Cough variant asthma and atopic cough
Asma variante con tosse e tosse atopica

Chiara Magni[1], Elisa Chellini[1], Alessandro Zanasi[2,3]
[1] Dipartimento di Medicina Interna, Malattie dell'Apparato Respiratorio e Terapie Cellulari, Università di Firenze
[2] UO Pneumologia, S. Orsola-Malpighi, Bologna
[3] Presidente AIST (Associazione Italiana per lo Studio della Tosse)

ABSTRACT
Chronic cough has been reported to be the fifth most common complaint seen by primary care physicians in the world, the third in Italy. Chronic cough in non-smoking, non-treated with ACE-inhibitor adults with normal chest radiogram could be a symptom of asthma and can be sub-classified into: cough-variant asthma, atopic cough, and eosinophilic bronchitis. This review discusses the differential diagnosis of these three disorders.

Keywords: Atopic cough, bronchial hyperresponsiveness, cough-variant asthma, eosinophilic bronchitis.

RIASSUNTO
La tosse cronica è la quinta causa che induce a consultare il proprio medico di famiglia nel mondo, in Italia è la terza. La tosse cronica in un adulto non fumatore che non assume ACE-inibitori ed ha una Rx torace nella norma può essere un sintomo indicatore di asma in una delle sue tre varianti: asma variante con tosse, tosse atopica e bronchite eosinofila. La diagnosi differenziale di queste tre patologie è oggetto di questa rassegna.

Parole chiave: Asma variante con tosse, bronchite eosinofila, iperreattività bronchiale, tosse atopica.

In some patients cough is a chronic unremitting symptom leading to a marked decrement in quality of life [1,2]. Chronic cough has been reported to be the fifth most common complaint seen by primary care physicians [3]. For instance, in USA up to 38% of a pulmonologist's outpatient practice is accounted for by persistently troublesome chronic cough [4]. In Japan, cough is the most frequent reason (11.7% of all) why patients visit clinics [5]. In Italy, cough is the third most common cause of medical visits with about 25 million consultancies for cough per year of which 5 million for the acute problem and 2 million for the chronic one (Dal Negro, personal communication). According to questionnaire surveys, the prevalence of chronic cough in the general population, including children, may vary from 9 to 33% [6]. Chronic cough is present in older subjects as may be seen from the average age of patients seen in cough clinics (Table I).

The most common causes worldwide of chronic cough in non-smoking, non-treated with ACE-inhibitor adults with normal chest radiogram include the upper airway cough syndrome (UACS), gastro-esophageal reflux disease (GERD) and asthma syndromes [4,7-15]. This indicates a group of related airway disorders including the "classic" asthma, the so-called cough variant asthma, nonasthmatic eosinophilic bronchitis (NAEB), and atopic cough. However, even if the guidelines on cough diagnosis and management [16-18] are followed in detail, the cause of chronic cough may remain unexplained in up to 33-46% of cases [6,19]. The prevalence of UACS, GERD and asthma syndromes varies in different reports [4,7-15]. This suggests the necessity of further examination to elucidate cough mechanisms and etiology [20]. The differences in prevalence may depend upon racial and life style differences, access to specialists or differences in the definition of some cough causes [21,22]. For instance, in the United Kingdom and Australia the two most common causes of cough are rhinitis for both (24% and 93% respectively), followed by asthma in UK (17.6%) and GERD in Australia (70%) [11,23]. In Turkey, eosinophilic bronchitis is the cause of chronic cough in 33.3% of patients, while post-nasal drip syndrome and GERD are each responsible for chronic cough in 22.2% of patients [24]. In Japan, cough variant asthma and atopic cough are

Alessandro Zanasi
UO Pneumologia, S. Orsola-Malpighi
Via Massarenti 9, 40138 Bologna (Italia)
email: alessandro.zanasi@aosp.bo.it

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TABLE I: COMMONEST CAUSES OF CHRONIC COUGH IN PATIENTS INVESTIGATED IN SPECIALIST CLINICS

Author	Patients' mean age in years (range)	Diagnosis (% of total)			
		Asthma syndrome	GERD	Rhinitis	Most common other causes
Irwin et al. 1981 [38]	50.3 (17-88)	25	10	29	Chronic bronchitis (12)
Poe et al. 1982 [39]	? (15-89)	36	0	8	Postinfectious (27)
Poe et al. 1989 [7]	44.8 (19-79)	35	5	26	Idiopathic (12)
Irwin et al. 1990 [4]	51 (6-83)	24	21	41	Chronic bronchitis (5)
Hoffstein 1994 [40]	47	25	24	26	Postinfectious (21)
O'Connell et al. 1994 [41]	49 (19-83)	6	10	13	Idiopathic (22)
Smyrnios et al. 1995 [42]	58 (18-86)	24	15	40	Chronic bronchitis (11)
Mello et al. 1996 [43]	53.1 (15-83)	14	40	38	Bronchiectasis (4)
Marchesani et al. 1998 [44]	51	14	5	56	Chronic bronchitis (16)
McGarvey et al. 1998 [10]	47.5 (18-77)	23	19	21	Idiopathic (18)
Palombini et al. 1999 [13]	57 (15-81)	59	41	58	Bronchiectasis (18)
Brightling et al. 1999 [11]	*	31	8	24	Postviral (13)

Definition of abbreviation: GERD, gastroesophageal reflux disease.
*No figures given for the total sample but mean age of 12/91 patients with eosinophilic bronchitis given as 52 (28-76) years.

major causes of isolated chronic non-productive cough [25]. Gastro-esophageal reflux-associated cough and post-nasal drip-induced cough, which are major causes of chronic cough in Western countries [26], are very rare in Japan [27].
Chronic cough can arise in asthma in various clinical settings, and is not always associated with airflow obstruction, wheezing or dyspnea. In addition, asthma may predominantly present with cough, which is often nocturnal; the diagnosis is supported by the presence of bronchial hyper-responsiveness [28]. Elderly people with asthma can also present with a history of chronic cough, with little or no wheezing. Cough is often the symptom most report-

TABLE II: COUGH CAUSED BY EOSINOPHILIC AIRWAY DISEASES

	Asthma	Cough variant asthma	Atopic cough	Eosinophilic bronchitis
Symptoms	Cough, breathlessness, wheeze	Cough only	Cough only	Cough and sputum
Atopy	Common	Common	Common	As in general population
Variable airflow obstruction	+	±	-	-
Airway hyper-responsiveness	+	+	-	-
Capsaicin cough hyper-responsiveness	±	±	-	+
Bronchodilator response	+	+	-	-
Corticosteroid response	+	+	+	+
Response to H_1 antagonist	±	±	+	NK
Progression to asthma	n/a	30%	rare	10%
Sputum eosinophilia (> 3%)	Frequent	Frequent	Frequent	Always (by definition)
Submucosal eosinophils	↑	↑	↑	↑
BAL eosinophilia	↑	↑	↓	↑
Mast cells in ASM	↑	↓	NK	↓
Basement membrane thickness	↑	↑	NK	↑

Definition of abbreviations: ASM, airway smooth muscle; BAL, bronchoalveolar lavage; n/a, not applicable; NK, not known.
+ = often present.
± = sometimes present.
– = not present.
↑ = increased.
↓ = not increased.

ed by patients with chronic asthma, despite the fact they have achieved good asthma control with inhaled corticosteroids [29]. Finally, cough can be the first sign of worsening of asthma; doctors should look for a fall in early morning peak flows [30].

As mentioned above, three asthma-related conditions, which are accompanied by chronic cough, have been described: cough-variant asthma, atopic cough, and eosinophilic bronchitis (Table II) [30].

Whether atopic cough represents a self-standing airway disease is still the object of debate [31]. In 1992 Fujimura and others proposed the existence of a bronchodilator-resistant non productive chronic cough associated with atopy which they termed "atopic cough" [32]. According to the authors [31], the pathological characteristics of atopic cough include eosinophilic tracheobronchitis without bronchoalveolar lavage (BAL) eosinophilia, and the physiological characteristics of atopic cough include cough hypersensitivity without bronchial hyperresponsiveness (BHR) [33]. Conversely, cough variant asthma [34] appears to be similar to asthma, with mild BHR and eosinophilic inflammation of central and peripheral airways, and a cough responsive to bronchodilator treatment [28].

Until the 1970s cough was commonly associated with episodic wheezing and dyspnea in symptomatic asthmatic patients. Corrao et al. [28] studied six patients with chronic persistent cough as the sole manifestation of bronchial asthma as diagnosed according to the criteria of the American Thoracic Society [35]: all had persistence for an average of six months, inducible diffuse airway bronchoconstriction and disappearance of cough with specific bronchodilator therapy. The return of cough when bronchodilators were discontinued, the disappearance of cough with the re-institution of this medication and the subsequent development of wheezing in two patients further supported the authors' contention that these cases represented a variant group of asthma [28]. Some years later Braman and Corrao [3] re-studied patients diagnosed with cough variant asthma and found that 37% of these patients had developed intermittent wheezing. As nearly 30% of patients with cough variant asthma have been found to develop typical asthma, cough variant asthma has been considered a precursor of typical asthma. However, the evolution of atopic cough, particularly with regard to its progression to typical asthma, has not been elucidated [31]. Determining whether atopic cough is a precursor of asthma may be important [36] in terms of the possibility of early intervention in asthma therapy.

In 2003 Fujimura et al. [31] examined retrospectively the onset of typical asthma, defined as wheezing and/or a dyspneic attack responding to inhaled β_2-agonists, in 82 patients with atopic cough (with probable or definite diagnosis) and in 55 patients affected by cough variant asthma with or without long term treatment with inhaled steroids. The median follow up period for patients with atopic cough and cough variant asthma was 4.8 and 3.7 years, respectively.

The diagnosis of **atopic cough** was made according to the following criteria proposed by the Japanese Cough Research Society:

1. Non-productive cough lasting for more than 8 weeks without wheezing or dyspnea.
2. Presence of one or more findings indicative of an atopic constitution, including a past history and/or complications of allergic diseases excluding asthma, peripheral blood eosinophilia (≥ 6% or ≥ 400 cells/mL), raised total IgE level in serum (≥ 200 IU/mL), positive specific IgE antibody to aeroallergens and positive allergen skin test and/or induced sputum eosinophilia (≥ 2.5%).
3. No bronchial reversibility, defined as less than a 10% increase in forced expiratory volume in 1 sec (FEV_1) after inhalation of 300 μg salbutamol sulphate.
4. Normal bronchial responsiveness (positive responsiveness being the provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) < 10 mg/mL).
5. Increased cough reflex sensitivity (capsaicin concentration eliciting five or more coughs (C5) ≤ 3.9 mmol/L).
6. Cough resistant to bronchodilator therapy (oral clenbuterol 40 mg/day plus inhaled procaterol or salbutamol at bedtime and on demand for ≥ 1 week).
7. No abnormal findings indicative of cough etiology on chest X-ray.
8. Normal FEV_1 (≥ 80% of predicted value), forced vital capacity (FVC) (≥ 80% of predicted value), and FEV_1/FVC ratio (≥ 70%).

When all criteria were satisfied, a definite diagnosis of atopic cough was made. If one or more criteria were not satisfied (or assessed), a diagnosis of probable atopic cough was made when all of the following were present: i) non-productive cough lasting more than 8 weeks without wheezing or dyspnea; ii) cough resistant to bronchodilator therapy; iii) presence of one or more findings indicative of atopic constitution as a global feature described above and/or induced sputum eosinophilia (≥ 2.5%); and iv) complete relief of cough after treatment with histamine H1-antagonists and/or corticosteroid therapy.

The complete relief of cough within 2 months of treatment was an important factor in making a probable diagnosis of atopic cough even if 2–3 weeks of oral corticosteroids were required for severe patients.

The diagnosis of **cough variant asthma** was made according to the following criteria proposed by the Japanese Cough Research Society: i) isolated chronic non-productive cough lasting more than 8 weeks; ii) absence of a history of wheeze or dyspnea, and no adventitious lung sounds on physical examination; iii) absence of postnasal drip to account for the cough; iv) FEV_1, FVC, and FEV_1/FVC ratio within normal limits; v) presence of bronchial hyperresponsiveness (PC_{20} < 10 mg/mL); vi) cough reflex sensitivity within normal limits (C5 > 3.9 mmol/L); vii) no abnormal findings indicative of cough etiol-

ogy on chest radiograph; and viii) relief of cough with bronchodilator therapy.

The efficacy of bronchodilator therapy was assessed according to the following criteria: i) 'excellent' when cough was totally resolved; ii) 'good' when sleep and daytime quality of life were improved; iii) 'fairly good' when severity and frequency of cough were somewhat decreased; and iv) 'poor' when the cough was unchanged. An assessment of 'excellent' or 'good' was judged as effective. When all criteria were satisfied, a definite diagnosis of cough variant asthma was made. If one or more criteria were not satisfied (or assessed), a diagnosis of probable cough variant asthma was made when all of the following were present: i) cough without wheezing lasting 8 weeks or more and no wheezes on auscultation; ii) no upper respiratory tract infection within 8 weeks; and iii) relief of cough with bronchodilator therapy.

The results showed that in patients with cough variant asthma the onset of typical asthma occurred in 5.7% of patients in the group treated with inhaled corticosteroid therapy and in 30% of patients in the group not treated. In patients with atopic cough the onset of typical asthma was confirmed in only 1.2% of the total. The onset of typical asthma was thus significantly less prevalent in patients with atopic cough than in those with cough variant asthma. In addition, long term inhaled steroids significantly decreased the development of typical asthma in patients with cough variant asthma. If mild asthma benefits from early intervention with long term inhaled steroids, it will be also useful for cough variant asthma. As atopic cough differs from cough variant asthma with regard to both outcome and pathophysiological features, the authors recommended that atopic cough be recognized as a new clinical entity characterized by isolated chronic non-productive cough [31].

Morice and McGarvey [37] in a letter to Fujimura and collegues expressed their dismay at reading the paper [31]. The diagnosis of "atopic cough", they claimed, would succeed only in adding further unnecessary complexity to the cough-related conditions [37]. The evidence to support a new clinical entity "atopic cough" they felt was tenuous and further hampered by the extremely vague term "probable atopic cough", that merely described atopic individuals with cough predominant asthma. Such diagnostic imprecision may yet have therapeutic consequences but Morice and McGarvey claimed that the authors did not provide sufficient information in the paper to conclude that these patients had failed to respond to steroids, and claimed that the response to bronchodilators was tested in neither a randomized nor a controlled way [37]. The "absence of transformation to typical asthma" was considered too heavily to differentiate atopic cough from asthmatic cough [37]. The lack of progression to typical asthma is well described both in atopic cough and in cough variant asthma, so it cannot be used to support the proposition that atopic cough is unique [37]. Summing up, Morice and McGarvey believe their clinical understanding of asthmatic cough is enhanced by the recognition that an individual patient may show different features of the disease process. The unnecessary subdivision into an arbitrarily defined "disease" such as atopic cough (or, indeed, eosinophilic bronchitis) is not helpful either diagnostically or therapeutically.

In conclusion, the confusion or lack of consensus in cough-related disorders may be affecting the etiology of chronic cough reported from various countries [21]. Issues such as site of inflammation, mediators involved, and allergens in "atopic" causes for these entities remain to be clarified in more detail in future studies [45].

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