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1 **Chronic Obstructive Pulmonary Disease Associated with Hypocomplementemic Urticarial**  
2 **Vasculitis**

3 Clémence David, M.D.<sup>1,2</sup>, Marie Jachiet, M.D.<sup>3</sup>, Marc Pineton de Chambrun, M.D.<sup>4</sup>, Anne Sophie  
4 Gamez, M.D.<sup>5</sup>, Anas Mehdaoui, M.D.<sup>6</sup>, Thierry Zenone, M.D.<sup>7</sup>, Delphine Gobert, M.D.<sup>8</sup>, Achille  
5 Aouba, M.D., Ph.D.<sup>9</sup>, Anne Peterschmitt, M.D.<sup>10</sup>, Sylvain Palat, M.D.<sup>11</sup>, François Lifermann,  
6 M.D.<sup>12</sup>, Daniel Blockmans, M.D., Ph.D.<sup>13</sup>, Séverine Feuillet-Soummer, M.D.<sup>14</sup>, Luc Mouthon,  
7 M.D., Ph.D.<sup>1,2,15</sup>, Benjamin Terrier, M.D., Ph.D.<sup>1,2,15</sup>, for the French Vasculitis Study Group.

8 <sup>1</sup>Department of Internal Medicine, Cochin Hospital, Paris, France; <sup>2</sup>National Referral Centre for  
9 Systemic and Autoimmune Diseases, Cochin Hospital, Paris, France; <sup>3</sup>Department of  
10 Dermatology, Saint-Louis Hospital, Paris, France; <sup>4</sup>Department of Internal Medicine and Intensive  
11 Care Medicine, Pitié-Salpêtrière Hospital, Paris, France; <sup>5</sup>Department of Pulmonology,  
12 Montpellier University Hospital, Montpellier, France; <sup>6</sup>Department of Pulmonology, Evreux  
13 Hospital, Evreux, France; <sup>7</sup>Department of Internal Medicine, Valence Hospital, Valence,  
14 France; <sup>8</sup>Department of Internal Medicine, Saint-Antoine Hospital, Paris, France; <sup>9</sup>Department of  
15 Internal Medicine, Caen University Hospital, Caen, France; <sup>10</sup>Department of Internal Medicine,  
16 Grenoble Mutualist Hospital Group, Grenoble, France; <sup>11</sup>Department of Internal Medicine,  
17 Limoges Hospital, Limoges, France; <sup>12</sup>Department of Internal medicine, Dax Hospital, Dax,  
18 France; <sup>13</sup>Department of Internal Medicine, Leuven University Hospital, UZ Leuven, Belgium;  
19 <sup>14</sup>Department of Thoracic and Vascular Surgery and Heart-Lung Transplantation, Marie  
20 Lannelongue Hospital, Le Plessis Robinson, France; <sup>15</sup>Paris Descartes University, Université de  
21 Paris, Paris, France.

22 **Correspondence:** Pr. Benjamin Terrier, Department of Internal Medicine, Hôpital Cochin, 27, rue  
23 du Faubourg Saint-Jacques, 75679 Paris Cedex 14, France. Phone: +33 (0)1 58 41 14 61; Fax: +33  
24 (0)1 58 41 14 50; E-mail: [benjamin.terrier@aphp.fr](mailto:benjamin.terrier@aphp.fr).

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26 **Keywords:** Chronic Obstructive Pulmonary Disease, Hypocomplementemic Urticarial Vasculitis,  
27 COPD, HUV

28 **Word count:** 999words

29 **Clinical Implications:**

30 COPD is overwhelmingly severe during HUV with a high risk of death or requirement for lung  
31 transplantation and occurs mainly in mild-to-moderate smokers. It is crucial to screen for COPD  
32 and strongly recommend smoking cessation in all patients presenting with HUV.

33 Hypocomplementemic urticarial vasculitis (HUV) is a small vessel vasculitis characterized  
34 by chronic urticarial lesions, hypocomplementemia and systemic manifestations (1). In 1982,  
35 Schwartz et al. proposed criteria to define it and reported an association with chronic pulmonary  
36 obstructive disease (COPD) (2). Since this description, rare cohorts (3–5) and case reports (6,7)  
37 have been published but data on these rare patients and their therapeutic management are lacking.  
38 Therefore, we decided to focus on this uncommon complication of HUV by describing its clinical,  
39 immunological, functional and radiological features and its response to therapy.

40 This retrospective multicenter study was conducted in 11 departments of Internal Medicine  
41 and Pulmonology. Inclusion criteria for the diagnosis of HUV were the presence of chronic  
42 urticarial lesions and low complement levels (C3 and/or C4), associated with at least two of the  
43 following criteria: leukocytoclastic vasculitis on skin biopsy, arthralgias or arthritis, ocular  
44 inflammation, glomerulonephritis, abdominal pain and/or presence of anti-C1q antibodies (2).  
45 COPD was defined by a ratio of forced expiratory volume in one second (FEV1) on forced vital  
46 capacity (FVC) of less than 70% after bronchodilator(8). Characteristics of the patients were  
47 compared to those of 52 patients with HUV but without COPD previously reported (4). Data on  
48 clinical, immunological, functional and radiological features were collected as well as treatment  
49 characteristics and response to therapy. Data are presented as median (range) for continuous  
50 variables and number (%) for qualitative variables. Analyses were performed using Prism version  
51 8 (GraphPad Software Inc.). The study was approved by the Institutional Review Board of Cochin  
52 Hospital.

53 We included 11 patients with HUV associated with COPD (9 females and 2 males), with a  
54 median age at diagnosis of HUV of 52 (38-68) years. Clinical and immunological characteristics  
55 of the HUV are described in **Table 1**. No obvious difference in these characteristics was noted  
56 between HUV patients with and without COPD, except for more frequent angioedema and lymph  
57 node enlargement.

58 All patients had pulmonary manifestations, including dyspnea in 10 (90.9%), wheezing in  
59 8 (72.7%) and cough in 6 (54.5%) (**Table 2**). Nine (81.8%) patients were active or previous  
60 smokers, with a median consumption estimated of 20 (5-40) pack years. Median FEV1/FVC ratio  
61 at diagnosis of COPD was 58% (31-70) with median FEV1 of 42% (27-81) after bronchodilator.  
62 Evolution of FEV1 during follow-up in 8 patients is shown in **Figure E1**. Thoracic CT scan was  
63 abnormal in 9 (81.8%) patients at diagnosis, showing centrilobular emphysema in 4 patients  
64 (44.4%), mosaic perfusion in 3 (33.3%) and bronchiectasis in 3 (33.3%).

65 Median number of therapeutic lines received was 4 (2-6) (**Figure E2**). All patients received  
66 glucocorticoids (GCs). Adjunctive treatments included hydroxychloroquine in 9 (81.8%) patients,  
67 rituximab in 7 (63.6%), mycophenolate mofetil in 6 (54.5%), cyclophosphamide in 5 (45.5%),  
68 azathioprine in 5 (45.5%), colchicine in 2 (18.2%), dapsone in 2 (18.2%), and intravenous  
69 immunoglobulins and cyclosporin in one case each. Two patients did not receive  
70 immunosuppressive agents and were controlled with GCs and hydroxychloroquine or colchicine.  
71 In comparison to HUV patients without COPD, patients with COPD were more refractory to  
72 treatments (9 of the 11 patients with COPD (81.8%) vs. 22 of 50 patients without (44.0%),  $p=0.04$ )  
73 emphasizing COPD dissociated response to therapy from other organs involvement.

74 All but one patient (90.9%) had severe adverse events during follow-up. Three (27.3%)  
75 patients died, 2 because of unfavorable outcome of COPD and one because of major cardiovascular

76 event. Three (27.3%) patients are currently awaiting lung transplantation. Three (27.3%) patients  
77 required noninvasive ventilation and two (18.1%) long-term oxygen. Seven (63.6%) patients  
78 presented with exacerbations requiring several hospitalizations, in intensive care unit for 3 (27.3%)  
79 of them.

80 This study reports the largest descriptive analysis of HUV presenting with COPD. The  
81 prevalence of COPD in HUV varies from 10.5% to 61% (3–5). This variation could be explained  
82 by different tobacco consumption ranging from 36% to 91% in these cohorts. The link between  
83 smoking and COPD development seems obvious but the severity of the COPD is disproportionate  
84 compared to tobacco exposure. Worsening of FEV1 was much faster in HUV patients with COPD  
85 than in COPD patients without HUV : we noted a decline of FEV1 of 225 ml per year for patient  
86 3 which was an active smoker at 40 pack-years and 78 mL per year for patient 6 who only smoked  
87 5 pack-years before stopping. These decline rates are noticeably higher than the reported ones in  
88 active or previous smokers without HUV, respectively 62 ml per year and 31 mL per year (9).  
89 These observations highlight the potential synergistic role of tobacco use in the development of  
90 COPD in HUV, but smoking is not mandatory since some patients had never smoked (3,5).  
91 Thoracic CT scans were abnormal in 82%, showing mainly centrilobular emphysema, mosaic  
92 perfusion, and bronchiectasis. No correlation between radiological abnormalities and severity of  
93 the disease was noted.

94 COPD associated with HUV was remarkable for its severity and poor prognosis. In our  
95 study, 90.9% develop severe adverse events including 27.3% of deaths and 27.3% of respiratory  
96 failure requiring lung transplantation. This poor evolution was also noted in other studies (6,7).  
97 Although treatments were mainly effective on cutaneous, musculoskeletal and systemic

98 involvements, COPD seemed to worsen on its own and no therapy appeared to control its  
99 progression.

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

106         In conclusion, our data support a specific obstructive pulmonary disease in HUV, affecting  
107 mainly young patients and leading to significant morbidity and mortality. A synergistic role of  
108 tobacco exposure and immunological mechanisms seems to contribute to the development of  
109 COPD. It is therefore essential to screen for COPD and obtain smoking cessation in all patients  
110 with HUV.

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	<b>Patients with COPD (n=11)</b>	<b>Patients without COPD (n=52)</b>
<b>Demographics</b>		
Female	9 (81.8%)	37 (71.2%)
Age at diagnosis, median (range), years	52 (38-68)	45 (15-83)
<b>HUV characteristics</b>		
Isolated HUV	9 (81.8%)	40 (76.92%)
Associated with systemic disease	2 (18.2%)	12 (23.08%)
<b>Clinical manifestations</b>		
Angioedema	<b>8 (72.7%)</b>	<b>25 (48.1%)</b>
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*	<b>5 (45.5%)</b>	<b>12 (23.1%)</b>
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%)
<b>Complement level</b>		
C3 level, median (range), mg/liter	450 (250-800)	455 (40-760)
C4 level, median (range), mg/liter	78 (20-131)	70 (20-320)
Low CH50	<b>7 (77.8%)</b>	<b>45 (97.8%)</b>
Low C1q	7 (100%)	26 (92.9%)
Anti-C1q antibodies	6 (66.7%)	19 (55.9%)
Antinuclear antibodies	7 (63.6%)	25 (48.1%)

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

CH50: total complement activity; COPD: chronic obstructive pulmonary disease; HUV: hypocomplementemic urticarial vasculitis; n: number.

\*Mediastinal for one patient, peripheral for the others

**Table 1. Baseline characteristics of HUV according to the presence or not of chronic obstructive pulmonary disease (COPD).**

<b>Previous pulmonary history</b>	
History of pulmonary disease, n (%)	1 (9.1%)
Tobacco use, n (%)	9 (81.8%)
<i>Current smoker</i>	4
<i>Previous smoker</i>	5
Pack-years, median (range)	20 (5-40)
COPD at diagnosis of HUV, n (%)	8 (72.7%)
<b>Clinical manifestations</b>	
Dyspnea, n (%)	10 (90.9%)
Wheezing, n (%)	8 (72.7%)
Cough, n (%)	6 (54.5%)
<b>Pulmonary function test at diagnosis</b>	
FEV1/FVC, median (range), %	58 (31-70)
FEV1, median (range), %	42 (27-81)
FVC, median (range), %	66 (49-120)
DLCO, median (range), %	58 (32-88)
<b>Blood gas analysis</b>	
pH, median (range)	7.45 (7.43-7.46)
pO <sub>2</sub> , median (range), mmHg	67 (64-104)
pCO <sub>2</sub> , median (range), mmHg	33 (33-45)
HCO <sub>3</sub> <sup>-</sup> , median (range), mmol/L	22 (22-31)
<b>Thoracic CT</b>	
Abnormal	9 (81.8%)
<i>Emphysema</i>	4
<i>Mosaic perfusion</i>	3
<i>Bronchiectasis</i>	3
<b>Last pulmonary function test</b>	
FEV1/FVC, median (range), %	48 (31-70)
FEV1, median (range), %	34 (20-75)
COPD: chronic obstructive pulmonary disease; CT: computed tomography; DLCO: diffusing capacity of lung for carbon monoxide; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; HUV: hypocomplementemic urticarial vasculitis; n: number.	

**Table 2. Clinical, biological, functional and radiological characteristics of HUV-related COPD.**

— Patient 1 — Patient 2 — Patient 3 — Patient 4  
- - Patient 5 - - Patient 6 - - Patient 7 - - Patient 8



