The challenge of diagnosing a mixed asthma–COPD phenotype (ACOS) in clinical practice

Ther Adv Respir Dis

2016, Vol. 10(2) 175–178

DOI: 10.1177/1753465816630209

María del Carmen García-García, Jacinto Hernández-Borge, Miriam Barrecheguren and Marc Miravitlles

Correspondence to:
Marc Miravitlles, MD
Pneumology Department, Hospital General Universitari Vall d´Hebron, P. Vall d'Hebron 119-129, 08035, Barcelona, Spain
mmiravitlles@vhebron.net

María del Carmen García-García, MD
Jacinto Hernández-Borge, MD
Pneumology Department, Complejo Hospitalario Universitario Infanta Cristina, Badajoz, Spain

Miriam Barrecheguren, MD
Pneumology Department, Hospital General Universitari Vall d´Hebron, Ciber de Enfermedades Respiratorias (CIBERES), Barcelona, Spain

Introduction

The diagnosis of the asthma–COPD overlap syndrome (ACOS) in a patient with chronic obstructive pulmonary disease (COPD) has therapeutic implications since these patients present a higher frequency of exacerbations and better response to inhaled corticosteroids (ICSs) [Alcázar *et al.* 2015; Miravitlles *et al.* 2013b]. Different guidelines for the management of COPD recognize and characterize the ACOS [Kankaaranta *et al.* 2015; Koblizek *et al.* 2013; Miravitlles *et al.* 2014]. Similarly, the GINA-GOLD document describes the ACOS and proposes a series of criteria to identify these patients in clinical practice [GINA-GOLD, 2015]. However, the lack of consensus regarding the diagnostic criteria or the scarce accessibility to some diagnostic tests, make the identification of these individuals difficult in clinical practice [Miravitlles *et al.* 2015]. We present four cases of patients with different clinical expression and disease severity to highlight the variability of this syndrome (Table 1).

Clinical observations

Case 1

A 66-year-old male exsmoker of 50 pack-years was diagnosed with asthma during adolescence, presenting sensitization to multiple allergens. He reported cough, wheezing and rhinoconjunctivitis almost daily, and grade 2 dyspnea according to the modified Medical Research Council scale (mMRC). He presented an obstructive spirometry with a positive bronchodilator test and immunoglobulin (Ig)E levels of 434 U/ml. He had had two exacerbations requiring hospitalization in the previous year. His usual treatment consisted of high doses of ICSs, long-acting beta adrenergic (LABA) every 12 hours, a long-acting muscarinic antagonist (LAMA) as well as antileukotrienes and oxygen therapy. Nonetheless, the patient continued to present numerous exacerbations with clinical worsening and marked functional impairment. Omalizumab was therefore initiated, which led to clinical improvement with a reduction in the number of exacerbations as well as in the dose of systemic corticosteroids, although the latter could not be completely withdrawn.

Case 2

A 54-year-old woman exsmoker of 12 pack-years presented a history of asthma since infancy with sensitization to mites, intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs) and nasal polyposis. She had grade 1 dyspnea based on the mMRC scale. She reported cough, wheezing, and occasional rhinitis as well as an obstructive disease with a positive bronchodilator test and IgE levels of 124 U/ml. The patient presented one exacerbation treated as an outpatient in the previous year. She remains stable with ICSs and LABA every 12 hours and antileukotrienes.

Case 3

A 63-year-old male smoker of 160 pack-years, until 8 months previously, reported repeated respiratory infections when young, wheezing and dyspnea for which he frequently received courses of oral corticosteroids and occasionally went to the emergency department without requiring hospital admission. He was diagnosed with COPD by spirometry compatible with moderately severe obstructive disease, a positive bronchodilator test and IgE levels of 22 U/ml. The patient presents persistent bronchospasm, grade 3 mMRC dyspnea and continuous audible wheezing. He has required hospitalization twice in the last year. His treatment consists of high doses of ICSs and LABA together with LAMA every 12 hours, antileukotrienes,

Table 1. Clinical characteristics of patients with asthma–chronic obstructive pulmonary syndrome overlap syndrome.

	Case 1	Case 2	Case 3	Case 4
Sex	Man	Woman	Man	Man
Age (years)	66	54	63	83
Smoking habit (pack-years)	Exsmoker (50)	Exsmoker (12)	Exsmoker (160)	Exsmoker (30)
Previous diagnosis of asthma	Yes, at age of 20	Yes, at age of 12	No	No
History of allergies	Allergy to pollen, mites, fungus, dog and cat epithelium	Intolerance to NSAIDs. Nasal polyposis. Allergy to house dust mites	No	No
IgE (U/ml)	434	124	22	1978
FVC, ml	3160	2260	3150	2350
FVC, %	88	87	71	77
FEV1, ml	1430	1320	1700	1550
FEV1, %	51	61	53	68
FEV1/FVC%	45	58	54	65
BDT	Positive, 12% and 220 ml on 3 occasions	Positive, 14% and 210 ml on 2 occasions	Positive, 21% and 300 ml	Positive, 14% and 440 ml on 2 occasions
Dyspnea (mMRC)	Grade 2	Grade 1	Grade 3	Grade 1
History of atopy	Yes	Yes	No	Yes
Peripheral eosinophilia, % (absolute value in cell/mm^3)	0.3% (0)	9.4% (610)	1.4% (120)	2.9% (210)
Respiratory symptoms	Cough, dyspnea, wheezing, rhinoconjunctivitis	Cough, dyspnea, wheezing, rhinitis	Dyspnea, wheezing, severe bronchospasm	Dyspnea, rhinoconjunctivitis
Exacerbations in the previous year	Two exacerbations requiring hospitalization	One ambulatory exacerbation	Two exacerbations with hospitalization	Three ambulatory exacerbations

Ig, immunoglobulin; PFT, pulmonary function tests; BDT, bronchodilator test; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; NSAID, nonsteroidal anti-inflammatory drug; mMRC, modified Medical Research Council scale.

theophyllines and N-acetylcysteine. No further hospitalizations have been required, but the patient remains symptomatic with dyspnea and wheezing.

Case 4

An 83-year-old male exsmoker of 30 pack-years with sensitization to multiple allergens, presented with dyspnea, occasional wheezing and rhinoconjunctivitis. Spirometry was compatible with a moderate obstructive disease, and he presented a positive bronchodilator test and IgE levels of 1978 U/ml. Treatment was initiated with ICSs and LABA every 12 hours as well as LAMA every 24 hours. On presenting clinical stability the ICSs were withdrawn and double bronchodilatation was maintained. He has presented three moderate exacerbations in the last year together with marked loss of pulmonary function. The ICS were therefore re-initiated, and the patient has shown clinical and functional improvement and a reduction in the number of exacerbations.

Discussion

Although asthma and COPD are two diseases with different pathogenesis and risk factors, both share similar clinical and functional characteristics, which may overlap. Interest in characterizing the ACOS phenotype from the perspective of COPD has been growing in recent years since it allows the identification of a subgroup of patients with clinical characteristics different from those of COPD without an asthmatic component and with better response to treatment with ICSs [Barrecheguren *et al.* 2015a]. The prevalence of this phenotype varies greatly and is estimated to be found in 12–25% of patients with COPD based on the population studied and the diagnostic criteria used [Gibson and McDonald, 2015].

ACOS has two predominant clinical presentations: asthmatic patients with a history of smoking who develop nonreversible airflow obstruction and patients with COPD with a previous history or characteristics of asthma, predominance of eosinophilic inflammation and increased reversibility [Barrecheguren *et al.* 2015a; Postma and Rabe, 2015]. Moreover, there is evidence that some chronic asthmatics with persistent airflow limitation may develop centrilobular emphysema without smoking exposure, due to an inflammatory response leading to a proteolytic cascade with destruction of lung tissue [Gelb *et al.* 2015]. Patients with ACOS present more symptoms, have a worse quality of life and more frequently present exacerbations than other COPD patients [Miravitlles *et al.* 2013b; Nielsen *et al.* 2015]. The recent GOLD-GINA document describes ACOS as the presence of different findings associated with asthma and COPD [GINA-GOLD, 2015], while Spanish, Finnish and Czech COPD guidelines define major and minor criteria which should be fulfilled to establish the diagnosis [Miravitlles *et al.* 2014; Kankaanranta *et al.* 2015; Koblizek *et al.* 2013].

Other authors have defined ACOS including the need for pulmonary function tests such as the diffusing capacity of the lung for carbon monoxide (DLCO) or evidence of emphysema [Izquierdo-Alonso *et al.* 2013]. This diagnostic variability and the lack of specific biomarkers demonstrated the need to simplify the identification of these patients. In addition, some of the criteria proposed, such as the presence of eosinophilia in sputum or the fraction of exhaled nitric oxide (FeNO), are not available within the primary care setting where these patients can be identified early. Recent studies have shown that peripheral eosinophilia is a marker of response to treatment with ICSs in COPD [Pascoe *et al.* 2015] and that a previous history of asthma before the age of 40 years in patients with COPD may be an indicator of the presence of ACOS [Barrecheguren *et al.* 2015b]. These two characteristics, together with others such as wheezing or a positive bronchodilator test may help in suspecting this phenotype in COPD and are accessible in any healthcare setting [Soler-Cataluña *et al.* 2012].

Conclusion

We present four patients with COPD in whom the diagnosis of asthma during youth or symptoms compatible with a history of smoking, and not completely reversible airflow obstruction, were of note. All the patients were symptomatic (dyspnea, wheezing, cough) and some had a history of frequent, and even severe, exacerbations.

Eosinophilia in sputum could not be assessed in any of the patients, although peripheral eosinophilia was detected in half, and one patient who did not present this characteristic frequently received treatment with systemic corticosteroids. It is important to highlight that all measurements were performed in stable state at least 6 weeks from the recovery of an exacerbation.

In conclusion, variables which are accessible in clinical practice, such as a history of asthma before 40 years of age, peripheral eosinophilia or a positive bronchodilator test are useful criteria which can help orient the diagnosis of ACOS in COPD patients until more specific biomarkers are defined.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

Alcázar Navarrete, B., Casanova, C., Miravitlles, M., de Lucas, P., Riesco, J. and Rodríguez González-Moro, J. (2015) Correct use of inhaled corticosteroids in chronic obstructive pulmonary disease: A consensus document. *Arch Bronconeumol* 51: 193–198.

Barrecheguren, M., Esquinas, C. and Miravitlles, M. (2015a) The asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS): opportunities and challenges. *Curr Opin Pulm Med* 21: 74–79.

Barrecheguren, M., Román-Rodríguez, M. and Miravitlles, M. (2015b) Is a previous diagnosis of asthma a reliable criterion for asthma–COPD overlap syndrome (ACOS) in a patient with COPD? *Int J Chron Obst Pulm Dis*. 10: 1745–1752.

Gelb, A., Yamamoto, A., Verbeken, E. and Nadel, J. (2015) Unraveling the pathophysiology of the asthma–COPD overlap syndrome. *Chest* 148: 313–320.

Gibson, P. and McDonald, V. (2015) Asthma–COPD overlap 2015: now we are six. *Thorax* 70: 683–691.

GINA-GOLD (2015) Diagnosis of disease of chronic airflow limitation: asthma, COPD and asthma–COPD overlap syndrome (ACOS). http://www.goldcopd.org/asthma–COPDoverlap.html [accessed 5 November 2015].

Izquierdo-Alonso, J., Rodriguez-Gonzálezmoro, J., de Lucas-Ramos, P., Unzueta, I., Ribera, X., Antón, E. *et al.* (2013) Prevalence and characteristics of the three clinical phenotypes of chronic obstructive pulmonary disease (COPD). *Respir Med* 107: 724–731.

Kankaanranta, H., Harju, T., Kilpeläinen, M., Mazur, W., Lehto, J., Katajisto, M. *et al.* (2015) Diagnosis and pharmacotherapy of Stable Chronic Obstructive Pulmonary Disease: The Finnish Guidelines. *Basic Clin Pharmacol Toxicol* 116: 291–307.

Koblizek, V., Chlumsky, J., Zindr, V., Neumannova, K., Zatroukal, J., Zak, J. *et al.* (2013) Chronic Obstructive Pulmonary Disease: Official diagnosis and treatment guidelines of the Czech Pneumological and Phthisiological Society: a novel phenotypic approach to COPD with patient oriented care. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 157: 189–201.

Miravitlles, M., Alcázar, B., Alvarez, F., Bazús, T., Calle, M., Casanova, C. *et al.* (2015) What pulmonologists think about the asthma–COPD overlap syndrome (ACOS). *Int J Chron Obst Pulm Dis* 10: 1321–1330.

Miravitlles, M., Soler-Cataluña, J., Calle, M., Molina, J., Almagro, P., Quintano, J. *et al.* (2014) Spanish guideline for COPD (GesEPOC) update. *Arch Bronconeumol* 50: 1–16.

Miravitlles, M., Soler-Cataluña, J., Calle, M. and Soriano, J. (2013a) Treatment of COPD by clinical phenotypes. Putting old evidence into clinical practice. *Eur Respir J* 41: 1252–1256.

Miravitlles, M., Soriano, J., Ancochea, J., Muñoz, L., Duran-Tauleria, E., Sanchez, G. *et al.* (2013b) Characterisation of the overlap COPD-asthma phenotype. Focus on physical activity and health status. *Respir Med* 107: 1053–1060.

Nielsen, M., Boslev Barnes, C. and Suppli Ulrik, C. (2015) Clinical characteristics of the asthma–COPD overlap syndrome – a systematic review. *Int J Chron Obst Respir Dis* 10: 1443–1454.

Pascoe, S., Locantore, N., Dransfield, M., Barnes, N. and Pavord, I. (2015) Blood eosinophil counts, exacerbations and response to the addition of inhaled fluticasona furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomized controlled trials. *Lancet Respir Med* 3: 435–442.

Postma, D. and Rabe, K. (2015) The asthma–COPD overlap syndrome. *N Engl J Med* 373: 1241–1249.

Soler-Cataluña, J., Cosío, B., Izquierdo, J., López-Campos, J., Marín, J., Agüero, R. *et al.* (2012) Consensus document on the overlap phenotype COPD-Asthma in COPD. *Arch Bronconeumol* 48: 331–337.