

Clinical, Radiologic, and Induced Sputum Features of Chronic Obstructive Pulmonary Disease in Nonsmokers

A Descriptive Study

Surinder S. Biring, Christopher E. Brightling, Peter Bradding, James J. Entwisle, Dhiraj D. Vara, Jonathan Grigg, Andrew J. Wardlaw, and Ian D. Pavord

Departments of Respiratory Medicine, Radiology, and Respiratory Physiology, and Leicester Children's Asthma Centre, Institute for Lung Health, Glenfield Hospital, Leicester, United Kingdom

Epidemiologic studies show that 5–12% of subjects with chronic obstructive pulmonary disease (COPD) are nonsmokers. Little is known about the pathophysiology of the fixed airflow obstruction in these subjects. We have prospectively identified 25 patients with COPD who had never smoked or had a less than 5 pack years smoking history and present the clinical, radiologic, and induced sputum features. Our population represented 5.7% of total referrals with fixed airflow obstruction over 2 years. Patients had a mean age of 70 years, were predominantly female (86%), and had a mean duration of respiratory symptoms of 7 years. The mean FEV₁ was 58%, and the FEV₁/FVC was 55%. Features on high-resolution computed tomographic scanning were nonspecific and were considered typical of a wider population with COPD. An induced sputum differential inflammatory cell count suggested the presence of two distinct groups. Nine had significant sputum eosinophilia (mean, 8.1%; normal, less than 1.9%), and the remaining 13 had a normal sputum eosinophil and tended to have a raised sputum neutrophil count (mean, 70.1%; normal, less than 65%). Organ-specific autoimmune disease was present in 7 of the 22 patients (32%) and was particularly prevalent in those without sputum eosinophilia (6 of 13). In conclusion, COPD in nonsmokers predominantly affects females and has at least two pathologic subgroups, one of which may be associated with organ-specific autoimmune disease. Further investigation of this group may disclose novel mechanisms of fixed airflow obstruction.

Keywords: chronic obstructive pulmonary disease; nonsmokers; autoimmune diseases

Chronic obstructive pulmonary disease (COPD) is largely attributable to smoking—the major known environmental risk factor. However, only 15% of smokers develop significant airflow obstruction and COPD (1), suggesting that other factors are involved. Epidemiologic studies show that 5–12% of patients with a diagnosis of COPD have never smoked, and there is evidence of increasing incidence with increasing age (2). These subjects are predominantly female, and there is an association with lower income (3); otherwise, little else is known about the clinical, radiologic, physiologic, and pathologic features of COPD in this group. A clearer understanding of the mechanism of airflow obstruction might iden-

tify novel pathogenic mechanisms relevant to a wider population of patients. We set out to characterize the clinical, radiologic, physiologic, and induced sputum features of COPD in nonsmokers attending our clinic over a 2-year period in a prospective descriptive study.

METHODS

Subjects

We recruited patients who had symptoms of chronic airflow obstruction and who fulfilled lung function criteria as set out by the National Heart and Lung Institute/World Health Organization Global Initiative for Chronic Obstructive Lung Disease guidelines (4) from our respiratory outpatient clinics. All patients had postbronchodilator FEV₁/FVC of less than 70% and no substantial improvement in FEV₁ after taking 2.5 mg of nebulized albuterol (less than 15% or, if is FEV₁ less than 1.2 L, less than a 200-mL improvement) and after a corticosteroid trial (2-week course of 30 mg of prednisolone daily or 2 months of high-dose inhaled corticosteroids, with reassessment of symptoms and spirometry). We excluded patients if they had a clinical diagnosis of asthma, variability of symptoms not associated with infections, or a history of acute wheeze, breathlessness, or deterioration associated with allergens. Other exclusion criteria were a history of childhood respiratory disorders (5), significant bronchiectasis (6), inflammatory bowel disease (7), rheumatoid arthritis (8), and chest wall deformity (9) because of their association with fixed airflow obstruction. All subjects were life-long nonsmokers or had a smoking history of less than 5 pack years. The smoking status was validated by exhaled carbon monoxide monitoring or urine cotinine levels and by review of hospital and general practitioner records. The study was approved by the Leicestershire Research Ethics Committee.

Data Collection

Clinical data were collected by an operator-led standardized questionnaire designed to obtain a symptom history, a detailed occupation history, and details of current (last 12 months) and past passive smoking history at home (at least one household smoker), at work, and during childhood (0–16 years old). These data were obtained together with a four-generation family history. All patients were asked to have a venous blood sample to measure peripheral blood eosinophil and lymphocyte count, immunoglobulin (Ig) levels (IgG, IgA, IgM), total IgE, and radioallergosorbent tests (timothy grass, cat epithelium, dog dander, Dermatophagoides pteronissinus), serum angiotensin-converting enzyme level, α_1 -antitrypsin level, and an autoantibody screen; antinuclear (in-house indirect immunofluorescence), rheumatoid factor (nephelometry, Dade Behring BNII protein analyzer; UK), islet cell (in-house indirect immunofluorescence), adrenal (indirect immunofluorescence; Biodiagnostics Ltd., Worcestershire, UK), parietal (in-house indirect immunofluorescence), endomysial (indirect immunofluorescence; Binding Site Ltd., Birmingham, UK) (10), and thyroid peroxidase autoantibodies (fluorescent enzyme-linked immunosorbent assay system; Pharmacia Diagnostics, Milton Keynes, UK). All patients had a chest radiograph and high-resolution computed tomographic (HRCT) scanning with both inspiration and expiration phases. An estimate of traffic-derived particle exposure was obtained from the Leicester City Council

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Correspondence and requests for reprints should be addressed to Dr. Surinder Biring, Institute for Lung Health, Department of Respiratory Medicine, Glenfield Hospital, Leicester LE3 9QP, UK. E-mail: sb134@le.ac.uk

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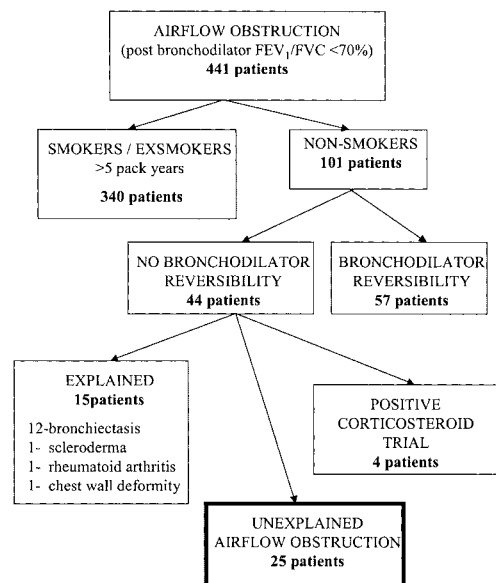


Figure 1. Patients seen in a respiratory outpatient clinic over 2 years. Reversibility to bronchodilator (2.5 mg of nebulized albuterol) or corticosteroid (2-week course of 30 mg of prednisolone daily or 2 months of high-dose inhaled corticosteroids): more than 15% improvement is seen in FEV₁, or if FEV₁ is less than 1.2 L, an improvement of more than 200 mL is seen. No nonsmoking patients with fixed airflow obstruction declined to take part in the study.

as the annual average daily traffic flows (vehicles per day on nearest main road). A road effect is considered to be present if the residence was less than 100 meters from the main road (more than 10,000 vehicles per day); otherwise, emissions were considered to be background (11, 12).

Pulmonary Function Tests

Spirometry was done with a Vitalograph spirometer (Vitalograph, Buckinghamshire, UK) before and at 15 minutes after a 2.5 mg of salbutamol administered via a Flaem Nouva Type II nebulizer (Deva Medical, Runcorn, Cheshire, UK) with a median particle size of 2 μ m and the patient breathing tidally. We recorded FEV₁ as the better of two successive readings within 100 ml. Lung-function tests were done with a benchmark (PK Morgan, Chatham, UK), and lung volumes were assessed by the helium dilution method.

Sputum was induced and processed in all patients as previously described (13). We have shown that this technique is safe and effective in subjects with moderate to severe COPD (14). Briefly, sputum was induced by use of 3, 4, and 5% saline, inhaled in a sequence for 5 minutes via an ultrasonic nebulizer (Medix, Harlow, UK) at 30 minutes after 2.5 mg of nebulized albuterol. Once expectorated, we stored sputum on ice for analysis within 2 hours. A differential cell count was obtained by counting more than 400 nonsquamous cells on Romanovsk-stained cytopins. Sputum induction was done at least 2 months after an exacerbation and the last use of corticosteroids.

Data Analysis

All results are expressed as mean (SE) or geometric mean (log SE). Pulmonary function test results are expressed as a percentage of predicted values (15).

RESULTS

We identified 25 nonsmoking patients with COPD, which represented 5.7% of total referrals with COPD over 2 years (Figure 1). Sixteen were life-long nonsmokers. One patient had significant bronchiectasis on the HRCT scan despite unremarkable physical examination and chest radiograph. Investigation of another pa-

tient revealed a carcinoid tumor obstructing the right upper lobe, and a third patient was found to have severe α_1 -antitrypsin (ZZ) deficiency. Characteristics of the remaining patients are given in Tables 1 and 2. Patients had a mean \pm SE age of 70 \pm 2 years, were predominantly female (n = 20, 83%), and had a mean \pm SE duration of symptoms of 7.3 \pm 1.5 years. No patients were current passive smokers (last 12 months). The mean \pm SE body mass index for subjects was 24 \pm 2 kg/m². All had normal serum angiotensin-converting enzyme and Ig levels. Features on the HRCT scan were nonspecific and were considered typical of a wider population with COPD (Table 3; emphysema, n = 2; bronchial wall thickening, n = 4; air trapping, n = 4; bronchial dilation, n = 5; bulla, n = 1; mosaic oligemia, n = 0; and normal, n = 8).

Patient's lung function results are presented in Table 2 and Figure 2. Patients had a mean \pm SE FEV₁ of 1.2 \pm 0.1 L, a mean \pm SE percentage predicted: FEV₁ of 58 \pm 5%, an FEV₁/FVC of 55 \pm 2%, a residual volume of 117 \pm 7%, a total lung capacity of 93 \pm 3, a residual volume/total lung capacity of 53 \pm 2%, a diffusing capacity for carbon monoxide of 81 \pm 5%, and a carbon monoxide diffusion coefficient of 107 \pm 6%. The induced sputum inflammatory cell count suggested the presence of two subgroups (Table 3). Nine patients (Patients 1–9) had a significant sputum eosinophilia (geometric mean differential cell count \pm log SE, 8.1 \pm 0.1%; normal, less than 1.9%), and the remaining 13 (Patients 10–24) had a normal sputum eosinophil and a raised mean \pm SE sputum neutrophil differential cell count of 70.1 \pm 6.3% (normal, less than 65%). The mean \pm SE sputum neutrophil differential cell count for the eosinophilic group was 64.5 \pm 5.8%. There was no significant difference in sputum neutrophil counts between the two groups. Six (27%) of the patients (two in the sputum eosinophilia group) had positive allergen-specific IgE to one or more allergen. Organ-specific autoimmune disease was present in 7 of the 22 patients (32%) and was particularly prevalent in those without sputum eosinophilia (6 of 13; Table 2). Similarly, there was a high prevalence of autoantibodies in the noneosinophilic group (n = 4, 31%; four thyroid). There was one patient with diabetes in the eosinophilic group, but none had positive autoantibodies. No patients had positive antinuclear antibody or rheumatoid factor. Six (46%) noneosinophilic patients had a low peripheral blood lymphocyte count (0.7–1.3; our laboratory normal range was 1.5–4.0 \times 10⁹ cells/L) compared with two (22%) eosinophilic patients. There were no significant differences between the two subgroups with reference to age, symptom scores, and lung function (Tables 1–3 and Figure 2).

DISCUSSION

This is the first study to address the clinical, radiologic, and induced sputum features of nonsmoking patients with COPD. We chose to study subjects who had never smoked or whose smoking history was trivial and very unlikely to be important in the development of respiratory disease. Smoking histories were validated by review of medical records and objective measurements. We found that 5.7% of the COPD population met our inclusion criteria. These patients were predominantly female, consistent with epidemiologic evidence (2, 3). Induced sputum analysis suggested the presence of at least two subgroups, one of which was associated with a high prevalence of organ-specific autoimmune disease.

Our demonstration of heterogeneity of induced sputum features in nonsmokers with COPD is consistent with evidence in smoking-related COPD, where both eosinophilic and neutrophilic patterns have been demonstrated (16, 17). Although the long-term stability of the sputum phenotype in these subjects is

TABLE 1. PATIENT CHARACTERISTICS

Patient Number	Age (years)	Sex	Symptom VAS	Sputum	Occupation	Family History	Passive Smoking	Past Smoking (pack years)
1	64	F	96	0	Secretary	0	0 (+H20y)	0
2	64	M	40	+	Sales representative	0	0 (+C)	0
3	82	F	74	+	Nurse	0	0	5
4	69	F	—	+	Housewife	0	0	0
5	67	F	76	0	Waitress	0	0 (++CW20y)	0
6	80	F	95	+	Office worker	0	0 (+H20y)	0
7	67	F	67	0	Accountant	0	0 (+H20y)	0
8	77	F	57	+	Care assistant	Son/aunt-asthma	0 (+W20y)	5
9	73	F	50	0	Housewife	0	0 (+H20y)	0
10	77	F	56	0	Hosiery worker	0	0 (+H10y)	5
11	67	F	70	+	Office worker	0	0	0
12	70	M	72	+	Iron foundry	0	0 (+H20y)	5
13	68	F	65	+	Retail manager	0	0 (+H20y)	0
14	54	F	50	+	Cleaner	F(s)-bronchitis	0	0
15	68	F	72	0	Housewife	0	0 (+H10y)	0
16	55	M	42	0	Builder	0	0	0
17	78	F	87	0	Teacher	0	0 (+H30y)	0
18	77	F	59	0	Hosiery worker	B(s)-bronchitis	0	0
19	55	F	20	0	Secretary	Son-asthma	0 (+H30y)	5
20	75	F	17	+	Cook	GF(s)-bronchitis	0	0
21	77	F	52	0	Hosiery worker	0	0	3
22	82	F	70	0	Shoe machinist	0	0 (++H20y)	0

Definition of abbreviations: B = brother; C = childhood; F = father; GF = grandfather; H = household; (S) = smoker; VAS = visual analogue score for most severe symptom out of breathlessness, cough and wheeze (0 = no symptoms, 100 = worst ever symptom); W = work; y = years of exposure.
 Current passive smoking (past passive smoking: +, less than 4 hours per day; ++, more than 4 hours per day. Sputum: +, less than 5 ml day and/or occasional; ++, more than 5 ml per day; 0, none).

unclear, repeatability studies in COPD suggest that these measures are stable over 2 weeks (14). The most obvious explanation for the fixed airflow obstruction in the eosinophilic inflammation subgroup is that it is the end result of airway remodeling second-

TABLE 2. PATIENT CHARACTERISTICS

Patient Number	Autoimmune Disease	α-1 Antitrypsin (g/L)	AADT
1	0	1.4 MM	NA
2	0	1.4 MM	3,020
3	0	ND	17,235
4	0	ND	6,555
5	0	2.0 MM	11,065
6	0	1.7 MM	14,915
7	Diabetes	1.3 MM	NA
8	0	1.6 MM	NA
9	0	1.8 MM	6,820
10	Hyperthyroid	1.7 MM	6,495
11	Hypothyroid (tpo 1:100)	1.5 MM	3,500
12	Hypothyroid	1.4 MM	10,995
13	0	1.6 MM	NA
14	0	1.4 MM	6,835*
15	Hypothyroid	1.4 MM	9,485
16	0 (tpo 1:163)	1.2 MM	NA
17	0	1.3 SS	5,490
18	Hyperthyroid (tpo 1:1,275)	1.8 MM	NA
19	0	2.0 MM	4,985
20	0	1.3 MS	11,645
21	0 (tpo 1:320)	1.6 MM	1,915
22	Coeliac disease	1.1 MZ	685

Definition of abbreviations: AADT = average annual daily traffic flows (vehicles per day on nearest main road; low = less than 10,000; medium = 10,000 to 30,000; high = more than 30,000); diabetes = juvenile onset, insulin dependent; NA = not available; ND = not done; tpo = thyroid peroxidase antibody titer where positive (strong positive 100–2,000 IU/ml).
 α₁-Antitrypsin normal range, 1.1–2.4 g/L (Pi phenotype).
 * Road effect.

ary to long-standing asthma. However, our patients had a relatively short history of symptoms, and none gave a history suggesting asthma. In addition, there was no evidence of reversibility after nebulized bronchodilators or a 2-week course of oral prednisolone at the time of assessment. It is also possible that eosinophilic COPD may complicate eosinophilic bronchitis, a common cause of isolated chronic cough in middle age (18). We have recently reported a case of eosinophilic bronchitis in a non-smoker where COPD developed over 2 to 3 years in association with poorly controlled eosinophilic airway inflammation (19). Corticosteroid-responsive eosinophilic bronchiolitis has also been described in a patient with fixed airflow obstruction with HRCT findings resembling diffuse panbronchiolitis, but none of our patients had radiologic features supporting this condition (20). Further study of the natural history of eosinophilic bronchitis is warranted, as it is a potentially preventable cause of COPD.

The other larger subgroup had no sputum evidence of eosinophilic inflammation and tended to have a neutrophilia. This group had a high prevalence of organ-specific autoimmune disease and autoantibodies, particularly thyroid disease. The prevalence was much higher than the sex- and age-adjusted prevalence of autoimmune disease in the general population (6–8%) (21) and the prevalence of 12% in the healthy control subjects in a recent case-control study (22). The significance of this finding is unclear, and it needs to be verified in a case-control study. However, a causal association between organ-specific autoimmune disease and airflow obstruction is plausible. The lungs and many organs involved in autoimmune disorders share common embryologic origins as foregut derivatives, and it is possible that homing of activated inflammatory cells into the pulmonary compartment as well as the primary site of autoimmune inflammation may cause airway wall inflammation and destruction leading to airflow obstruction. An alternative and intriguing mechanism is that the airflow obstruction might be a consequence of a hitherto unrecognized autoimmune bronchitis and that the association with other diseases simply reflects the well-

TABLE 3. LUNG FUNCTION, INDUCED SPUTUM DIFFERENTIAL CELL COUNTS, AND HIGH-RESOLUTION COMPUTED TOMOGRAPHY SCANNING FINDINGS

Patient Number	FEV ₁ Prealbuterol (L)	FEV ₁ Post-albuterol (L)	FEV ₁ /FVC (%)	Sputum Eosinophil Count (%)	Sputum Neutrophil Count (%)	HRCT Findings
1	1.79	1.88	63	14.3	67.5	ND
2	3.55	3.60	62	8.5	71.8	Normal
3	0.84	0.97	53	11.5	61.5	ND
4	0.71	0.75	50	27.5	47.0	Normal
5	0.77	0.84	35	3.8	86.5	Emphysema
6	1.41	1.53	69	5.5	89.5	BWT, BD
7	1.30	1.46	58	4.6	63.0	Normal
8	1.06	1.25	61	11.0	59.0	AT
9	1.25	1.34	58	3.8	35.0	ND
10	1.35	1.35	69	0.0	88.5	Normal
11	1.23	1.41	55	1.1	26.6	Normal
12	0.94	1.02	49	0.3	75.5	AT, minor BD, and PS
13	0.96	1.09	47	1.8	80.5	BD, minor PS
14	0.51	0.61	29	0.2	98.2	Minor PS and BD
15	1.45	1.60	69	0.3	41.0	AT, BWT
16	0.92	1.11	35	1.2	77.8	Emphysema, BWT
17	0.75	0.83	56	0.0	64.0	Normal
18	1.78	1.82	65	0.3	87.8	Normal
19	2.00	1.92	59	1.0	37.5	Small bulla
20	0.90	0.95	43	0.5	74.2	AT, minor atelectasis
21	0.84	1.02	54	1.3	64.3	Normal
22	0.75	0.85	61	0.7	95.0	BWT, BD

Definition of abbreviations: AT = air trapping; BWT = bronchial wall thickening; BD = minor bronchial dilation (less than 1.5 times the internal diameter of adjacent artery without bronchial wall thickening); ND = not done.

Subjects 1 through 9 are the eosinophilic group (normal eosinophil count of less than 1.9%, normal neutrophil count of less than 65%).

recognized association between different organ-specific autoimmune diseases. There is some recent evidence that thyroid disease, the most common organ-specific autoimmune disorder, may be associated with excess respiratory disease independently of thyroid hormonal status, as the odds ratio of death from respiratory disease was 2.8 in a recent large case series of subjects with normal thyroxine level but suppressed thyrotropin levels (23). Moreover, in a recent case control study, we have reported a marked excess of cases of organ-specific autoimmunity in a population of middle-aged patients with unexplained chronic cough (22). Further studies should investigate the possibility of

a link between unexplained chronic cough, COPD, and organ-specific autoimmunity.

Our view that some cases of COPD and chronic cough are due to immune dysregulation is supported by the association of cough and fixed airflow obstruction with other disorders with an immunologic basis such as inflammatory bowel disease (7), Sjogren's disease (24), rheumatoid arthritis (8), graft-versus-host disease (25), and more directly by the raised number of mononuclear cells seen in bronchial biopsies of nonsmoking patients with chronic cough (26). The significance of lymphopenia noted in just under half of our patients is unclear, but it could reflect pulmonary sequestration of activated lymphocytes, similar to that seen in sarcoidosis (27). We doubt that these patients had sarcoidosis, as there were no features of this on HRCT scanning and serum angiotensin-converting enzyme levels were normal.

One limitation of our study is the absence of pathologic material in the form of open or thoracoscopic lung biopsy. We found it difficult to justify invasive investigation with a low potential to alter management in an older population with slowly progressive disease. Previous studies in which biopsy has been performed in patients with fixed airflow obstruction of obscure etiology have identified discrete entities that may be relevant to our nonsmoking population. Kraft and colleagues (28) found pathologic evidence of constrictive bronchiolitis in four nonsmoking patients (two with airflow obstruction), and Turton and associates (29) have suggested a similar pathophysiology in a subgroup of 10 nonsmoking patients with fixed airflow obstruction on the basis of a strong association with rheumatoid arthritis. None of our patients had clinical features suggesting rheumatoid arthritis or positive rheumatoid factor; although we cannot exclude the possibility that constrictive bronchiolitis antedated onset of joint symptoms, such a sequence of events is unusual, and we doubt this is an important explanation (30).

It is possible that our patients had idiopathic constrictive

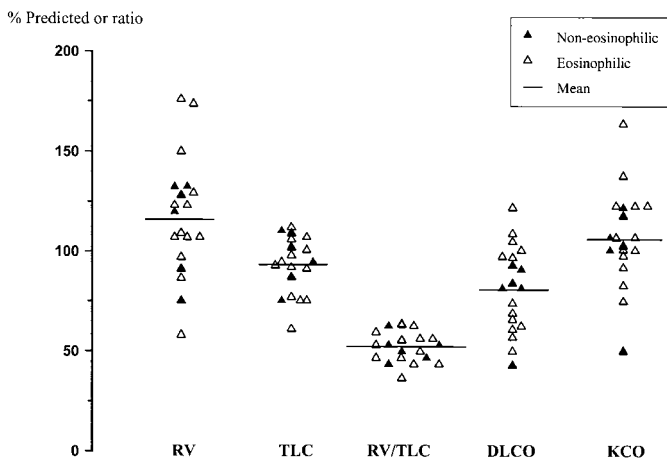


Figure 2. Detailed lung function. Data shown are the percent predicted values (15). DL_{CO} = diffusing capacity for carbon monoxide; KCO = diffusion coefficient; RV = residual value; TLC = total lung capacity.

bronchiolitis. Transplant-mediated constrictive bronchiolitis has been associated with a sputum neutrophilia (31), and the physiologic changes seen in our patients such as raised residual volume and preserved KCO are similar to those seen in the patients reported by Turton and colleagues (29). Although characteristic radiologic features of constrictive bronchiolitis have been defined, the sensitivity and specificity of these findings in mild disease are unclear (32). Diffuse panbronchiolitis seems unlikely in our population, as patients were predominantly white, did not report prominent sinusitis, and had no radiologic evidence of fine nodularity or "tree in bud" shadowing on HRCT (33). Aguayo and colleagues (34) have described a group of patients with fixed airflow obstruction, pathologic evidence of neuroendocrine cell hyperplasia, and the presence of pulmonary carcinoid tumor. This condition is unlikely in our patients because of the absence of reticulonodular infiltrates on imaging. We were particularly interested in whether this condition was present in our patient with fixed airflow obstruction and carcinoid tumor, although further pathologic examination of the resected lobe did not reveal the presence of neuroendocrine cell hyperplasia. Finally, the MZ genotype of the α_1 -antitrypsin gene has been associated with a more rapid decline in FEV₁ in smokers (35). α_1 -Antitrypsin testing identified one patient with the MZ genotype and one with severe disease (ZZ genotype), suggesting that testing should be considered a routine investigation in patients with nonsmoking fixed airflow obstruction as well as in smokers with COPD (36).

The use of a structured questionnaire provided us with an opportunity to explore the relationship between disease and other risk factors for COPD. A positive family history occurred with an incidence that was similar to that expected in smoking COPD patients (37). Similarly, although some patients had a possibly relevant occupational history, this was not common. The proportion of our patients exposed to passive smoking (work, 4%; parental, 8%; last 12 months at home, 0%) was less than that found in a recent UK/European general population survey (work, 11%; parental, 68%; home, 32%) (38). Most patients had a low to medium particle exposure, as reflected by the annual average daily traffic flows. Although this is not life-long exposure, there is little variation in these figures over time (11, 12), and it provides a reasonably robust estimate. Thus, no striking potential causal factors have been identified, although this is a small study with no control group, and thus, our ability to identify such relationships is limited.

HRCT scan changes included air trapping, bronchial wall thickening and dilation, emphysema, and bullae. These features are not dissimilar to what would be expected in a wider population of subjects with smoking-related COPD (39). However, we identified one subject with significant bronchiectasis and another with an obstructing carcinoid tumor, neither of which were expected after detailed clinical review and plain-chest x-ray. HRCT therefore had a reasonable pick up of abnormalities that might potentially alter management and should be considered in the investigation of subjects with unexplained airflow obstruction.

In summary, we have shown that COPD in nonsmokers predominantly affects older females and has at least two subgroups, one of which may be associated with organ-specific autoimmune disease. This is a preliminary observation of a poorly understood group and suggests some potentially novel pathogenic mechanisms. Further studies are required to investigate the relationship between organ-specific autoimmunity and airflow obstruction in more detail, characterize the nature of lower airway inflammation, and investigate the mechanisms involved.

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