CASE REPORT

Cough Variant Asthma: Case Report

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Abstract

Chronic cough prevalence was with the range of 11-13% of the global community. Higher prevalence rate was reported for Oceania, while the lower prevalence was in Africa. Chronic cough is with social, physical and psychological impact and many approaches proposed for its complex management**.** Cough is an important and common symptom of respiratory tract health problem. Cough variant asthma forms the etiology of cough in 30-50% of those with chronic cough. Chronic nonproductive may be the only symptom of asthma. We report a 54 year old male with chronic cough of 8 years duration. The case diagnosed by consultant allergologist as cough variant asthma and kept on treatment protocol. Unfortunately, immunotherapy is difficult to be performed in this case because of the wide range of hypersensitivity to food and inhalant allergens.

Keywords: Cough, Asthma, Cough variant asthma, Allergic rhinitis, Inhalant allergens, Food allergens, Refractory cough, Chronic cough, Allergic rhinitis.

Introduction

Chronic cough is defined as a cough lasting more than 8 weeks [1,2]. The cough may be of pulmonary or extra-pulmonary etiology [3]. Chronic cough prevalence was with the range of 11-13% of the community [4,5]. Recent meta-analysis of 90 studies reported a prevalence of 18.1% in Oceania, 12.7% in Europe, 11% in America, 4.4% in Asia and 2.3 in Africa [6].

Chronic cough is with social, physical and psychological impact and many approaches proposed for its complex management [1,2,5,7-10]. Multiple guidelines were developed for different geographical areas [1,11-17]. Recent review [3Poiten] summarized these guidelines. There are variable success in the treatment of chronic cough according to such guidelines [18-21].

In literature many studies reported the etiology and aggravating factors of chronic cough [2,7,20,22-28]. Cough is an important and common symptom of respiratory tract health problem [29]. Nonproductive chronic cough is a symptom of chronic health problem and thus in most cases the cough relieved during treatment course and relapsed after cessation of treatment [2,3]. Asthma is a chronic respiratory disease with prevalence of 4.4% to 7.6% in the Middle East [30] that characterized by immunologic, inflammatory and metabolic changes [31-40]. Comorbid allergic rhinitis was common in patients with asthma (61.6%) as compared to non-asthmatic individuals (6%) (Odd Ratio [OR] = 25.5;P< 0.0001).[41].

Recent studies may suggest that asthma is a syndrome and it is with several different phenotypes [42- 44]. Cough variant asthma forms the etiology of cough in 30-50% of those with chronic cough [43]. Chronic nonproductive may be the only symptom of asthma [44-47]. Although many definition were proposed for cough variant asthma, both classical asthma and cough variant asthma were the same, however, CVA preceded classical phenotype [42,46,48,49]. The pathophysiology of asthma is complicated and involved many inflammatory, immunological, enzymatic responses and activities that associated with nervous system involvement [42,44, 48-61].

Case report

A 56 years old Male presented to the clinic with prolonged dry cough with no history of wheezing. The cough was of 8 years duration. He consulted internist physician, ENT specialist,

Dermatologist, Allergologist, and General practioners. He received treatment that include antihistamine, Antibiotics, decongestant, and sore throat lozenges. Endoscopy of pharynx and larynx was normal, however, spirometry not performed. Ultrasonography of the thyroid gland was normal. Allergy test to determine IgE specific antibodies for food and inhalant allergens were performed using kit from MEDIWISS Analytic GmbH, Uerdinger Straße 3; D-47441, Moers, Germany and their results are shown in Table 1-3. There are high rate of hypersensitivity for both food and inhalant allergens. For food allergens, 16.7% (5/30) of the tested allergens show significant increase of IgE, while 30% (9/30) show slight increase, Table 1. For inhalant allergens, IgE significantly increased in 6.7% (2/30) of tested allergens, while slight increase demonstrated in 33.3% (10/30), Table 2. Unfortunately, immunotherapy is difficult to be performed in this case because of the wide range of hypersensitivity to food and inhalant allergens.

The case was diagnosed as CVA according to the criteria previously reported [54]. And kept on treatment protocol that include leukotriene receptor antagonist (Montelukast), Fexon, and aminophylline hydrate (phyllocontin prolonged release tablet).

Discussion

Asthma may be recognized as a syndrome that involve multiple organ of the entire airway and subsequent metabolic abnormalities [41]. The pathophysiology of asthma involved complicated scenario of events which involve a cascade of immune responses, inflammatory processes, and neurotic disorders that may attributed to metabolic and haematologic changes with time [31-41]. Glauser in 1972 first described cough variant asthma [62] as a phenotype of asthma. Both CVA and classical asthma are sharing airway hyperresponsiveness (AHR) as the main underlying pathophysiological mechanism [44]. However, AHR and airway remodeling are milder in CVA subjects as compared to classical asthma [48,55-57,63].

Previous studies indicated that there was no significant difference between classical asthma and CVA for many biomarkers in blood and sputum such as increased percentage of eosinophils [64], interleukin 8 (IL-8), eosinophilic cationic protein, levels of exhaled nitric oxide (FeNO) [64,65-68]. CVA early diagnosis is important as the treatment prevent the progression of CVA to classical asthma [29]. Recent studies suggested many biomarkers for diagnosis and treatment and prognosis monitoring of patients with asthma [29,31-

41,65,66,68-75]. Eosinophils oxidative injury to respiratory system in asthmatic patients was more substantial than that induced by neutrophils [76]. Thus hydrogen peroxide that was induced by eosinophils increased in asthmatic patients exhaled condensate [74,77-80]. Patients with CVA presented mostly with chronic nonproductive cough responsive to bronchodilator treatment.[81] Recognition of cough variant asthma is clinically important because bronchodilator treatment is only effective in cough variant asthma and can be prevented from progression to classical asthma [29].

Alobaidi [29] reported that hydrogen peroxide in breath condensate was significantly higher in patients with classical and cough variant asthma groups as compared to those with chronic cough nonasthmatic individuals and healthy control groups. patients with cough variant asthma show high level of expired breath condensate H_2O_2 than that in patients with chronic cough nonasthmatic and healthy control. Additionally, expired breath condensate pH was lower in CVA than that in subjects with chronic cough nonasthmatic subjects and healthy controls. Both the expired breath condensate H_2O_2 and pH in CVA were without significant difference between classical asthma and CVA.

The cough induction in CVA is not clear, however, previous study suggested that in CVA patients the inflammation was solely in large respiratory airway were cough receptors are abundant [82]. However, eosinophil tussive mediators may be responsible for the induction of cough in CVA [65,83]. Others suggested that local bronchoconstriction stimulated cough receptors and induced cough in subjects with asthma [67,69]. This explanation may be accepted since bronchodilators are effective in relieving cough in CVA [84]. However, previous studies reported normal pulmonary function test [85-87] or peripheral rather than central airway obstruction[88] at baseline. In CVA exercise [87] or methacholine challenge [85] revealed peripheral and central airways obstruction similar to classical asthma or predominant peripheral obstruction [87]. Baseline pulmonary function parameters did not show significant difference between CVA and classical asthma in the peripheral and central responsiveness [69].

Koh et al [89] suggest that CVA is without wheeze due to high wheezing threshold as compared to classical asthma. In addition, high

sensitivity of cough receptors in some individuals may be suggested as other mechanism for cough induction in CVA [90]. However, others not accept this explanation as mechanism for cough induction [84]. CVA is under-diagnosed in community [91] and thus CVA must be included in differential diagnosis of chronic cough [78,82,85,86] and this approach may prevent conversion of CVA to classical asthma.

Appropriate diagnostic procedures, including detection of inflammatory markers in expired breath condensate should be considered [29] . The presence of elevated H_2O_2 and reduced pH of expired breath condensate, which may suggest eosinophilic airway inflammation and possible diagnosis of cough variant asthma, may be of some help in the initial assessment of patients with chronic cough.[29].

In none proper treatment of classical asthma may lead to irreversible pathological changes that was induced by persistent inflammation [92]. This pathological changes may present in CVA as previous study indicated [29]. Inhaled corticosteroids early use may lead to good prognosis in classical asthma [93] and this may be the same in CVA, however, this warranted further detailed investigation. About 1/3 of CVA develop classical asthma [85,94]. Early diagnosis of CVA and the use of the inhaled corticosteroids is of good prognosis in prevention of conversion from CVA to classical asthma [82,95]. Some investigators suggested the use of steroids in the diagnosis of CVA [96-99], however, this may misclassify atopic cough with CVA as steroids also effective in control of atopic cough [82].

The patients kept on treatment protocol that include leukotriene receptor antagonist (Montelukast), Antihistamine (Fexon), and bronchodilator [aminophylline hydrate (phyllocontin prolonged release tablet)]. After 48 hours, patients improved clinically, however, the cough not completely disappeared. Good outcome of the treatment may be suspected if the guideline followed thoroughly. The new concept of central and peripheral hypersensitivity and neurophenotypes attributed to understanding of the physiopathological mechanisms of chronic cough including CVA [3]. This new concept encourage researchers to develop new drugs for the treatment of chronic or refractory cough or CVA. In chronic cough management, asthma assessment must be performed [100,101]. In 14% to 41.3% of

chronic cough cases classical and CVA are the underlying etiology [102,103].

The chronic hypersensitivity syndrome (CHS) concept developed [104] and considered clinically relevant by the European Respiratory Society (ERS) Task Force [105]. Upper airways and larynx were with hypersensitivity in those with CHS. The sensory nerve of the airway is hypersensitive to the irritants due to mucosal cough receptors upregulation and afferent nerve activity triggered by cough receptor as a response to cough provoking stimuli such as acids, heat and arachidonic acid derivatives [106-108].

Hull Airway Reflux Questionnaire was developed for the diagnosis of chronic hypersensitivity syndrome [109] with high specificity and sensitivity. Three phenotypes of CHS were identified: [110].

a) Th2-cell dominant phenotype (cough variant asthma or non-asthmatic eosinophilic bronchitis)
b) predominant phenotype of rhinal symptoms (such as Upper airway cough syndrome); and
c) predominant phenotype characterized by acid reflux and heartburn (gastroesophageal reflux cough). Additionally, refractory chronic cough is considered to be a phenotype of the cough hypersensitivity syndrome [10580].

Recent review [106] described the mechanisms that were involved in cough reflex hypersensibility. The mechanisms involve both *peripheral sensitization (inflammatory-mediated sensitization of cough fiber afferent nerve with subsequent reduced threshold for cough in upper and lower airways) and central sensitization (increased excitability in central sensory pathways).[106].* In addition, Belvisi [111] postulated the concept of neurophenotype in respiratory disease. He suggested that there were airway nerve function specific changes in response to irritants in different respiratory diseases [111]. However, this concept warranted detailed analysis to clarify the involved underlying mechanisms [3].

Refractory and unexplained chronic cough treatment reviewed recently [112] and four therapeutic approaches were proposed, which include: Inhaled corticosteroids (Eosinophilic airway inflammation); non-pharmacologic therapy (Speech pathology therapy); Neuromodulatory therapy (targeting neural pathways and others (Macrolides, esomeprazole, ipratropium.

Previous studies reported that centrally acting neuromodulators (amitriptyline, gabapentin, pregabalin, baclofen, and morphine) may improve the quality of life in those with chronic cough [113-119]. In contrast, erythromycin or esomeprazole or azithromycin treatment was not effective in control of chronic cough [120-122]. Smith et al [123] in a randomized, double-blind, placebo-controlled, cross-over study reported that sodium-channel inhibitor not shows any effect on the control of cough. Brozmanova and Pavelkova [124], In their review suggested that vagal C-fibers activity inhibition form a sound approach for the development of effective antitussive drugs. The research not revealed effective antitussive drugs and centrally acting antitussive drugs were with unwanted side effects. However, they suggests that topical drug application may conserve the effective antitussive activity without centrally induced side effects [124].

Sodium-channel inhibitor (voltage gated) are an attractive chronic cough therapeutic approach as there are many parallels between chronic cough and chronic neuropathic pain [124] . Transient receptor potential vanilloid receptors that trigger afferent nerve activity in response to cough-provoking stimuli (heat, acid, arachidonic acid derivatives) [106-108] antagonists (XEN-D0501 and SB-705498) did not induce any improvement on cough frequency despite a clear pharmacological effect on cough reflex sensitivity to caspain.[125,126]. While P2X3 receptors antagonists (AF-219) found to be effective in treatment of chronic cough and 75% of cough frequency reduced as tested in a double-blind, placebo-controlled, 2-period, crossover study in the UK [127].

Refractory cough in asthmatic patients may be controlled with treatment with tiotropium by modulating cough reflex sensitivity [128]. The emergence of neurobiological role in chronic cough induction and control may suggest an additional approach for antitussive drug development. Introduction of the cough hypersensitivity syndrome concept may open a new era in the determination and treatment of chronic cough [129]. In mice, emodin regulate notch pathway and mitigate airway inflammation of cough variant asthma [130]

In conclusion, cough variant asthma may treated with leukotriene receptor antagonist, Antihistamine and bronchodilator. However, the emergence of neurobiology concept in allergy induction and treatment

warranted performance of research for development of new safe drugs without central neural side effects. Inhaled lidocaine preceded by bronchodilator may be an alternative therapeutic protocol used in the treatment of CVA.

Table 1. IgE serum levels for Food Allergens

Allergen	IgE IU/Ml	Class
Control [Ctrl]	**53.5**	**5.0**
Milk [F2]	**0.00**	**0.0**
Egg white [F1]	**0.00**	**0.0**
Sunflower seed [F114]	**1.00**	**2.0**
Egg yolk [F75]	**0.02**	**0.0**
Peach [F95]	**2.50**	**2.0**
Soy bean [F14]	**0.00**	**0.0**
Banana [F92]	**0.00**	**0.0**
Olive [F458]	**0.30**	**0.0**
Strawberry [F44]	**0.07**	**0.0**
Tomato [F25]	**2.30**	**2.0**
Carrot [F31]	**3.70**	**3.0**
Cacao [F93]	**0.00**	**0.0**
Kiwi [F84]	**0.43**	**1.0**
Fig [F328]	**8.20**	**3.0**
Broad bean [F500]	**0.41**	**1.0**
Orange [F33]	**4.30**	**3.0**
Hazelnut [F17]	**1.20**	**2.0**
Pistachio nut [F203]	**1.10**	**2.0**
Cod fish [F3]	**0.00**	**0.0**
Apricot [F237]	**5.90**	**3.0**
Meat mix [Fx23]	**0.00**	**0.0**
Gluten [F79]	**0.00**	**0.0**
Sesame seed [F10]	**2.10**	**2.0**
Potato [F35]	**1.50**	**2.0**
Garlic [F47]	**0.00**	**0.0**
Pepper [F263]	**0.27**	**0.0**
Aubergine [F267]	**1.00**	**2.0**
Walnut [F256]	**0.75**	**2.0**
Raspberry [F343]	**4.00**	**3.0**
Almond [F20]	**0.02**	**0.0**

Table 2. IgE serum levels for Inhalant Allergens

Allergen	IgE IU/Ml	Class
Control [Ctrl]	35.2	4.0
D. Pteronyssinus [D1]	0.00	0.0
D. farinae [D2]	0.00	0.0
Cockroach [l6]	0.00	0.0
Camel hair [E17]	0.13	0.0
Absinthe [W5]	2.00	2.0
Oak, White [T7]	0.40	1.0
Olive [T9]	2.80	2.0
Cypress [T23]	0.66	1.0
Mulberry [T70]	3.10	2.0
Timothy grass [G6]	0.74	2.0
Mixed grasses [Gx]	0.96	2.0
Grain pollen MIX [Gx12]	6.70	3.0
Ragweed [W1]	3.80	3.0
Mugwort [W6]	0.64	1.0
Parietaria (Wall pellitory)[W21]	2.10	2.0
Sweet vernal grass [G1]	0.54	0.0
Nettle [W20]	0.97	2.0
Chenopodium album [W10]	1.70	2.0
Camomile [W206]	0.00	0.0
Cat epithel [E1]	0.00	0.0
Candida albicans [M5]	0.00	0.0
Dog epithel [E5]	0.00	0.0
Feather mix. [Ex70]	0.27	0.0
Parrot/Budgerigar/Hollandicus [Ex8]	0.23	0.0
Cow/Sheep [Ex9]	0.00	0.0
Chicken feather [E85]	0.00	0.0
Penicillium notatum [M1]	0.00	0.0
Aspergillus fumigatous [M3]	0.00	0.0
Cladosporium herbarum [M2]	1.10	2.0
Alternaria alternate [M6]	0.83	2.0

Table 3. Classes Categorization Criteria

Class	IgE range IU/ml	Interpretation
0	0.00 – 0.34	Not or hardly present
1	0.35 – 0.69	Low threshold
2	0.70 – 3.49	Slight increase
3	3.50 – 17.49	Significantly increased
4	17.50 – 49.90	High
5	50.00 – 100.00	Very high
6	➢ 100	Extremely high

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