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Application of XOLAIR® (Omalizumab) in adolescent refractory chest tightness variant asthma

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Abstract. – BACKGROUND: Asthma can manifest in a variety of clinical phenotypes like cough variant asthma, chest tightness variant asthma (CTVA), and masked asthma. Patients with CTVA usually have a singular or primary complaint of chest tightness, which is often overlooked or misdiagnosed due to the lack of characteristic asthma symptoms. We hereby report a case of CTVA managed by omalizumab.

CASE REPORT: A 15-year-old female patient reported to us with repeated coughing persisting for 3 weeks. Initial treatment with standard asthma drugs had minimal effect. Later during the disease, chest tightness became the primary symptom, and she was managed with steroids, β2 receptor agonists, and leukotriene receptor agonists but without complete relief. Based on clinical signs and symptoms, the response to baseline drugs, and results of bronchial provocation test, the diagnosis was revised to CTVA, and the patient was started on Omalizumab in addition to baseline drugs, which significantly improved her condition.

CONCLUSIONS: CTVA is difficult to diagnose due to its insidious symptoms and poor characteristics. Improper treatment can lead to uncontrolled disease, negative psychological issues, and reduced quality of life. Comprehensive assessment of children's airway inflammation level, lung function, bronchial provocation test, and responsiveness to drug therapy should be performed for accurate diagnosis. Omalizumab in combination with standard drugs can significantly improve the outcomes of CTVA.

Key Words:
Asthma, Chest tightness, Monoclonal antibody, Diagnosis.

Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation and airway hyperresponsiveness, with recurrent episodes of wheezing, coughing, shortness of breath, and chest tightness. The onset or exacerbation often occurs at night and/or early morning. The specific manifestations of respiratory symptoms and severity vary with time and are often accompanied by reversible expiratory airflow limitation and obstructive ventilation dysfunction[1,2].

In addition to these typical symptoms, asthma can also manifest in a variety of clinical phenotypes like cough variant asthma (CVA), chest tightness variant asthma (CTVA), and masked asthma. Patients with CTVA usually have a singular or primary complaint of chest tightness, which is often overlooked or misdiagnosed due to the lack of characteristic asthma symptoms[3]. Chest tightness and chest tension can be accompanied by breathlessness and are relieved by deep breathing. Due to the limited expressive ability in children, such patients often show sigh-like breathing, which is an important clinical manifestation of chest tightness[4-7].

As early as 1973, Farr et al[8] have reported patients with chief complaints of chest tightness, normal physical examination, laboratory tests, and pulmonary function who were effectively treated with bronchodilators. In 2013, Shen et al[6] proposed the concept of CTVA, and in 2014 Zhong[9] and Irwin[10] confirmed the existence of CTVA phenotype. Such variations have important clinical implications to recognize that chest tightness may be asthma, rather than a common cardiovascular disease. While most of the reported cases of CTVA have been treated with standard asthma therapy, there is limited information in the literature on the management of CTVA refractory to conventional treatment. We hereby report a case of CTVA managed by Omalizumab.

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Case Report

A 15-year-old female patient reported to our institute with repeated coughing persisting for 3 weeks. Coughing episodes were severe, seen mostly in the morning and night, and were aggravated by exercise, irritating odor, and cold air. There was no history of fever, wheezing, dyspnea, hoarseness, chest tightness, sighing, acid reflux, belching, early satiety, night sweats, weight loss, hemoptysis, or nocturnal sleep snoring. The patient was prescribed nebulized albuterol at a local hospital without any relief. At our institute, the patient was initially treated as a case of cough-variant asthma and managed by Singulair + Zyrtec which resulted in an improvement in symptoms.

The patient reported back after two weeks with sudden onset paroxysmal chest tightness and pain on deep breathing. The patient's medical history showed that she was born full-term and was delivered by cesarean section. She had a history of allergic rhinitis, chronic urticaria, and adenoid hypertrophy (no longer present), and the penicillin skin test was positive. There were no food allergies, no postnatal asphyxia rescue history, no underlying diseases, no recent respiratory tract infection and medication history, no history of foreign body inhalation, no involvement in strenuous exercise, and she did not have any apparent stressful relationships with her classmates or family. There was no history of chronic cough and smoking from her immediate family, but her father had chronic pharyngitis. On physical examination her BMI was normal, there was no three-concave sign, no cyanosis. Chest movements and breath sounds were normal. Cardiovascular, abdominal, and central nervous system examination was normal. Chest computed tomography, blood routine, electrocardiogram, echocardiography, myocardial enzymes, and the pulmonary ventilation function tests were normal. She was prescribed Seretide (100 μg) inhalation bid and oral Singulair (10 mg) QD, which improved her symptoms. However, after three months of therapy, the chest tightness became severe along with an episode of gasping and slight wheezing. The medications were changed to Seretide (250 μg) inhalation bid for six months + Singulair (10 mg) for three months + intermittent use of mometasone furoate nasal spray for symptomatic relief. With this treatment, she had occasional chest tightness (1-2 times/month, lasting less than one minute and relieved spontaneously after deep breathing). After three months of therapy, her rhinitis symptoms were assessed and she was found to have moderate nasal congestion, mild sneezing, mild runny nose, no nasal itching [Visual analog scale (VAS): 3 points], mild chest tightness, moderate shortness of breath, mild cough, and mild wheezing (VAS: 4 points). She was free from asthma symptoms for 20 days and her asthma control test score (ACT) score was 20.

After another three months, the patient developed a cough after exercising and had chest tightness and frequent gasping. At a local hospital she was prescribed Symbicort + Singulair + Asmemet + Salbutamol (1 inhalation each time, 2 inhalations in total), but without any significant improvement in symptoms. She later reported to our institute and was given intravenous methylprednisolone sodium succinate + montelukast sodium + nebulization which resulted in partial relief of symptoms. On clinical re-examination, we noted no nasal itching, mild nasal congestion, no sneezing, and no runny nose (VAS: 2 points). She had moderate chest tightness, mild shortness of breath, mild cough, no wheezing (VAS: 5 points), and an ACT score of 18. Bronchial provocation test was positive. She was then prescribed Seretide (250 μg) 1 inhalation bid + Singulair (10 mg) + Omalizumab. With this treatment, the bronchial provocation test turned negative and with three months of treatment, she was completely relieved of her symptoms. At the same time, the patient underwent a psychiatric evaluation which was suggestive of adolescent-onset behavioral and emotional disorders, and she was prescribed Zoloft. On further questioning of the family, it was noted that the suicide of the patient's classmate after the COVID-19 pandemic might have had a psychological influence on the patient.

Discussion

Chest tightness is a non-specific clinical manifestation seen in about 90% of adults and 49% of pediatric patients with asthma[11-14]. Research suggests that around 95% of pediatric chest tightness and chest pain symptoms are benign and mostly attributable to non-cardiac causes[15-17]. In a study by Kenar et al[18], out of the 76 children examined by the cardiologist for chest pain, none of them had actual heart disease. Chest tightness in children can be due to organic diseases like cardiac abnormalities, acquired heart disease, various arrhythmias; respiratory system diseases, such as respiratory infections, bronchial asthma, bronchial dysplasia, pleural effusion, pneumothorax;

digestive disorders like gastroesophageal reflux, peptic ulcers or related to non-organic causes like orthostatic intolerance and mental/psychological disorders[19,20]. Considering the several differential diagnoses of the symptom, the importance of detailed medical history and physical examination cannot be underestimated[15]. Chest tightness/pain should also be considered with other signs and symptoms like loss of consciousness, palpitations, and sweating which may suggest cardiac abnormalities, fever may indicate the possibility of infection, while rapid breathing and alteration of breath sounds are indicative of pulmonary diseases[21,22]. A Norwegian study[20] of 3,796 children aged 3-5 years assessing the association between chest tightness and respiratory infection in asthmatic and non-asthmatic children has shown a higher incidence of chest tightness in children with a history of infection. Furthermore, the prevalence of chest tightness was just 3.7% among children without asthma compared to 59.3% with asthma. Thus, it should be noted that chest tightness and chest pain could be the important presenting symptom of atypical asthma.

In the current case, the patient started coughing after strenuous work and her symptoms deteriorated with crowd gathering and exposure to an air conditioner. She had obvious chest tightness and chest pain along with fever during the disease but did not have any wheezing, syncope, heart palpitations, vomiting, or acid reflux. Physical examination showed no abnormality. Considering that the child and her father both had an atopic constitution, the child has no typical symptoms of asthma. Furthermore, as the initial anti-asthma treatment had achieved a certain effect, we proposed the diagnosis of CTVA. We believe that which examining such patients, physicians should consider a broader range of possibilities and conduct detailed examinations to improve the differential diagnosis. After excluding rare but potentially life-threatening conditions, the correct diagnosis can be achieved, and if necessary, empirical treatment can be used to improve the diagnostic accuracy.

The diagnosis of CTVA is indeed challenging and reports suggest a varying type of airway inflammation in such patients[6,7]. The variable airway airflow limitation and airway hyperresponsiveness often require further evaluation with pulmonary function tests[23-25]. Song et al[26] in a comparative study of CTVA, typical asthma, and healthy controls have shown that children with CTVA had levels of airway inflammation between normal and typical asthmatic children. There was no significant difference in pulmonary function parameters between CTVA and typical asthma, but there was more decreased small airway function than healthy children. Also, the results of the bronchial provocation test in the CTVA group were all positive. Similar findings have been reported by other studies[5,27]. Bronchial provocation test is an objective test of airway hyperresponsiveness, which is helpful for the diagnosis and differential diagnosis of asthma (especially for children with normal lung function). It also acts as an important guide for the early treatment of asthma[5,23-27]. In our case, chest tightness was the main manifestation, and based on medical history, physical examination, and various other diagnostic tests, we were unable to identify the root cause of the disease. In addition, empirical anti-asthma treatment did not completely control the disease. Regardless, while the bronchial provocation test was positive, we led to the diagnosis of CTVA.

Despite being a different variant, CTVA is treated on the same principles as typical asthma[16]. β2 receptor agonists [or inhaled corticosteroids (ICS) or leukotriene receptor antagonists (LTRA)] can be administrated first as a diagnostic treatment for 1 to 2 weeks. Relief of symptoms such as chest tightness is helpful for final diagnosis. Once verified, the course of treatment is no lower than 8 weeks. Long-term treatment is required if recurrence occurs after discontinuation of the drug. In patients with a long history of the disease, combined treatment with ICS with long acting β2 receptor agonists (LABA) or LTRA is recommended as the initial treatment[19]. In our case, since the patient's initial course of the disease was short, LTRA was used for initial treatment, which achieved a certain effect. However, later during the disease, chest tightness became the main clinical manifestation, and the treatment plan was therefore adjusted to ICS+LABA+LTRA. However, even with intravenous corticosteroids (grade 5 anti-asthma drug treatment), the condition could not be controlled. Therefore, based on the clinical signs and symptoms, the response to baseline drugs, and results of bronchial provocation test, the diagnosis was revised to CTVA, and the patient was started on ICS+LABA+LTRA+Omalizumab (300 mg, once a month), which significantly improved the condition[28-30].

XOLAIR® (Omalizumab) is a new type of drug used for the treatment of severe or refractory asthma in recent years[28,31]. It is a highly humanized anti-IgE monoclonal antibody that has been

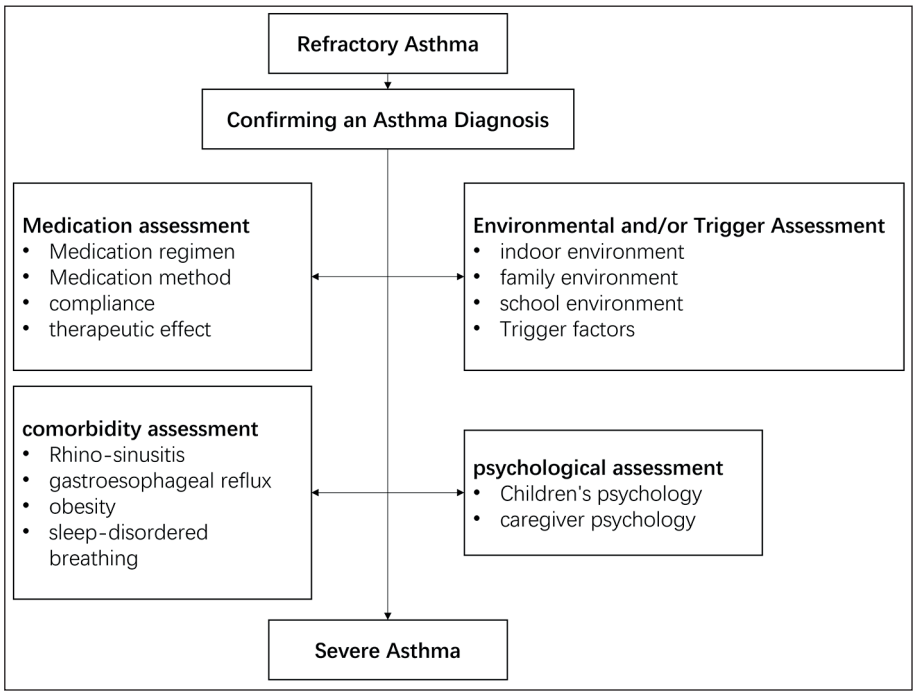

Figure 1. The evaluation process of refractory asthma.

approved for use in patients aged > 6 years with moderate to severe allergic asthma which cannot be controlled with ICS/LABA therapy[28,31]. The drug has a good safety profile and can be used for long-term treatment[28,29]. Research[29] suggests that adding biological agents to conventional treatment can more effectively control asthma, reduce exacerbation rates, reduce emergency room and hospitalization rates, and improve children's quality of life. However, it should be noted that the peak serum concentration of Omalizumab is reached 7-8 days after injection, and the half-life is 26 days[29]. For this specific case, after 3 weeks of Omalizumab treatment, the patient complained that the "drug had lost its effect" and chest tightness re-appeared. However, after adjusting the Omalizumab treatment to 150 mg, once every 2 weeks, the child's condition improved.

During the initial course of treatment, the lack of response to conventional therapy led us to repeatedly confirm if the child's anti-asthma drug administration technique was correct, and the drug compliance was good. We ensured that there was no adenoid hypertrophy, and the mild rhinitis symptoms were also controlled. It was repeatedly confirmed by the patient and the family that there were no triggering factors. Since the patient was an adolescent female, and her condition became worsened at the beginning of the school year, we suspected psychological factors (Figure 1 shows the evaluation process of refractory asthma[1]. The psychologist diagnosed the patient with adolescent-onset behavioral and emotional disorders. Zoloft was prescribed together with asthma control drugs; after that, the child's asthma was completely controlled.

Indeed, up to 20% of preschool children have mental health problems related to asthma and allergic diseases, and school-age children and adolescents are at higher risk for neurodevelopmental problems[32-34]. Data shows that 25% to 30% of asthma exacerbations in children and adolescents with asthma are associated with mood swings[32]. Therefore, for adolescent patients with asthma, especially when they are poorly controlled, screening for social, environmental, and psychological factors should be carried out, and appropriate intervention measures should be formulated[33,34].

Conclusions

CTVA is difficult to diagnose due to its insidious symptoms and poor characteristics. Improper treatment can lead to uncontrolled diseases, negative psychological issues, and reduced quality of life. Comprehensive assessment of children's

airway inflammation level, lung function, bronchial provocation test, and responsiveness to drug therapy should be performed for accurate diagnosis. Omalizumab, in combination with standard drugs, can significantly improve the outcomes of CTVA. Further studies on this uncommon variant shall aid in the diagnosis and management of CTVA.

Conflicts of Interest

The authors declare no conflicts of interest.

Ethical Statement

This study was approved by the Ethics Committee of Renji Hospital Affiliated to ShangHai JiaoTong University School of Medicine, with the No. 2021-037.

Informed Consent

Written consent was obtained by the patients.

Acknowledgments

Not applicable.

Authors' Contribution

BD conceived and designed the study; YL and YL were involved in literature search and data collection; YL and BO analyzed the data; YL wrote the paper; and YL reviewed and edited the manuscript. All authors read and approved the final manuscript.

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