

Clinical Communications

Chronic obstructive pulmonary disease associated with hypocomplementemic urticarial vasculitis

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Clinical Implications

- Chronic obstructive pulmonary disease is overwhelmingly severe during hypocomplementemic urticarial vasculitis, with a high risk of death or requirement for lung transplantation, and occurs mainly in mild to moderate smokers. It is crucial to screen for chronic obstructive pulmonary disease and strongly recommend smoking cessation in all patients presenting with hypocomplementemic urticarial vasculitis.

Hypocomplementemic urticarial vasculitis (HUV) is a small-vessel vasculitis characterized by chronic urticarial lesions, hypocomplementemia, and systemic manifestations.¹ In 1982, Schwartz et al² proposed criteria to define it and reported an association with chronic obstructive pulmonary disease (COPD). Since this description, rare cohorts³⁻⁵ and case reports^{6,7} have been published, but data on these rare patients and their therapeutic management are lacking. Therefore, we decided to focus on this uncommon complication of HUV by describing its clinical, immunologic, functional, and radiological features and its response to therapy.

This retrospective multicenter study was conducted in 11 departments of Internal Medicine and Pulmonology. Inclusion criteria for the diagnosis of HUV were the presence of chronic urticarial lesions and low complement levels (C3 and/or C4), associated with at least 2 of the following criteria: leukocytoclastic vasculitis on skin biopsy, arthralgias or arthritis, ocular inflammation, glomerulonephritis, abdominal pain, and/or presence of anti-C1q antibodies.² COPD was defined by a ratio of FEV₁ on forced vital capacity of less than 70% after bronchodilator.⁸ Characteristics of the patients were compared with those of 52 patients with HUV but without COPD previously reported.⁴ Data on clinical, immunologic, functional, and radiological features were collected as well as treatment characteristics and response to therapy. Data are presented as median (range) for continuous variables and number (%) for qualitative variables. Analyses were performed using Prism version 8 (GraphPad

Software Inc, San Diego, Calif). The study was approved by the Institutional Review Board of Cochin Hospital.

We included 11 patients with HUV associated with COPD (9 females and 2 males), with a median age at diagnosis of HUV of 52 (38-68) years. Clinical and immunologic characteristics of the HUV are described in Table I. No obvious difference in these characteristics was noted between patients with HUV with and without COPD, except for more frequent angioedema and lymph node enlargement.

All patients had pulmonary manifestations, including dyspnea in 10 (90.9%), wheezing in 8 (72.7%), and cough in 6 (54.5%) (Table II). Nine (81.8%) patients were active or previous smokers, with a median consumption estimated of 20 (5-40) pack-years. Median FEV₁/forced vital capacity ratio at diagnosis of COPD was 58% (31%-70%), with median FEV₁ of 42% (27%-81%) after bronchodilator. Evolution of FEV₁ during follow-up in 8 patients is shown in Figure E1 in this article's Online Repository at www.jaci-inpractice.org. Thoracic computed tomography scan was abnormal in 9 (81.8%) patients at diagnosis, showing centrilobular emphysema in 4 patients (44.4%), mosaic perfusion in 3 (33.3%), and bronchiectasis in 3 (33.3%).

Median number of therapeutic lines received was 4 (2-6) (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org). All patients received glucocorticoids. Adjunctive treatments included hydroxychloroquine in 9 (81.8%) patients, rituximab in 7 (63.6%), mycophenolate mofetil in 6 (54.5%), cyclophosphamide in 5 (45.5%), azathioprine in 5 (45.5%), colchicine in 2 (18.2%), dapsone in 2 (18.2%), and intravenous immunoglobulins and cyclosporin in 1 case each. Two patients did not receive immunosuppressive agents and were controlled with glucocorticoids and hydroxychloroquine or colchicine. In comparison to patients with HUV without COPD, patients with COPD were more refractory to treatments (9 of the 11 patients with COPD [81.8%] vs 22 of 50 patients without [44.0%]; $P = .04$), emphasizing COPD-dissociated response to therapy from other organs' involvement.

All but 1 patient (90.9%) had severe adverse events during follow-up. Three (27.3%) patients died, 2 because of unfavorable outcome of COPD and 1 because of major cardiovascular event. Three (27.3%) patients are currently awaiting lung transplantation. Three (27.3%) patients required noninvasive ventilation and 2 (18.1%) long-term oxygen. Seven (63.6%) patients presented with exacerbations requiring several hospitalizations, in intensive care unit for 3 (27.3%) of them.

This study reports the largest descriptive analysis of HUV presenting with COPD. The prevalence of COPD in HUV varies from 10.5% to 61%.³⁻⁵ This variation could be explained by different tobacco consumption rates, ranging from 36% to 91%, in these cohorts. The link between smoking and COPD development seems obvious, but the severity of the COPD is disproportionate compared with tobacco exposure. Worsening of FEV₁ was much faster in patients with HUV with COPD than in patients with COPD without HUV: we noted a decline in FEV₁ of 225 mL/y for patient 3, who was an active smoker at 40 pack-years, and 78 mL/y for patient 6, who only smoked 5 pack-years before stopping. These decline rates are noticeably higher than the reported ones in active or previous smokers without HUV, respectively 62 mL/y and 31 mL/y.⁹ These observations highlight the potential synergistic role of tobacco use in

TABLE I. Baseline characteristics of HUV according to the presence or not of COPD

Characteristic	Patients with COPD (n = 11)	Patients without COPD (n = 52)
Demographic characteristic		
Female	9 (81.8)	37 (71.2)
Age at diagnosis (y), median (range)	52 (38-68)	45 (15-83)
HUV characteristics		
Isolated HUV	9 (81.8)	40 (76.92)
Associated with systemic disease	2 (18.2)	12 (23.08)
Clinical manifestations		
Angioedema	8 (72.7)	25 (48.1)
Purpura	3 (27.3)	19 (36.5)
Livedo reticularis	1 (9.1)	8 (15.4)
Constitutional symptoms	6 (54.5)	29 (55.8)
Musculoskeletal involvement	9 (81.8)	44 (84.6)
Ocular involvement	7 (63.6)	29 (55.8)
Lymph node enlargement*	5 (45.5)	12 (23.1)
Gastrointestinal tract involvement	2 (18.2)	8 (15.4)
Glomerulonephritis	2 (18.2)	8 (15.4)
Ear, nose, and throat involvement	1 (9.1)	4 (7.7)
Neurologic involvement	1 (9.1)	2 (3.8)
Complement level		
C3 level (mg/L), median (range)	450 (250-800)	455 (40-760)
C4 level (mg/L), median (range)	78 (20-131)	70 (20-320)
Low CH50	7 (77.8)	45 (97.8)
Low C1q	7 (100)	26 (92.9)
Anti-C1q antibodies	6 (66.7)	19 (55.9)
Antinuclear antibodies	7 (63.6)	25 (48.1)

CH50, Total complement activity.

Results are expressed in n (%) unless indicated differently.

Bold values indicate statistical significance ($P < .05$).

*Mediastinal for 1 patient, peripheral for the others.

the development of COPD in HUV, but smoking is not mandatory because some patients had never smoked.^{3,5} Thoracic computed tomography scans were abnormal in 82%, showing mainly centrilobular emphysema, mosaic perfusion, and bronchiectasis. No correlation between radiological abnormalities and severity of the disease was noted.

COPD associated with HUV was remarkable for its severity and poor prognosis. In our study, 90.9% develop severe adverse events including 27.3% of deaths and 27.3% of respiratory failure requiring lung transplantation. This poor evolution was also noted in other studies.^{6,7} Although treatments were mainly effective on cutaneous, musculoskeletal, and systemic involvements, COPD seemed to worsen on its own and no therapy appeared to control its progression.

The pathophysiology of the disease is still poorly understood. The main hypothesis is the synergistic association of pulmonary vasculitis, emphysema worsened by tobacco exposure, and a specific role of anti-C1q antibodies that could bind to collagen-like regions of the surfactant and contribute to alveoli destruction.⁶ In our study, no patient had lung biopsies. In the literature, severe emphysema and direct or indirect evidence of small-vessel vasculitis has been found in lung biopsies.³

In conclusion, our data support a specific obstructive pulmonary disease in HUV, affecting mainly young patients and leading to

TABLE II. Clinical, biological, functional, and radiological characteristics of HUV-related COPD

Characteristic	Value
Previous pulmonary history	
History of pulmonary disease, n (%)	1 (9.1)
Tobacco use, n (%)	9 (81.8)
Current smoker	4
Previous smoker	5
Pack-years, median (range)	20 (5-40)
COPD at diagnosis of HUV, n (%)	8 (72.7)
Clinical manifestations, n (%)	
Dyspnea	10 (90.9)
Wheezing	8 (72.7)
Cough	6 (54.5)
Pulmonary function test at diagnosis, %	
FEV ₁ /FVC, median (range)	58 (31-70)
FEV ₁ , median (range)	42 (27-81)
FVC, median (range)	66 (49-120)
DLCO, median (range)	58 (32-88)
Blood gas analysis	
pH, median (range)	7.45 (7.43-7.46)
pO ₂ (mm Hg), median (range),	67 (64-104)
pCO ₂ (mm Hg), median (range)	33 (33-45)
HCO ₃ ⁻ (mmol/L), median (range)	22 (22-31)
Thoracic CT, n (%)	
Abnormal	9 (81.8)
Emphysema	4
Mosaic perfusion	3
Bronchiectasis	3
Last pulmonary function test, %	
FEV ₁ /FVC, median (range)	48 (31-70)
FEV ₁ , median (range)	34 (20-75)

CT, Computed tomography; DLCO, diffusing capacity of lung for carbon monoxide; FVC, forced vital capacity.

significant morbidity and mortality. A synergistic role of tobacco exposure and immunologic mechanisms seems to contribute to the development of COPD. It is therefore essential to screen for COPD and obtain smoking cessation in all patients with HUV.

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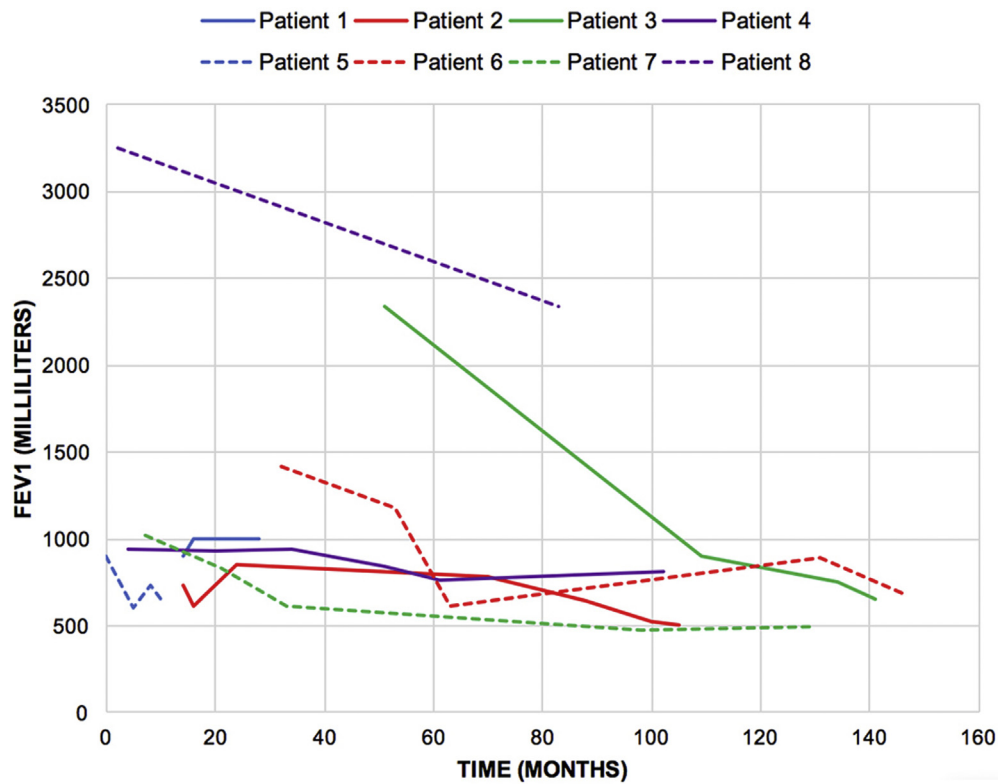


FIGURE E1. Evolution of FEV₁ during follow-up in 8 patients. Month 0 represents the date of HUV diagnosis.

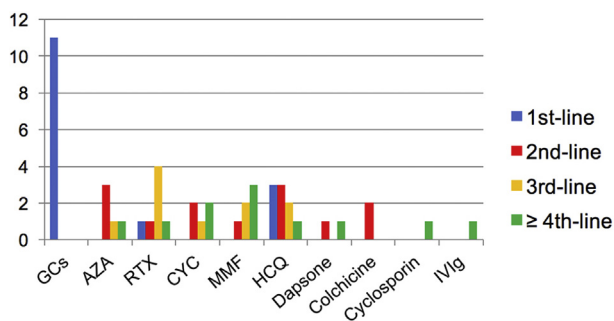


FIGURE E2. Therapeutic management used in the 11 patients with HUV-related COPD. AZA, Azathioprine; CYC, cyclophosphamide; GC, glucocorticoid; HCQ, hydroxychloroquine; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; RTX, rituximab.