prednisone therapy. Over the ensuing 18 months, she had recurrent episodes of bronchitis and sinusitis requiring treatment with antibiotics and continued to carry the diagnosis of sarcoidosis. She experienced worsening exertional dyspnea and was re-evaluated. Results of repeat tests for antinuclear antibodies and rheumatoid factor and erythrocyte sedimentation rate were normal. Repeat chest x-ray film demonstrated worsening bilateral, reticulonodular, lower lobe infiltrates without hilar adenopathy. PFTs with lung volumes demonstrated a restrictive pattern, diminished lung volumes, and decreased diffusing capacity of carbon monoxide (Table I). With exercise desaturation from 93% to 85% occurred. High-resolution chest computed tomography was performed and demonstrated diffuse basilar interstitial densities with focal nodularity and mediastinal adenopathy (Fig. 1). Repeat transbronchial biopsy and bronchoalveolar lavage failed to reveal a cause. Repeat cultures for acid-fast bacilli and fungi also failed to identify a cause. Open lung biopsy was performed and demonstrated diffuse interstitial fibrosis with a sparse interstitial mononuclear cell infiltrate with areas of focal nodular inflammation believed to be consistent with UIP (Fig. 2). No granulomas were observed. A simultaneously obtained lymph node biopsy specimen demonstrated reactive hyperplasia without granulomas. The patient was noted to have hepatosplenomegaly at the time of her open lung biopsy, and a low gamma fraction was seen on serum protein electrophoresis. Quantitative immunoglobulins were: IgA, less than 6.7 mg/dl (70-312); IgG, 200 mg/dl (723-1685); and IgM, 29.4 mg/dl (63-277). The hypogammaglobulinemia was not further evaluated, and the patient was started on prednisone therapy for idiopathic pulmonary fibrosis (IPF) with improvement in her PFT results and diminished exertional dyspnea. After 4 months of therapy she discontinued the high-dose steroids and experienced worsening exertional dyspnea coupled with deterioration in her PFT results. In September 1993 she began combination therapy with daily low-dose prednisone and oral cyclophosphamide. Her exertional dyspnea and PFT results improved with

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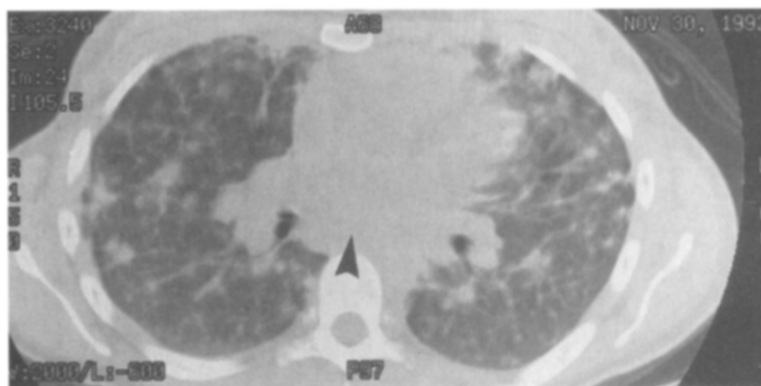


FIG. 1. High-resolution chest computed tomography from November 1992 demonstrating diffuse increased interstitial density with focal nodular interstitial densities and mediastinal adenopathy (arrowhead).

TABLE I. Serial PFT results, lung volumes, and DLCO for this patient

Date (mo/yr)	FVC (L)	FEV ₁ (L)	TLC (L)	RV (L)	TGV (L)	DLCO/Va	DLCO/Va* (% pred)	Therapy
11/92	2.39	2.15	3.36	.85	1.81	3.56	59	
01/93	1.75	1.44	2.67	.77	1.56	2.15	36	Pred (60 mg/day)
04/93	2.33	2.04	3.61	.93	1.94	2.38	40	Pred discontinued
09/93	1.51	1.29	2.58	.71	1.38	4.49	75	Pred, 15 mg/day; Cyclophos, 100 mg/day
02/94	2.34	1.98	3.06	.84	1.95	3.83	64	
06/94	2.41	2.18	3.81	1.42	2.21	3.71	62	Pred and Cyclophos discontinued 11/94
09/95	1.82	1.62	2.89	1.13	1.72	6.19	110	

FVC, Forced vital capacity; TLC, total lung capacity; RV, residual volume; TGV, thoracic gas volume; DLCO/Va, diffusing capacity of carbon monoxide adjusted for alveolar volume; Pred, prednisone; Cyclophos, cyclophosphamide.

*DLCO/Va was calculated by the method of Crapo and Morris.²⁵

this regimen. However, throughout the course of her illness, she continued to have frequent episodes of sinusitis and bronchitis.

In November 1994, panhypogammaglobulinemia was again noted. Her cytotoxic therapy was discontinued and she was referred to the Department of Immunology for evaluation. At the time of presentation, her physical examination was notable for: purulent nasal discharge and postnasal drip; dry, bibasilar inspiratory rales; and a palpable spleen tip. Repeat quantitative immunoglobulins were: IgA, less than 7 mg/dl (68-378); IgG, 159 mg/dl (694-1618); and IgM, 22 mg/dl (60-263). A low level IgA was 4.51 mg/dl. Specific antibody responses to tetanus and conjugated *Haemophilus influenzae* immunization were normal. However, there was no response to pneumococcal immunization. An anergy panel demonstrated a normal response to *Candida albicans* and tetanus. Results of polymerase chain reaction (PCR) for HIV and p24 antigen were both negative. In vitro lymphocyte transformation studies demonstrated normal responses to T-cell mitogens but no response to the B-cell mitogen *Staphylococcus aureus* Cowan. Flow cytometry demonstrated normal phenotypic distribution of peripheral blood lymphocytes with mature peripheral blood B cells. In vitro immunoglobulin production was an order of magnitude below control values at baseline and with mitogen stimulation. Results of kinetic studies of the patient's IgG half-life were normal. Repeat high-resolution chest computed tomography demonstrated worsening linear interstitial densities, worsening interstitial nodularity, anterior honeycomb lung, and areas of bronchiectasis (Fig. 3). Additional pertinent studies included a negative PCR result for hepatitis C and positive PCR result

in peripheral blood mononuclear cells (PBMCs) and plasma for Epstein-Barr virus (EBV). Liver function tests were mildly elevated in August 1995, and a liver biopsy specimen demonstrated noncaseating granulomas. She had diffuse retroperitoneal and paraaortic lymphadenopathy with anemia and was therefore further evaluated for a possible lymphoma. Results of subsequent repeat bone marrow aspirate and bone marrow biopsy were normal. An excisional lymph node biopsy specimen demonstrated reactive hyperplasia without granulomas. Results of fungal cultures of the liver biopsy, bone marrow, and lymph node specimens were negative. Flow cytometry performed on the liver biopsy specimen, bone marrow aspirate, and lymph node biopsy specimen demonstrated normal phenotypic distribution of the lymphocyte population.

The patient was believed to have CVID with UIP and began receiving replacement intravenous immunoglobulin with 400 mg/kg/28 days. She had an excellent initial response to therapy but had recurrent bronchitic infections 18 to 21 days after her last infusion. The intravenous immunoglobulin dose was titrated up to 1 gm/kg/28 days in conjunction with antibiotics to control her infections. The patient received no immunosuppressive therapy during this time, and her PFT results and functional status deteriorated. She again improved with resumption of prednisone therapy but was intolerant of the side effects, so she self-discontinued her steroid therapy. She refused resumption of treatment with cyclophosphamide, but agreed to be treated with intravenous immunoglobulin, 2 gm/kg/28 days, and stabilization of her PFT results was achieved.

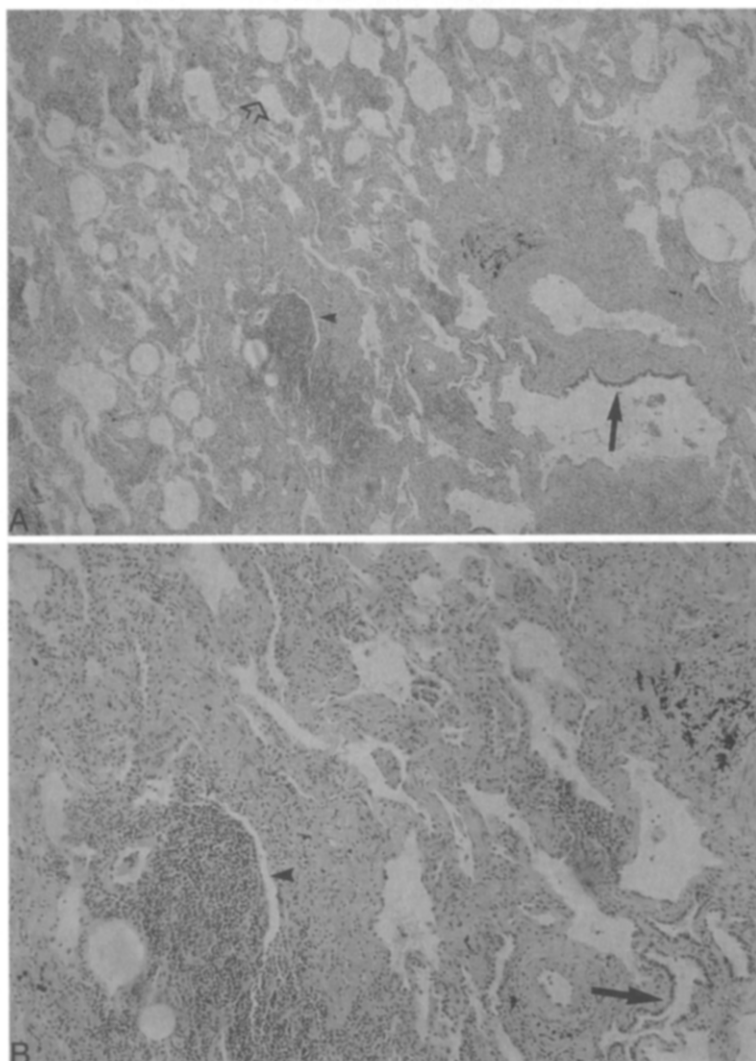


FIG. 2. **A**, Low-power view (hematoxylin and eosin $\times 40$) of open lung biopsy specimen from December 1992 demonstrating diffuse interstitial fibrosis with scattered mononuclear cell infiltrate, honeycombing (*open arrow*), lymphoid nodule (*solid arrowhead*), and type II pneumocyte hyperplasia (*arrow*). Staining artifact is seen in the central right section. **B**, High-power view (hematoxylin and eosin $\times 200$) of same specimen demonstrating same findings as in **A** (indicators unchanged from **A**). Staining artifact is seen in the upper right section.

DISCUSSION

UIP is a histopathologic term originally coined to describe an idiopathic interstitial pneumonitis characterized by septal and alveolar inflammation, variable septal fibrosis, type II pneumocyte hyperplasia, and "honeycombing." In the original description, it was believed that UIP was clinically and pathologically distinct from other interstitial lung diseases.¹⁵ Since the original description, the histopathologic pattern characteristic of UIP has been recognized from pulmonary pathology associated with numerous autoimmune diseases, drug reactions, radiation injury, pneumoconioses, sarcoidosis, chronic hypersensitivity pneumonitis, and a host of other conditions.¹⁶ Additionally, UIP is frequently found in biopsy specimens obtained from patients with the clinical entity IPF.¹⁶⁻¹⁸

The histopathology found at lung biopsy in IPF is variable. From a given biopsy specimen, the histology may be consistent with desquamative interstitial pneumonitis or UIP, or both patterns may be present.^{17, 18} Cases of LIP progressing to end-stage fibrosis in hypergammaglobulinemic states have also been described.^{11, 12} From these observations, it has been concluded that desquamative interstitial pneumonitis, and possibly LIP, are the nonspecific pathologic findings from an earlier stage of a disease process that will, if left untreated, likely progress to UIP and ultimately to end-stage pulmonary fibrosis.

Thus pulmonary fibrosis is likely a common pathologic outcome from a variety of pulmonary insults. In dysgammaglobulinemic conditions with hypergammaglobuline-

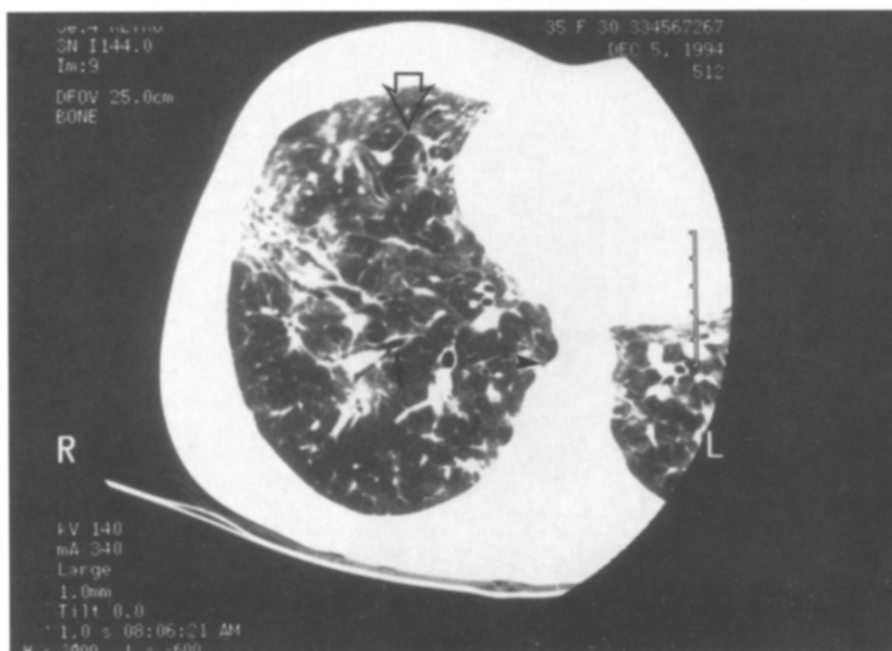


FIG. 3. High-resolution chest computed tomography from December 1994 demonstrating development of honeycombing (*open arrow*), interstitial linear and nodular densities, and bronchiectasis (*arrow*) with minimal residual mediastinal adenopathy (*arrowhead*).

mia, immune complexes have been postulated as one of the etiologies leading to immunologic activation and ultimately fibrosis. However, given that UIP developed in our patient with marked panhypogammaglobulinemia, it appears that antibody-mediated mechanisms are not essential in the immunopathogenesis of UIP. In IPF a genetic basis is supported by familial studies and reports of monozygotic twins being similarly affected despite being reared separately.¹⁶ Viral etiologies have been postulated on the basis of serologic evidence. A high rate of seropositivity to hepatitis C virus was reported from Japan in association with IPF.¹⁹ This finding was not duplicated in a genetically different population from Great Britain.²⁰ EBV has also been serologically implicated as a causative agent of IPF.²¹ Stronger evidence for a viral etiology of interstitial pneumonitis is provided by *in situ* hybridization studies. In one such study, open lung biopsy specimens were subjected to *in situ* hybridization for EBV, and nine of 14 patients with LIP and two of 10 control subjects with IPF were positive for EBV.²² Actively replicating EBV has also been found in pulmonary epithelial cells in 70% of patients with IPF but in only 9% of control subjects.²³ EBV has also been described to transform smooth muscle cells in patients who were immunosuppressed after solid organ transplantation.²⁴

The patient in this report has characteristics of CVID manifested by recurrent sinopulmonary infections, lymphadenopathy, splenomegaly, history of ITP, hypogammaglobulinemia, intact cellular immunity, no reaction to pneumococcal immunization, normal lymphocyte phenotypic distribution, and sarcoid-like granulomas on liver biopsy specimen. She may have had LIP that has

progressed to UIP; however, the rapid progression of her pulmonary disease and response to immunomodulatory therapy, despite frank fibrosis, is atypical. Immune complex deposition and immunologic activation are unlikely causes of her UIP because she has profound hypogammaglobulinemia.

It is intriguing that her PBMCs and plasma PCR for EBV are positive. The PBMC-positive PCR may be explained by prior infection with EBV and the episome from the virus persisting in her PBMCs. However, the plasma PCR for EBV is indicative of re-activation of a previously quiescent infection. It is plausible that as she became more immunoincompetent, the EBV was re-activated and was a significant contributing factor in the rapid progression of her pulmonary disease. It is also possible that if EBV can transform smooth muscle cells in immunosuppressed transplant recipients, it may have transforming capability in fibroblasts from an immunodeficient host; however, we have no direct evidence of this phenomenon. Clearly, the role that EBV plays in the development of pulmonary fibrosis in immunologically intact hosts, as well as in immunocompromised hosts, deserves further intensive scrutiny.

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Allergic reactions to North African scorpion venom evaluated by skin test and specific IgE

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In Algeria, hundreds of deaths per year are caused by scorpion stings (Benguedda, oral communication, 1995), mainly because of the presence in the venom of a variety of toxic proteins,^{1,2} which are immunogenic in animal models.³ Acute allergic reactions caused by scorpion venom have been reported recently in Texas⁴ but have never been documented for the North African *Androctonus australis Hector* (AaH) (Buthidae family) scorpion venom. The aim of this study was to determine whether an IgE-mediated mechanism could be responsible for the clinical symptoms in subjects stung by AaH.

Abbreviations used

AaH: *Androctonus australis Hector*
RU: RAST units
SPT: skin prick test

METHODS

Thirty-nine Algerians (37 male and 2 female subjects aged 5 to 63 years), living in the Sahara area of El Oued, were studied 3 to 24 months after the last sting: 16 had been stung only once, 14 had been stung between two and five times, and nine had been stung more than eight times. During the last sting, 32 patients had only a local reaction, and seven had a local reaction plus mild or severe systemic symptoms. According to the classification of Goyffon et al.,¹ the clinical effects of scorpion stings are classified in four stages of increasing severity: stage I, local burning pain with or without edema; stage II, stage I plus general symptoms (sweating, shivering, nausea, tachycardia); stage III, stage II plus hyperthermia, cardiovascular disturbances, and disturbances of consciousness; stage IV, neurotoxic stage leading to cardiovascular collapse. The local reactions observed were of the immediate type, and no delayed

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