EDITORIALS

Bronchiectasis: Still an Orphan Disease?

M.A. Martínez García

Unidad de Neumología, Hospital General de Requena, Requena, Valencia, Spain.

Nearly 2 centuries have passed since Laënnec wrote the first clinical description of a patient with bronquiectasis,[1] more than 80 years since bronchography became the standard diagnostic method, and more than half a century since Reid used histological findings and bronchography to describe and classify the diverse types of bronchiectasis approximately as they are known today.[2] Bronchiectasis is currently defined as the irreversible and sometimes progressive dilatation and destruction of the bronchial wall caused by a vicious pathogenic circle of impaired local defense mechanisms, infection, and airway inflammation.[3] All types of bronchiectasis are characterized by predominately neutrophilic and mononuclear inflammation with scores of cellular mediators that modulate both acute and chronic inflammatory response and perpetuate the bronchial lesion.[4,5] The characteristic clinical picture is chronic purulent sputum, functional impairment in the form of air flow obstruction, multiple exacerbations of an infectious type that occasionally involve atypical microorganisms,[6] and dyspnea in advanced stages of the disease—all of which cause progressive deterioration of the patient's quality of life.[1,7] To this day, the etiology of bronchiectasis is unknown in half the cases.[8] The present editorial is devoted to types of bronchiectasis that cannot be attributed to cystic fibrosis, an entity which is normally studied separately due to its special characteristics.

From the perspective of epidemiology, bronchiectasis has passed through various stages in its bicentennial history. Before antibiotics, the prevalence of the disease and the associated mortality rate were high: patients died before 40 years of age. The high prevalence kept pace with that of other infectious diseases that led to bronchiectasis, such as tuberculosis and necrotizing pulmonary processes.[9] Later, prevalence dropped as a result of the development of preventive medicine, especially immunizations and the antibiotic arsenal.[10] Scientific and commercial attention to the disease relaxed during this period of relative epidemiological calm, in which bronchiectasis was thought to be a thing of the past, condemned to extinction. At the end of the 1980s, Barker warned the scientific community in an update on the subject[11] by referring to bronchiectasis as "an orphan disease," the term established by Brewer a few years earlier for diseases abandoned by science and marketplace interests, especially with regard to the development of new treatments, as a consequence of a supposed decline in prevalence.[12]

Now, 15 years later, advances in science and technology and the return of old, forgotten diseases have awakened some sleeping dogs. Although even today we lack reliable studies on the real prevalence of bronchiectasis, it seems more than likely that it continues to be a major cause of morbidity and mortality in the developing world, and areas of the developed world where health care is inadequate.[13] In the industrialized world, the gradual replacement of bronchography by high resolution computed tomography since the end of the 1980s,[14] the resurgence of old diseases, new medical situations (with reference to pulmonary tuberculosis, the onset of the epidemic of acquired immune deficiency syndrome in the 1980s, and the advent of organ transplants and immunodepressant treatment[1] for example) and, finally, the increasing longevity of the population[15] have all had an impact on the current prevalence of bronchiectasis, which is probably much higher than supposed.

Nevertheless, in spite of the new epidemiological situation, the scientific community still lacks sufficient interest in bronchiectasis, especially in therapeutic innovation. In fact, only 41 clinical trials involving bronchiectasis have been indexed in MEDLINE from 1975 through the present, whereas the number is 20 times higher for pneumonia, 25 times higher for chronic obstructive pulmonary disease (COPD), and 100 times higher for asthma—remarkable differences, even taking into account the acknowledged greater prevalence among the general population of pneumonia, COPD, and asthma. More important is that from 2000 through 2004, therapeutic research for these diseases either increased (as was the case of COPD) or at least

Correspondence: Dr. M.A. Martínez García.
Unidad de Neumología. Servicio de Medicina Interna. Hospital General de Requena.
Pasaje Casablanca, s/n. 46230 Requena. Valencia. España.
E-mail: med013413@nacom.es

Manuscript received December 28, 2004. Accepted for publication January 18, 2005.

remained the same (as was the case of asthma and pneumonia), whereas the case of bronchiectasis was just the contrary: only 13 clinical trials were run in those 5 years, the same number as in the 2 preceding years (1998-1999). Moreover, according to the Cochrane Collaboration systematic reviews, there are hardly any studies with sufficient evidence to demonstrate a beneficial effect of drugs such as long- or short-acting beta-adrenergics, inhaled or oral corticosteroids, anticholinergics, certain mucolytics, methylxanthines, and other types of treatment, such as respiratory physiotherapy and noninvasive mechanical ventilation.[16] Some of these treatments, however, continue to be administered to patients with stable bronchiectasis or with exacerbations in the same manner they are prescribed for other airway diseases for which their beneficial effect has been demonstrated. Nevertheless, such treatment "by extrapolation" should in no case be taken to be proof of efficacy. Suffice it to remember the case of DNase, a mucolytic that has proven effective in cystic fibrosis but which is not effective in bronchiectasis of other origins and which can even be dangerous.[17] Antibiotic treatment has perhaps been the most studied therapy so far although there are still questions pending resolution concerning types of antibiotics, methods of administration, and appropriate duration. This is especially so for patients with chronic bronchial colonization by *Pseudomonas aeruginosa*, possibly the most devastating microorganism in terms of related morbidity and mortality and quality of life and also one of the most common ones.[18,19] However, recent statistics from the British Department of Health show that bronchiectasis in fact has great impact on public health. Seventy-eight percent of patients seeking care at emergency departments due to exacerbations are hospitalized; a third of them (mean age, 60 years) annually suffer at least 1 exacerbation that requires hospitalization lasting a mean 10.5 days.[20] Moreover, the mortality rate for bronchiectasis is between that of COPD and asthma (25% of bronchiectasis patients die within 9 years of diagnosis[21]) and is approximately the same as that of multiple sclerosis.[20]

Apart from today's distressing panorama in therapeutic research for bronchiectasis, the past few years have not brought all bad news. Some authors have made notable contributions to the pathophysiologic and clinical description of this "other" obstructive airway disease. Watt et al[4] found that in periods of exacerbation there is a significant increase in neutrophils, proteolytic enzymes (such as elastase), and certain proinflammatory cytokines and chemoattractants in sputum (such as interleukin 8 and tumor necrosis factor-α), and that the increase is associated with a decrease in anti-inflammatory cytokines (such as interleukin 10). The authors postulated that this mediator imbalance may be an important mechanism of progression in bronchiectasis and a possible target for antibiotic and anti-inflammatory treatment. Other recent studies reported higher concentrations in exhaled air of free radicals—hydrogen peroxide,[22] carbon monoxide,[23] and nitric oxide[24]—even for patients in stable clinical condition. In some cases these increases changed little with antibiotic or anti-inflammatory treatment, evidence of underlying chronic bronchial inflammation refractory to treatment. Zheng et al[25] evaluated the role of intercellular and vascular adhesion molecules (ICAM-1 and VCAM-1) and E-selectin in the migration of neutrophils toward the airways and studied the clinical and functional correlations involved. Chan et al[26] analyzed the modulating factors in the balance between elastase and anti-elastase in the genesis of bronchiectasis. The functional and clinical evolution of patients with bronchiectasis has been studied in recent years. Sheehan et al[27] found that certain observations on high resolution computed tomography of the chest —such as a thick bronchial wall—are related to later deterioration in lung function. Meanwhile, Koulouris et al[28] found interrelations among greater extension, more severe dyspnea, poorer lung function, and decrease in exercise capacity in patients with bilateral bronchiectasis. Angrill et al[5] showed that bronchial obstruction, long-standing bronchiectasis, and certain forms of cysts were risk factors for chronic bronchial colonization by potentially pathogenic microorganisms, such as *Haemophilus influenzae* and *P aeruginosa*, which are associated with poor prognosis. Lastly, Martínez-García et al[7] recently reported that dyspnea, quantity of daily sputum production, and obstruction of air flow are the independent variables that most affect the quality of life of patients with stable bronchiectasis. Those authors introduced the first validated questionnaire in Spanish for use with bronchiectasis patients: St. George's Respiratory Questionnaire.[29]

Especially noteworthy is a recent study by Patel et al[30] in which the authors observed that as many as half the patients with COPD, and with a mean forced expiratory volume in the first second of 38%, habitually presented with cylindrical lower lobe bronchiectasis that was clinically silent but of considerable size and extension. These patients showed more pronounced airway inflammation associated with greater bacterial colonization of the bronchial mucosa, which led to a more prolonged exacerbation of COPD. This finding may tie in with the latest theories regarding the negative effects on COPD prognosis of the number and severity of exacerbations[31] and chronic bronchial bacterial colonization,[32,33] and it opens up an intriguing area of investigation into the role of bronchiectasis in the natural history of COPD.

Therefore, using Brewer's term,[12] although bronchiectasis is no longer an orphan disease from the epidemiologic point of view, it is still an orphan with regard to clinical suspicion, commercial interest, and certainly research activity. Studies are urgently needed to demonstrate the effectiveness of drugs presently used on a wide scale to treat bronchiectasis patients, without a firm evidence base. It behooves the scientific community to address this situation, and all professionals to foment

clinical suspicion of a disease that today is more prevalent than might be expected—a disease that has its own pathophysiologic features and therapies. Recent findings that associate bronchiectasis with other more "attractive" diseases, such as COPD, seem an excellent starting point.

REFERENCES

1. Barker AF. Bronchiectasis. N Engl J Med. 2002;346;1383-93.
2. Reid LM. Reduction in bronchial subdivision in bronchiectasis. Thorax. 1950;5:233-47.
3. Cole PJ. Inflammation: a two-edged sword—the model of bronchiectasis. Eur J Respir Dis Suppl. 1986;147:6-15.
4. Watt AP, Brown V, Courtney J, Kelly M, Garske L, Elborn JS, et al. Neutrophil apoptosis, proinflammatory mediators and cell counts in bronchiectasis. Thorax. 2004;59:231-6.
5. Angrill J, Agusti C, de Celis R, Filella X, Rañó A, Elena M, et al. Bronchial inflammation and colonization in patients with clinically stable bronchiectasis. Am J Respir Crit Care Med. 2001;164:1628-32.
6. Vilas A, Suárez J. Infección de bronquiectasias por Flavimonas oryzihabitans en paciente inmunocompetente. Arch Bronconeumol. 2004;40:384-5.
7. Martínez-García MA, Perpiñá M, Román P, Soler JJ. Determinants of quality of life in patients with clinically stable bronchiectasis. Chest. In revision 2005.
8. Pasteur MC, Helliwell SM, Houghton SJ, Webb SC, Foweraker JE, Coulden RA, et al. An investigation into causative factors in patients with bronchiectasis. Am J Respir Crit Care Med. 2000;162;1277-84.
9. Perry KMA, Kings DS. Bronchiectasis: a study of prognosis based on a follow-up of 400 patients. Am Rev Tuberc. 1940;41:531-48.
10. Säynäjäkangäs O, Keistinen T, Tuuponen T, Kivela SL. Bronchiectasis in Finland: trends in hospital treatment. Respir Med. 1997;91:395-8.
11. Barker AF, Bardana EJ. Bronchiectasis: update of an orphan disease. Am Rev Respir Dis. 1988;137:969-78.
12. Brewer GJ. The orphan drug/orphan disease problem: has it been resolved? Pharm Int Dec. 1984;5:297-300.
13. Tsang KW, Tipoe GL. Bronchiectasis: not an orphan disease in the East. Int J Tuberc Lung Dis. 2004;691-702.
14. Grenier P, Cordeau MP, Beigelman C. High resolution computed tomography of the airways. J Thorac Imag. 1993;8:213-29.
15. Nicotra MB, Rivera M, Dale AM, Shepherd R, Carter R. Clinical, pathophysiologic, and microbiologic characterization of bronchiectasis in an aging cohort. Chest. 1995;108:955-61.
16. Barker AF. Treatment of bronchiectasis. In: UpToDate Online, Vol. 12.2, 2004. BDR, Inc., Wellesley, MA, USA. Available at: http://www.uptodate.com/.
17. Crockett AJ, Cranston JM, Latimer KM, Alpers JH. Mucolytics for bronchiectasis (Cochrane review). In: The Cochrane Library, Issue 4. Chichester, UK: John Wiley and Sons, Ltd.; 2004.
18. Barker AF, Couch L, Fiel SB, Gotfried MH, Ilowite J, Meyer KC, et al. Tobramycin solution for inhalation reduces sputum Pseudomonas aeruginosa density in bronchiectasis. Am J Respir Crit Care Med. 2000;162:481-5.
19. Evans DJ, Greenstone M. Long-term antibiotics in the management of non-CF bronchiectasis — do they improve outcome? Respir Med. 2003;97:851-8.
20. Hospital Episode Statistics 2002-2003. Department of Health. NHLBI.
21. Keistinen T, Säynäjäkangäs O, Tuuponen T, Kivela SL. Bronchiectasis: an orphan disease with a poorly-understood prognosis. Eur Respir J. 1997;10:2784-7.
22. Loukides S, Horvath I, Wodehouse T, Cole PJ, Barnes PJ. Elevated levels of expired breath hydrogen peroxide in bronchiectasis. Am J Respir Crit Care Med. 1998;158:991-4.
23. Horvath I, Loukides S, Wodehouse T, Kharitonov SA, Cole PJ, Barnes PJ. Increased levels of exhaled carbon monoxide in bronchiectasis: a new marker of oxidative stress. Thorax. 1998;53:867-70.
24. Kharitonov SA, Wells AU, O'Connor BJ, Cole PJ, Hansell D, Logan-Sinclair RB, et al. Elevated levels of exhaled nitric oxide in bronchiectasis. Am J Respir Crit Care Med. 1995;151:1889-93.
25. Zheng L, Tipoe G, Lam WK, Ho JC, Shum I, Ooi GC, et al. Endothelin-1 in stable bronchiectasis. Eur Respir J. 2000;16:146-9.
26. Chan SC, Shum DK, Ip MS. Sputum sol neutrophils elastase activity in bronchiectasis: differential modulation by syndecam-1. Am J Respir Crit Care Med. 2003;168:192-8.
27. Sheehan RE, Wells AU, Copley SJ, Desai SR, Howling SJ, Cole PJ, et al. A comparison of serial computed tomography and functional change in bronchiectasis. Eur Respir J. 2002;20:581-7.
28. Koulouris NG, Retsou S, Kosmas E, Dimakou K, Malagari K, Mantzikopoulos G, et al. Tidal expiratory flow limitation, dyspnea and exercise capacity in patients with bilateral bronchiectasis. Eur Respir J. 2003;21:743-8.
29. Martínez-García MA, Perpiñá M, Román P, Soler JJ. Consistencia interna y validez de la versión española del St. George's Respiratory Questionnaire para su uso en pacientes afectos de bronquiectasias clínicamente estables. Arch Bronconeumol. 2005;41:110-7.
30. Patel IS, Vlahos I, Wilkinson TMA, Lloyd-Owen SJ, Donaldson GC, Wilks M, et al. Bronchiectasis, exacerbations indices, and inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2004;170:400-7.
31. Kanner RE, Anthonisen NR, Connett JE. Lower respiratory illnesses promote FEV_1 decline in current smokers but not ex-smokers with mild chronic obstructive lung disease: results from the Lung Health Study. Am J Respir Crit Care Med. 2001;164:358-64.
32. Wilkinson TMA, Patel IS, Wilks M, Donaldson GC, Wedzicha JA. Airway bacterial load and FEV_1 decline in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2003;167:1090-5.
33. Monsó E. Colonización bronquial en la enfermedad pulmonar obstructiva crónica: algo se esconde debajo de la alfombra. Arch Bronconeumol. 2004;40:543-6.