To the Editor: Atypical asthma, such as chest pain variant asthma (CPVA), often leads to misdiagnosis. Patients with atypical asthma often do not present with wheezing and dyspnea and are frequently misdiagnosed with coronary artery disease (CAD), gastroesophageal reflux disease (GERD), and other diseases. The gold standard for diagnosing asthma is pulmonary function testing (PFT), although therapeutic tests are sometimes used. Several cases of CPVA have been reported in previous studies; however, this phenotype is sometimes overlooked.

Herein, we present two cases of CPVA at a tertiary hospital and show the clinical characteristics and pulmonary function of patients with chest pain, which subsided with bronchodilator use and without bronchial asthma attacks.

Case 1: On December 11, 2018, a 71-year-old woman presented with a complaint of migratory chest pain that had lasted for 3 years. She had no history of cough, wheezing, expectoration, or dyspnea. Her pain was not associated with nausea, vomiting, diaphoresis, pyrosis, or abdominal pain. The pain was non-pleuritic and was not fixed to any area but was mainly present in the upper left chest region. Sometimes the patient’s pain was induced after walking up three floors. Chest pain subsided spontaneously in summer and re-emerged in winter. The patient was a non-smoker and had no history of allergic rhinitis. She also had no family history of asthma. Three years previously, the patient was admitted to the cardiology department with suspected angina pectoris; however, the associated tests, including myocardial enzymology, electrocardiography (ECG), exercise testing, and computed tomography (CT) of the coronary artery, were normal. The patient was prescribed isosorbide dinitrate and metoprolol, but these medications did not relieve the pain.

The patient’s physical examination results were normal, with a blood pressure of 105/68 mmHg, a pulse rate of 80 beats/min, and a normal body temperature. Breathing sounds were normal on auscultation. Chest CT, ECG, complete blood counts, immunoglobulin E (IgE) concentration, and D-dimer concentration were also normal. Baseline pulmonary function studies [Table 1] revealed mild restrictive ventilatory dysfunction. Following four inhalations of albuterol (400 µg), the patient demonstrated a 45.5% improvement in forced expiratory volume in 1 s (FEV1), returning to her normal levels and establishing a diagnosis of asthma.

The patient initially inhaled formoterol and budesonide, and her pain subsided after 3 days. The patient ceased therapy after 3 months and did not experience pain until the following autumn. In October 2019, the patient used the inhaler again after experiencing pain recurrence, and we identified small airway obstruction, despite a normal forced vital capacity (FVC) and FEV1.

Case 2: A 56-year-old woman presented with an 8-year history of chest pain. She complained of severe chest pain in the evening, which was located behind the sternum. Sometimes the patient’s chest pain was relieved by sitting forward and taking shallow breaths. The patient reported no associated nausea, vomiting, diaphoresis, tobacco use, hypertension, diabetes mellitus, or hyperlipidemia. She had no family history of asthma but had mild allergic rhinitis for several years. She had an occasional cough without sputum. The patient was diagnosed with CAD 8 years before; however, coronary artery and chest CT, ECG, myocardial enzymology, IgE, and D-dimer concentration were normal. Clopidogrel and isosorbide dinitrate failed to provide symptomatic relief. In 2018, the patient was diagnosed with cholelithiasis and GERD. She underwent endoscopic retrograde cholangiopancreatography and anti-reflux treatment. However, chest pain persisted.

On October 10, 2019, the patient visited our hospital and underwent a scheduled methacholine inhalation challenge test. Her baseline pulmonary function was normal...
Table 1: PFT results of the two patients with chest pain variant asthma.

<table>
<thead>
<tr>
<th>Items</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Post-albuterol</td>
</tr>
<tr>
<td>FVC (L)</td>
<td>1.41 (predicted 1.95)</td>
<td>2.05</td>
</tr>
<tr>
<td>FEV₁ (L)</td>
<td>1.12 (predicted 1.59)</td>
<td>1.63</td>
</tr>
<tr>
<td>FEV₁% pred (%)</td>
<td>70.44</td>
<td>102.52</td>
</tr>
<tr>
<td>FEF₅₀/FVC (%)</td>
<td>79.43</td>
<td>79.51</td>
</tr>
<tr>
<td>PEF (L/s)</td>
<td>4.78 (predicted 5.07)</td>
<td>6.24</td>
</tr>
<tr>
<td>MMEF (L/s)</td>
<td>0.59 (predicted 2.39)</td>
<td>1.70</td>
</tr>
<tr>
<td>FEF₅₀ (L/s)</td>
<td>1.10 (predicted 3.08)</td>
<td>2.41</td>
</tr>
<tr>
<td>FEF₇₅ (L/s)</td>
<td>0.18 (predicted 0.92)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

FEV₁: Forced expiratory flow; FEF₅₀/₇₅: Forced expiratory flows at 50% and 75% of the exhaled vital capacity; FEV₁: Forced expiratory volume in 1 s; FEV₁% pred: Percentage of predicted FEV₁; FVC: Forced vital capacity; MMEF: Maximum mid-expiratory flow; PEF: Peak expiratory flow; PFT: Pulmonary function testing.

The methacholine challenge test revealed a significant bronchoconstrictive response with a decrease in FEV₁ by 37.2% compared with baseline, indicating a diagnosis of asthma.

The patient was first treated with a combination of inhaled formoterol and budesonide. PFT revealed that both FEV₁ and FVC were raised compared with the first PFT (2.06 vs. 1.72 L and 2.44 vs. 2.02 L, respectively). Two months later, the patient’s symptoms subsided.

Asthma presents in various ways apart from typical symptoms of recurrent episodes of wheezing, dyspnea, chest tightness, and coughing. Asthma also manifests as various clinical phenotypes, including chest pain. Improving physicians’ awareness of these clinical phenotypes can help to reduce asthma misdiagnosis. However, CPVA is under-recognized; thus, efforts to analyze this asthma phenotype are warranted.

The concepts of CPVA and bronchial asthma with chest pain should be differentiated. CPVA is defined as chest pressure that improves in response to a bronchodilator, without characteristic attacks, whereas bronchial asthma with chest pain is defined as chest pressure with bronchial asthma attacks, including wheezing and dyspnea. However, chest pain as one of the chief symptoms of asthma is frequently neglected and underestimated. Golshan analyzed a total of 232 non-smoking patients with chest pain in whom heart disease had been ruled out. They found that 33 of these patients had asthma and chest pain which disappeared with asthma treatment in all patients. Another study found that 14.8% of patients who attended a chest pain cardiology clinic had airflow obstruction, suggesting that airflow obstruction may be an important differential diagnosis in patients referred to a secondary care chest pain clinic.

Both cases in this study presented with chest pain as the main symptom in the absence of wheezing and persistent cough. The diagnosis of CPVA was confirmed by documentation of reversible airway obstruction with a PFT in case 1 and remarkable sensitivity to the methacholine inhalation challenge in case 2.

The severity, frequency, duration, and onset time of chest pain can vary among patients with CPVA. Because this is a subjective sensation, the location and the severity of chest pain are not necessarily the same for all diseases. In some patients with CPVA whose symptoms occur while they were climbing stairs (case 1) or performing mild physical activity, chest pain could be relieved spontaneously by resting or stopping the activity. However, chest pain persists in some patients even at rest, which increases the difficulty of diagnosis.

Symptoms of chest pain often lead to a misdiagnosis of angina pectoris or CAD, but CPVA can be differentiated from CAD by careful analysis of medical and family history. There are important clues that suggest a diagnosis of CPVA. First, attacks emerge recurrently, as was the case in this study where patients’ symptoms appeared or were exacerbated in winter and disappeared spontaneously in summer. In case 2, chest pain worsened in the evening. These phenomena manifested as typical characteristics of asthma; especially, they were paroxysmal, reversible, and recurring. Second, chest pain appears as patients engage in physical activity (eg, climbing stairs), but symptoms cannot be relieved using anti-anginal drugs. Third, most patients experience chest tightness, cough, and mild dyspnea, but in these cases, symptoms are mild and may be overlooked by doctors and patients themselves.

The mechanism underlying the development of chest pain in patients with asthma is unclear. The lungs and the bronchi are innervated by mechanoreceptors that respond to stretch, such as lung inflation or deflation. Inhalation of irritants can trigger a cough reflex and can produce a sensation of chest tightness and pain. It has been speculated that in some patients with asthma, the chest pain threshold decreases, resulting in increased muscle tone and decreased chest activity. Vempilly et al. also speculated that breathing at a higher residual volume can...
lead to stress on rib joint mechanics, which can lead to dull or sharp chest pain in patients with asthma.

Taniguchi et al[6] suspected that the following two mechanisms may be involved in CPVA: (1) airway constriction and (2) a non-constrictive mechanism. We suspect that, in our patients, chest pain was mostly induced by airway constriction because pain decreased in response to bronchodilator administration. Furthermore, the unpredictability of asthma attacks and the chronic nature of the disease may cause anxiety and fear; thus, patients with high levels of stress may experience chest pain.

The symptoms of case 1 were aggravated in winter and relieved spontaneously in summer. The effects of cold exposure on the respiratory tract are mediated through skin cooling or inhalation of cold air. Skin cooling causes unfavorable reflexive airway changes, and cooling and drying of the nasal and airway mucosa can lead to hyperosmolality, leading to neural activation and bronchoconstriction.[7]

Patients with CPVA should be treated in the same manner as those with typical asthma. Case 1 recovered within 3 days, but recovery was prolonged in case 2. The longer the symptoms last, the longer the patients take to recover. Chest pain persists in some patients with CPVA, even after being treated with inhaled corticosteroids and long-acting bronchodilators; however, chest pain subsides with the administration of a leukotriene receptor antagonist, suggesting that this subset of CPVA may be induced by mechanisms involving leukotrienes.[6]

For chest pain, we believe that it is necessary to develop diagnostic and therapeutic guidelines and procedures for physicians. For patients with chest pain with negative findings on ECG or chest radiography, which are often concluded as an unknown cause of chest pain, the possibility of asthma should be considered. PFT and bronchial challenging tests are recommended to confirm the diagnosis of asthma.

Declaration of patient consent
The author certifies that all appropriate patient consent forms have been obtained. In the form, the patients have given their consent for the clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, although anonymity cannot be guaranteed.

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Conflicts of interest
None.

References

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