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ORIGINAL RESEARCH

Clinical Characteristics of 31 Patients with Chest Pain Variant Asthma

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Purpose: Asthma is a major public health challenge in China. Although chest pain variant asthma (CPVA) is not common in clinical practice, there are still a few people who only or mainly manifest as chest pain. Here, we aim to introduce the characteristics of their symptoms, lung function and chest imaging features to arouse the attention of physicians to know better of the disease.

Patients and Methods: We retrospectively analyzed thirty-one patients who had been diagnosed with CPVA based on clinical data and positive bronchial provocation tests (BPTs).

Results: The mean age of all enrolled patients was forty-seven years, and females accounted for 64.5%. Main features of chest pain manifested as dull pain and mild pain with unfixed location, and several patients were presented with distending pain, pinprick pain, chest pain related to breathing, chest pain position-related and chest pain like angina pectoris. The median duration of their chest pain was four months, and 77.4% of the patients did not find any trigger. Among the 31 patients, 10 were with normal lung function, 14 were with mild obstructive ventilation dysfunction, 6 were with small airway dysfunction and 1 was with mild restrictive ventilation dysfunction. The predicted values of forced expiratory volume in 1 s (FEV_1) were greater than 80% in 29 out of 31 patients, and the values of other two patients were 74% and 79%, respectively. Additionally, 35.5% of the patients meanwhile had allergic rhinitis, and 64.5% of the patients exhibited type 2 inflammation. Among the 31 patients, 22 (71.0%) showed abnormalities on inspiratory computed tomography (CT) scans, including bronchiolar (38.7%), bronchial (25.8%) or pulmonary parenchyma abnormalities (32.3%). Only 7 patients (22.6%) had normal inspiratory CT scans.

Conclusion: CPVA is relatively rare in clinical practice. Understanding its manifestations, lung function, chest CT features and comorbidities is helpful for diagnosis and evaluation of patients with such symptoms.

Keywords: chest pain, atypical asthma, bronchial provocation test, chest computed tomography

Introduction

Asthma is a major public health challenge in China, which is worthy of attention. According to the results of China Pulmonary Health study, there are about 45.7 million adults with asthma among those aged 20 years or older.[1] Respiratory symptoms of wheeze, shortness of breath, cough and/or chest tightness are common typical features of asthma.[2] Patients with recurrent wheezing, shortness of breath, with or without chest tightness or cough whose symptoms are often worse at night or in the early morning and triggered by allergens, cold air, physical and chemical irritation, upper respiratory tract infection, exercise et al are considered to be with typical asthma.[3] Patients diagnosed as atypical asthma only show repeated cough, chest tightness or other respiratory symptoms without wheezing symptoms or wheezing sounds include cough variant asthma (CVA),[4] chest tightness variant asthma (CTVA)[5] and subclinical or potential asthma which manifests as asymptomatic bronchial hyperresponsiveness.[6] These atypical asthmatics form part of mild asthma and their pulmonary ventilation function is relatively normal, which is not easy to be paid attention to by doctors or patients themselves, resulting in more difficult to be diagnosed and easier to be missed or misdiagnosed.

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Bronchial provocation test (BPT) is the gold standard for the diagnosis of mild asthma.[7] People with mild asthma can still have severe acute attacks and even death after exposure to allergens or respiratory viral infection.[8] In addition, compared with adults, children with mild asthma have a higher prevalence, more symptomatic, and worse control.[8] Therefore, because of the genetic characteristics of asthma, the identification of atypical asthma in adults may also help to identify asthma in children. Nowadays, apart from the typical symptoms, atypical forms of asthma, such as CVA and CTVA were more easily diagnosed and treated by respiratory specialists compared to primary care practitioners.[9]

Although based on the Global Initiative for Asthma (GINA) chest pain decreases the probability of respiratory symptoms are due to asthma[10] there are still a few patients may only manifest or mainly manifest as chest pain.[11,12] They often cannot be correctly diagnosed for a long time, so they may go to visit the cardiologist or gastroenterologist. Sometimes they may be misdiagnosed as angina pectoris, reflux esophagitis or even mental illness, but their symptoms still did not relieve after taking related drugs. Here, we aim to introduce the characteristics of their chest pain, lung function and chest imaging to attract the attention of different levels of physicians, so that more patients can get correct diagnosis and treatment.

Materials and Methods

Patients and Study Design

Thirty-one outpatients who were diagnosed with chest pain variant asthma (CPVA) at Beijing Chao-Yang hospital were retrospectively studied from November 1, 2021 and October 31, 2022. We conducted a one-year follow-up of all patients through face-to-face interviews. The general information, clinical characteristics and complications such as rhinitis, urticaria and gastroesophageal reflux were recorded. We recorded the characteristics and causes of chest pain, chest tightness, cough and other clinical symptoms in detail. We recorded the characteristics and the causes of chest pain, chest tightness, cough and other clinical symptoms in detail. In this study, we used an 11-point Numerical Pain Intensity Rating Scale (PI-NRS) to measure pain intensity and record pain location.[13] The pain intensity includes none (0), mild (1–3), moderate (4–6), severe (7–10). We also collected the results of routine blood test, electrocardiogram, data of pulmonary ventilation function, BPT and chest high-resolution computed tomography (HRCT).

Inclusion Criteria

Chest pain was the only or main clinical manifestation; all patients underwent inspiratory chest HRCT scans to make sure there was no pulmonary infection, malignant tumor, pneumothorax and other conditions that can cause chest pain. All patients completed ECG examination to exclude related heart disease. At least one of the following tests has been performed: blood routine, serum immunoglobulin E (IgE), fractional exhaled nitric oxide (FeNO). All patients completed pulmonary ventilation function and BPTs.

Exclusion Criteria

Typical asthmatic patients with chest pain; CVA patients with chest pain; CTVA patients with chest pain; Acute respiratory infection within 2 months; Angina pectoris diagnosed by ECG and other examinations; patients with pneumothorax or hemoptysis in last two months; patients with comorbid severe systemic diseases.

Pulmonary Function Test

Spirometry measurements were performed by well-trained technicians using the PFT spirometer (Jaeger or Ganshorn) based on standard techniques according to ATS/ERS recommendations.[14] The following pulmonary function parameters were reviewed and analyzed in our study: forced vital capacity (FVC) and its predicted value, forced expiratory volume in 1 s (FEV_1) and its predicted value, FEV_1/FVC (FEV_1%), peak expiratory flow (PEF), forced expiratory flow (FEF) at 25% of FVC exhaled ($FEF_{25\%}$), FEF between 25% and 75% of FVC exhaled ($FEF_{25\%–75\%}$), FEF at 50% of FVC exhaled ($FEF_{50\%}$) and FEF at 75% of FVC exhaled ($FEF_{75\%}$). These parameters were presented the absolute value and/or as percentages of predicted values. These three parameters represent small airway function: $FEF_{25\%–75\%}$, $FEF_{50\%}$and $FEF_{75\%}$. Small airway dysfunction (SAD) was identified if two of the three parameters were lower than 80%.[15]

BPT was performed by using the forced oscillation technique (FOT). The Astograph Jupiter-21 airway reactivity meter is adopted to complete methacholine challenge test (MCT). The Astograph method (forced oscillation continuous tracing respiratory resistance method) is used. All patients were informed not to take montelukast, long-acting beta$_2$ agonists, theophylline, anticholinergic agents, inhaled or oral corticosteroids, antihistamines and other drugs that may affect airway reactivity within the previous 3 days before BPT. Operation process: the inhalation concentration of aerosol acetylcholine increases in turn, baseline airway resistance is measured, inhalation will be stopped when airway resistance level is twice the initial resistance, or wheezing occurs during auscultation, or airway resistance continues to rise for more than 2 minutes, then the minimum dose (Dmin) response threshold is recorded, according to the response threshold of excitation test. Divided into strong positive (0 ~ 3 unit), moderate positive (3 ~ 6 unit), positive (6 ~ 10 unit), weak positive (10 ~ 15 unit), negative (>15 unit). Respiratory specialists and well-trained technicians ensure the quality control and safety of the testing process.

FeNO

FeNO was measured at a constant flow (50 mL/s) in accordance with ATS/ERS recommendation[16] using a nitric oxide analyzer (NIOXMINO, Aerocrine, Solna, Sweden) before the spirometric assessments and BPT since the involved breathing maneuvers could distort FeNO results.[17]

Chest Images

Normally distal airways are not visible on CT, but when there is distal airway obstruction, chest CT can provide us with useful direct signs as outcome of direct visualization of the diseased small airways and indirect signs due to abnormalities in the parenchyma distal to the obstructed small airways.[18] Direct signs include centrilobular nodules and tree-in-bud opacities, while indirect signs include mosaic attenuation, air trapping, sub segmental atelectasis, wedge-shaped ground glass areas, cylindrical bronchiolectasis, centrilobular emphysema, mucoid impaction, and bronchiolar wall thickening.[18] We describe the above direct signs and part of indirect signs in this study, since all patients underwent only inspiratory chest HRCT scans. Definitions of terms for radiographic abnormalities refer to which published by Fleischner Society.[19] Analyses of chest CT were completed independently by two respiratory specialists who have worked for more than 15 years. When their opinions are different they would ask a senior radiologist for help to reach a consensus.

Type 2 Airway Inflammation

According to GINA definition of type 2 airway inflammation, we define type 2 airway inflammation in our study when the following criteria are met: blood eosinophils ≥150 cells/μL and/or FeNO ≥ 20 ppb and/or serum immunoglobulin E levels ≥ 100 IU/mL since no patients performed induced sputum detection in our study.[10,20,21]

Statistical Analysis

Analyses were performed using IBM SPSS Statistics 23.0. Continuous variables are presented as mean and standard deviation or median and interquartile range (IQR) and categorical variables are presented as numbers (n) and percentages (%). Spearman correlation analysis was used to examine the relationship between Dmin and other variables. All tests of statistical significance were two-sided, and *P* values of less than 0.05 were considered statistically significant.

Results

Baseline Characteristics

Clinical data of thirty-one patients diagnosed with asthma based on positive BPTs from thirty-seven patients with chest pain were ultimately included. Baseline demographics are shown in Table 1. The mean age was forty-seven years, with females accounting for 64.5%. There were four male patients who were current or former smokers. 35.5% of all the patients meanwhile suffered from allergic rhinitis (AR). Among the 31 patients, 10 were with normal lung function, 14 were with mild obstructive ventilation dysfunction, 6 were with SAD, and 1 was with mild restrictive ventilation dysfunction. Except for one patient whose PEF was 76% of the predicted values, all patients had a normal PEF. Among

the 31 patients, 29 had predicted forced expiratory volume in 1 second (FEV_1) values greater than 80%, while the predicted values for the other two patients were 74% and 79%, respectively. See details in Table 1. One of the female patients with chest pain for more than 10 years was diagnosed with anxiety disorder by a psychiatrist. Before she visited our department, she took appropriate anxiety medication, but her chest pain did not relieve.

The main features of chest pain: the main symptoms were often dull and mild pain, one patient was with distending pain, one patient was with pinprick pain, two patients had chest pain related to breathing, one patient's chest pain was position-related and two patients presented with chest pain like angina pectoris who sought treatment in the emergency department. According to the patient's recall of their own chest pain, the distribution of pain intensity is shown in Table 2A. The location and area of pain were usually not fixed and can occur behind the sternum, in the anterior chest, and on the back. See details in Table 2B. The results of the duration of their chest pain lasted from one month to over ten years as shown in Table 2C. Chest pain often occurred intermittently and irregularly. The duration of chest pain attack ranged from transient such as a few seconds to several hours or days. There were seven patients accompanied with occasional chest tightness, four patients with occasional slight dry cough, two patients with throat itching, one patient with gastrointestinal symptoms such as acid reflux and belching, two patients had a slight decline in activity endurance when going upstairs among whom one was meanwhile with throat itching, two patients could not breathe smoothly among whom one was meanwhile with occasional slight dry cough and the other was meanwhile with pharyngeal itch. More details are shown in Table 2D. Most patients (77.4%) did not find any triggers of chest pain, and only seven patients were sensitive to cold air, cooking oil fumes, dust, pollen and strong smell such as smoke, respectively. See details in Table 2E. The pain intensity in most patients was not severe. Although it may be relieved spontaneously or by

Table 1 Baseline Data of Thirty-One Patients with Chest Pain Variant Asthma

Variables	All (31 Patients)
Age, years	47 ± 12
Male, n (%)	11 (35.5%)
BMI, kg/m^2	25.07 ± 3.65
Smoking, n (%)	4 (12.9%)
Duration of chest pain, months	4 (2, 24)
With reflux, n (%)	1 (3.2%)
With AR, n (%)	11 (35.5%)
With urticaria, n (%)	1 (3.2%)
With anxiety disorder, n (%)	1 (3.2%)
Eosinophilic count, cells/μL	110 (60, 330)
Percentage of eosinophils (%)	1.80 (0.83, 4.48)
IgE (13 patients), IU/mL	23.1 (16.1,121.0)
FeNO (18 patients), ppb	24 ± 9
FEV_1 (L)	2.85 ± 0.66
FEV_1, % predicted	94.2 ± 9.40
FVC (L)	3.74 ± 1.01
FVC, % predicted	102.1± 13.8
FEV_1/FVC (%)	77.1 ± 7.6
PEF, % predicted	102.2 ± 15.0
$FEF_{25\%}$, % predicted	95.0 ± 19.5
$FEF_{50\%}$, % predicted	77.0 (60.5, 89.0)
$FEF_{25\%\sim75\%}$, % predicted	71.6 ± 23.2
$FEF_{75\%}$, % predicted	58.2 ± 23.4

Abbreviations: BMI, body mass index; AR, allergic rhinitis; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; $FEF_{25\%}$, FEF at 25% of FVC exhaled; $FEF_{50\%}$, FEF at 50% of FVC exhaled; $FEF_{25\%\sim75\%}$, FEF at 25% to 75% of FVC; $FEF_{75\%}$, FEF at 75% of FVC exhaled.

Table 2 (A-E) Detailed Characteristics of Chest Pain: Intensity, Location, Duration, Accompanying Symptoms and Inducing Factor

A	
Intensity of chest pain[a]	Patient numbers
No pain	0
Mild	26
Moderate	3
Severe	2
B	
Location of chest pain	Patient numbers
Unfixed	18
Retrosternal or anterior chest	4
Left chest	5
Right chest	2
Back	2
C	
Duration time of chest pain	Patient numbers
1 month ≤~≤ 3 months	16
3 months <~≤ 1 year	4
1 year <~≤ 3 years	7
3 years <~≤ 5 years	3
5 years <~≤ 10 years	0
10 years <~≤ 15 years	1
D	
Accompanying symptoms	Patient numbers
None	16
Occasional chest tightness	7
Occasional dry cough	4
Pharyngeal itch	2
Acid reflux or belching	1
Slight shortness of breath	2
Disturbance in respiration	2
E	
Inducing factors	Patient numbers
Undefined	24
Cold air	2
Cooking oil fume	1
Dusty environment	1
Strong smell	2
Pollen	1

Notes: [a]Pain intensity was measured based on an 11-point Numerical Pain Intensity Rating Scale (PI-NRS) by patients themselves.

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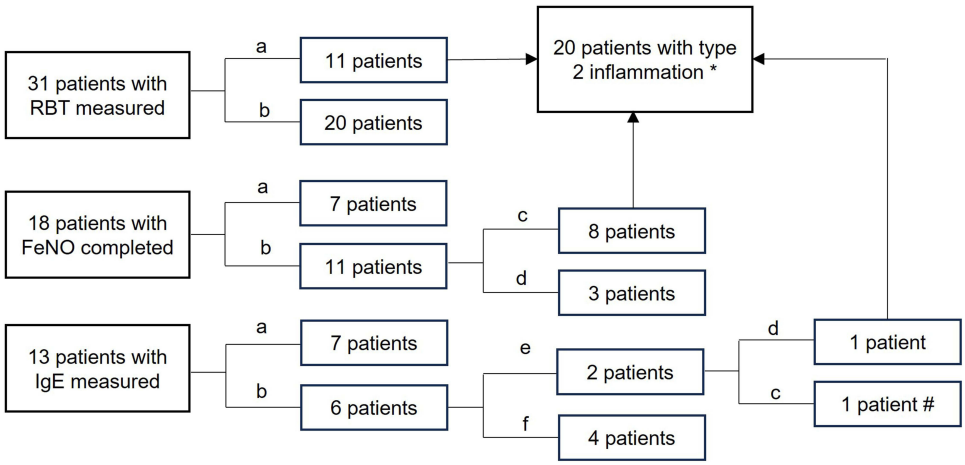

Figure 1 Patients with type 2 inflammation in 31 patients with chest pain variant asthma. Definition of abbreviations: RBT, routine blood test; a, eosinophil count (EC) ≥ 150 cells/μL; b, EC < 150 cells/μL; c, fractional exhaled nitric oxide (FeNO) ≥ 20 ppb; d, FeNO < 20 ppb; e, Immunoglobulin E (IgE) ≥ 100 IU/mL; f, IgE < 100 IU/mL. * Type 2 airway inflammation in our study when the following criteria are met: blood eosinophils ≥150 cells/μL and/or FeNO ≥20 ppb and/or serum IgE level ≥ 100 IU/mL. #One patient both had elevated FeNO and elevated level of serum IgE.

rest, taking oral traditional Chinese patent medicine, and going to community hospitals for infusion treatment, the pain could repeat at an uncertain time.

In this study, type 2 inflammatory asthma accounted for 64.5% (20/31). All patients took routine blood tests. FeNO was examined in 18 patients and serum levels of IgE were detected in 13 patients. There were 9 patients both with FeNO and IgE detected. The peripheral blood eosinophil count was above or equal to 150 cells/μL in 11 patients; 8 patients had FeNO ≥ 20 ppb in patients with eosinophils count less than 150 cells/μL; and 2 patients had elevated level of serum IgE ≥ 100 IU/mL in patients with eosinophils count less than 150 cells/μL among whom 1 patient both had elevated FeNO and elevated level of serum IgE. See details in Figure 1.

Among 31 patients, there were 22 patients (71.0%) with bronchiolar (38.7%) or bronchial (25.8%) or pulmonary parenchyma abnormality (32.3%) on inspiratory scan, and only 7 patients (22.6%) were with normal inspiratory CT scans. There were 4 patients with centrilobular nodules or tree-in-bud opacities, 8 patients with thickened lobular core, 8 patients with bronchial wall thickening, 4 patients (12.9%) with emphysema, 6 patients (19.4%) with mosaic attenuation, 1 patient with interstitial lung abnormality, and 1 patient with subsegmental bronchiectasis. See details in Table 3. Some patients had more than one abnormality so among them, 1 patient was with bronchiolitis and bronchitis and pulmonary emphysema on CT scan, 5 patients with thickened lobular core were meanwhile with bronchial wall thickening (2 patients), pulmonary emphysema (1 patients) and mosaic attenuation (2 patients), respectively. One patient with bronchial wall thickening was meanwhile with pulmonary emphysema. The chest CT images of female patient with chest pain for more than 10 years is showed in Figure 2A–C.

Table 3 Chest HRCT Images of Thirty-One Patients with Chest Pain Variant Asthma

Overall Evaluation	Signs on HRCT	Patient Numbers
Bronchiolar abnormality	Centrilobular nodules or tree-in-bud opacities	4
	Thickened lobular core	8
Bronchial abnormality	Bronchial wall thickening	8
Pulmonary parenchyma abnormality	Pulmonary emphysema	4
	Mosaic attenuation	6
Other abnormalities	Interstitial lung abnormality (ILA)	1
	Sub segmental bronchiectasis	1
Normal		7

Abbreviation: HRCT, high-resolution computed tomography.

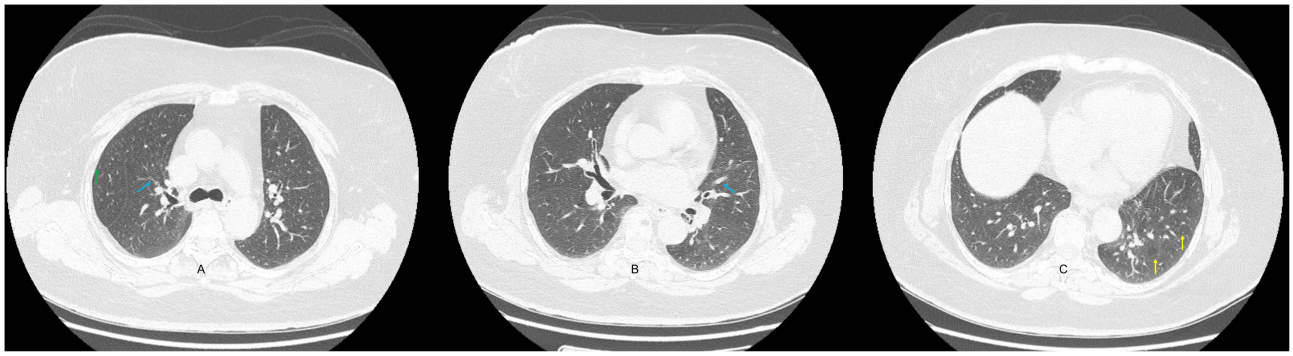

Figure 2 (**A**–**C**) HRCT of chest from a fifty-three-year-old female patient. She had intermittent chest pain for more than 10 years. The inspiratory CT was scanned on July 22th 2022 from which we can see the presence of subpleural bronchiolitis (**A**, green arrow), bronchial wall thickening with the presence of mucus plugs which suggests bronchitis (**A** and **B**, blue arrow) and also multiple low attenuation areas which indicates local hyperinflation in the lower left lung (**C**, yellow arrow).

Among the 10 patients with normal pulmonary ventilation function, three patients also had normal imaging examinations. In addition, one patient developed bronchitis, three patients experienced thickening of the lobular core and 3 patients experienced mosaic attenuation.

Treatment and Follow-Up

Among the thirty-one patients diagnosed with asthma, twenty-five patients received inhaled corticosteroid-long-acting beta$_2$ agonist (ICS-LABA) (twenty-one patients received budesonide-formoterol, four patients received salmeterol-fluticasone combined with salbutamol for emergency use) among whom seventeen patients received montelukast meanwhile, three patients took oral montelukast who refused to use ICS-LABA for fear of side effects of ICS inhalation, and the other three patients who believed that the symptoms were mild refused to use any other drugs except compound methoxyphenamine capsule.

We conducted face-to-face interviews with them one year after they were diagnosed with CPVA. Most of the patients had obvious relief of chest pain after 2–4 weeks of medication treatment. The duration of medication was 1 month in 21 patients, 2 months in 2 patients and was more than 3 months in 5 patients. The anxiety disorder in the female patient gradually disappeared with her chest pain after she received budesonide-formoterol for treatment. The reason for the short treatment time of patients included: chest pain completely or mostly relieved which does not affect normal work and life, unwilling to revisit the doctor because of busy work and worrying about the side effects of medication and so on.

Discussion

According to our study results, we mainly found that chest pain was often dull pain without a fixed location and the attacks were often irregular without precipitating factors. 35.5% of the patients were complicated with AR, 64.5% of the patients had the characteristics of type 2 inflammation, and 71.0% of the patients had abnormal chest HRCT findings including bronchiolar or bronchial abnormalities or pulmonary parenchyma abnormality due to the distal obstructed small airways. In our study, nearly one-third of the patients were with normal lung function.

In China, according to CPH study, the prevalence of asthma among adults over twenty years old is 4.2% and 26.2% of them already had airflow limitation.[1] The common symptoms of asthma include: wheeze, shortness of breath, chest tightness and cough.[10] Asthma is still a worldwide serious health issue, since there were great share of patients being far from correct and timely diagnosis and optimal management especially in atypical patients, in relatively sedentary patients or in undeveloped areas. Chest pain is also one of the atypical symptoms of asthma, with some patients being accompanied by wheezing or chest tightness, and some patients showing chest pain as only or main manifestation.[12]

Now, studies had shown that the asthma-associated inflammation evident in the large airways occurs in the distal airways as well. Although there are differences of inflammatory process between the two regions, the similarities are pronounced, including infiltration of activated T lymphocytes and eosinophils, increased mucus plugging, and smooth muscle hyperplasia.[22] Asthma is characterized by variable symptoms and expiratory airflow limitation, which may vary over time and intensity and may resolve spontaneously or in response to medication.[10] BPT is a good option for documenting variable

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expiratory airflow limitation, especially in patients with suspected atypical asthma or mild asthma to assess airway hyperresponsiveness (AHR).[7,10] Small airway function decreased more significantly and are easier to be detected compared to large airway. A previous retrospective research found that $FEF_{25\%-75\%}$ and $FEF_{75\%}$ were positively correlated with Dmin that means a lower $FEF_{25\%-75\%}$ or $FEF_{75\%}$ were associated with a lower Dmin that corresponds to higher AHR.[23] The similar results were found in our study (supplementary Table 1). Small airway parameters play good auxiliary diagnostic value in those areas where BPT cannot be performed. Detectable predictive cut-off values of $FEF_{25\%-75\%}$ for AHR do not exist since even normoreactive subjects can show lower $FEF_{25\%-75\%}$ values, whereas $FEF_{25\%-75\%}$ may play a role in the management of asthma when FEV_1 and FEV_1/FVC are normal.[23] Therefore, if we follow up patients with SAD parameters after treatment, it may be meaningful for patients, especially those with normal FEV_1/FVC and FEV_1.

Atopic asthma is the most common form of asthma, affecting 70%–90% of children and about 50% of adult sufferers.[24] According to the definition of type 2 inflammation indicated by GINA, the proportion of type 2 inflammation in our study was at least 64.5%, since no patients performed induced sputum detection in this study and not all of the patients were tested for FENO and serum IgE. $FEF_{25\%-75\%}$ and $FEF_{50\%}$ combined with FeNO could predict asthma diagnosis in patients with normal FEV_1; $FEF_{25\%-75\%}$ or $FEF_{50\%}$ combined with eosinophils is also a very economic method to predict AHR in suspected asthma subjects with chest tightness.[15] In summary, we can see that impaired small airway function and type 2 inflammation are important features of atypical asthma and should be worthy of attention to the diagnosis of patients suspected to be with asthma.

Imaging of chest becomes an important modality to identify small airway disorders. According to results of thoracic HRCT imaging, we know that the distal airways are a major site of airway obstruction in patients with asthma and may play a significant role in AHR.[22] The clinical symptoms of patients may be subjectively influenced based on the patient's own feelings and state of activity. Not all patients are sensitive to their symptoms, but chest imaging is objective and easy to achieve, requiring sensitive eyes to identify subtle abnormalities that are different from completely normal. Imaging provides a novel noninvasive method to assess small airways in obstructive pulmonary disease. HRCT not only provides a very simple and direct assessment of large and medium airways (diameter >2-2.5 mm), but also gives an assessment of smaller airways.[18] Chest HRCT has helped us a lot in identifying small airway disease in patients with asthma and COPD through direct signs and indirect signs on HRCT, which also helps doctors identify these diseases early.[18] HRCT has provided a wealth of information about airway structure and function in asthma. Asthma is a disease characterized by ventilation heterogeneity (VH) in which lower lobe-predominant small-airway diseases play an important role.[25] Studies have demonstrated that VH markers derived by using impulse oscillometry or multiple-breath washout are associated with key asthmatic patient-related outcome measures and AHR. Despite significant advances in severe asthma, there remain innumerable research areas requiring urgent attention in mild asthma.[26] In our study, the proportion of patients with abnormal chest CT findings was 71.0% at the time of symptoms occurred. There were 70% of the patients with normal lung function were found to be with abnormal chest CT, which deserves our attention. We should realize that chest CT, even in atypical asthmatic patients, will provide us with useful information to help improve diagnostic accuracy, especially in areas where BPT is not available. In addition to assisting in diagnosis, chest HRCT can also serve as an important biomarker in our treatment follow-up in patients with asthma, which deserve our attention that chest CT abnormalities may be reversible with the improvements of patients' symptoms and lung function after treatment. Early study show us that the prominence of centrilobular structures is partially reversible after the successful control of asthma symptoms.[27] Furthermore, an early recognition of small airway involvement and early treatment may prevent complications and delay decline of lung function in both COPD and asthma.[18] Studies have shown that small-particle aerosols improve small airway function and inflammation better than large-particle aerosols in patients with asthma.[28]

Assessing the degree of small airways inflammation and impairment appears to be a pivotal step in the asthmatic patient's management since the deeper lung inflammation plays a critical role in asthma pathogenesis. It is now possible to evaluate them through direct and indirect measurements.[29] Severe asthma places enormous physical, mental, emotional, social and economic burdens on patients, which is often associated with multimorbidity. Comorbidities were highly prevalent and included chronic rhinosinusitis (49%), nasal polyposis (19%), oesophageal reflux (36%), overweight and obesity (47%) and depression (19%) in severe asthma patients.[30] Studies show that inflammatory pathways in mild asthma are as heterogeneous as in severe asthma[31] and we should describe mild asthma phenotypes using a multidimensional approach that includes AHR, exacerbation patterns, symptom burden, and inflammation.[26]

Type 2 inflammation is responsible for several airway diseases that often coexist together. The respiratory symptoms and anyone of the co-existing features including commencement of respiratory symptoms in childhood, a history of AR or eczema, or a family history of asthma or allergy, can increase the probability of diagnosis of asthma. Based on previous research data, 10%–40% of patients with AR have asthma.[32] In a study designed to identify the cause of chronic cough in patients with AR, it was found that 24.7% of patients were diagnosed with CVA.[33] In our study 35.5% of patients were with AR, and 3.2% of patients were with urticaria.

Limitations of this study include: firstly, partial data were missing since it was a retrospective study, secondly the sample size of this study was too small because it is a preliminary experimental study and more patients will be included in subsequent studies; Thirdly, patients have poor compliance and lack follow-up data. In addition, we only conducted the empirical judgment of chest CT image, and all patients performed only the examination of inspiratory chest CT scans in this study, so quantitative CT data were lacking.

Conclusion

CPVA is relatively rare in clinical work. The main characteristic of chest pain manifest as dull pain with unfixed location. We should pay more attention to the characteristics of CPVA including type 2 inflammation, SAD and abnormal chest imaging features and so on. It will be particularly helpful to improve the diagnostic awareness of clinicians especially in primary care clinics where BPT is unavailable but routine lung function tests and chest HRCT are widely used.

Abbreviations

CPVA, chest pain variant asthma; BPT, bronchial provocation test; PEF, peak expiratory flow; FEV1, forced expiratory volume in 1 s; CT, computed tomography; CVA, cough variant asthma; CTVA, chest tightness variant asthma; GINA, the Global Initiative for Asthma; HRCT, high-resolution computed tomography; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide; FVC, forced vital capacity; allergic rhinitis (AR); SAD, small airway dysfunction; FOT, forced oscillation technique; Dmin, the minimum dose; IQR, interquartile range; ICS-LABA, inhaled corticosteroid-long-acting beta$_2$ agonist; AHR, airway hyperresponsiveness; MCT, methacholine challenge test.

Ethical Approval

The present study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board for Beijing Chao-Yang Hospital (2023-ke-260). All the data were anonymized and maintained with confidentiality. A waiver of informed consent was provided from our ethics committee because of the retrospective nature of the current study. The patient with identifiable information in our manuscript provided informed consent and the subject agreed that the results might be published in a journal.

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Disclosure

The authors declare no conflicts of interest in this work.

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