Asthmatic Attack Complicated with Takotsubo Cardiomyopathy after Frequent Inhalation of Inhaled Corticosteroids/Long-Acting Beta2-Adrenoceptor Agonists

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Abstract

A 63-year-old man was transferred to our hospital because of an exacerbation of asthma. His symptoms deteriorated even after increasing the dose of inhaled corticosteroids/long-acting beta2-adrenoceptor agonists (ICS/LABA). He had no chest pain and an electrocardiogram revealed ST elevation. A coronary angiogram revealed a reduced left ventricular function with an apical ballooning pattern without coronary stenosis. He was diagnosed with Takotsubo cardiomyopathy. Catecholamine elevation due to acute asthma and an over-dose of ICS/LABA may be triggers of this disease. We should remember that Takotsubo cardiomyopathy is a complication of asthma and that catecholamine plays an important role in its onset, although it is essential for asthma treatment.

Key words: asthmatic attack, Takotsubo cardiomyopathy, inhaled corticosteroids/long-acting beta2-adrenoceptor agonists, catecholamine


Introduction

Takotsubo cardiomyopathy represents an intermittent left ventricular dysfunction with a ballooning of the left ventricular apical myocardium without significant coronary artery disease and is triggered by acute emotional or physical stress (1, 2). Its manifestations are similar to acute coronary syndrome with ST elevation; therefore, diagnosis is crucial at emergency care sites.

The pathophysiology of this disease is not yet completely understood; however, catecholamine-induced myocardial stunning appears to play a major role (3, 4). There have been reports of Takotsubo cardiomyopathy following medical interventions for asthma (5, 6). Here, we present a patient with Takotsubo cardiomyopathy accompanied by a severe asthmatic attack following frequent exposure to inhaled corticosteroids/long-acting beta2-adrenoceptor agonists (ICS/LABA). This case demonstrated the importance of catecholamine in the onset and treatment of Takotsubo cardiomyopathy accompanied by an asthmatic attack.

Case Report

A 63-year-old man with a history of bronchial asthma was admitted to our hospital with deteriorating wheezing and dyspnea. He had come down with a cold the day before, and 10 hours before admission, he started wheezing and experienced dyspnea. He took 5 mg of oral prednisolone and increased the dose and frequency of ICS/LABA to two puffs every 6 hours at his own discretion. He had a medical history of bronchial asthma and lung abscess. His father had died of an asthmatic attack. Furthermore, he had a 40-year history of smoking (six cigarettes/day), occasional alcohol intake and no known allergies. He took a daily prescription of 250 μg of ICS/LABA every 12 hours, 400 mg of theophylline and approximately 100 mg of oral prednisolone once a month when he experienced wheezing, by his...
own judgment. On examination, his body temperature was 36.6°C, blood pressure was 200/110 mmHg, heart rate was 126 beats/min, respiration was 48/min and oxygen saturation was 77% with room air. Physical examination results were normal, except for polyphonic expiratory and inspiratory wheezes. Laboratory findings demonstrated elevated white blood cell count, C-reactive protein and troponin-I (peak troponin I was 3.45 ng/mL). Arterial blood gas analyses revealed a pH of 7.225, carbon dioxide partial pressure (pCO₂) of 65 mmHg and partial pressure oxygen (pO₂) of 246.5 mmHg using a 10-L reservoir mask (Table 1). Furthermore, a chest radiograph revealed hyperinflation of both lungs, and an electrocardiogram (ECG) revealed ST elevation in V2-V6 (Fig. 1). The echocardiogram revealed that the left ventricular ejection fraction (EF) was reduced to 49%. Coronary angiography revealed normal coronary arteries, and left ventriculography revealed a depressed left ventricular function and an apical ballooning pattern consistent with Takotsubo cardiomyopathy (Fig. 2). Mitral regurgitation, left ventricular outflow tract obstruction or left ventricular apical thrombus was not found. Therefore, he was diagnosed with Takotsubo cardiomyopathy associated with a severe asthmatic attack. Treatment was initiated with intravenous steroids, continuous nebulized short-acting beta-adrenergic agonist, transdermal long-acting beta-adrenergic agonist and noninvasive positive pressure ventilation. Brain natriuretic peptide at day 2 was elevated to 703.3 pg/mL, reflecting acute heart failure. We thought that high blood pressure and tachycardia due to an asthmatic attack and low EF due to Takotsubo cardiomyopathy were the main causes. Appropriate asthma treatment and the administration of a hypotensive drug improved the heart failure immediately. No complications of arrhythmia occurred. We added an inhaled anticholinergic bronchodilator with a diagnosis of chronic obstructive pulmonary disease overlap. On days 7 and 15, the wheezing and peak flow had improved, respectively. The serum catecholamine levels on day 8 were normal. The ECG showed a negative T wave in II, III, aVF, V2-V6 and a prolonged QT interval on day 4, and the negative T wave gradually improved, becoming normal two months later.
**Figure 2.** A coronary angiogram revealed normal coronary arteries and left ventriculography showed a depressed left ventricular function and an apical ballooning pattern consistent with Takotsubo cardiomyopathy. (a) diastole and (b) systole.

<table>
<thead>
<tr>
<th>Hydrocortisone 200mg/8h</th>
<th>PSL 30mg</th>
<th>20mg</th>
<th>10mg</th>
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<tbody>
<tr>
<td>Salbutamol</td>
<td>Salmeterol Fulticasone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tulobuterol</td>
<td>Tiotropium</td>
<td></td>
<td></td>
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<tr>
<td>Ipratropium</td>
<td></td>
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</tr>
</tbody>
</table>

**Figure 3.** Clinical course of laboratory data, vital signs, peak flow and therapies. PSL: prednisolone, NIV: noninvasive ventilation

Proved to 64% by day 15 without any specific treatment for the cardiomyopathy in this case (Fig. 3).

**Discussion**

Transient cardiac dysfunction with a ballooning shape is known as Takotsubo cardiomyopathy and it is commonly induced by emotional or physical stress (1, 2).

It is suggested that this disorder is caused by diffuse catecholamine-induced microvascular spasm or dysfunction, resulting in myocardial stunning, or by direct catecholamine-associated myocardial toxicity (2). Sympathetic excitation through the hypothalamus triggers the release of norepinephrine, mainly from the sympathetic nerve endings, and the release of epinephrine, mainly from the adrenal medulla. It has been reported that the concentrations of plasma norepinephrine and epinephrine increase more in patients with Takotsubo cardiomyopathy than in patients with acute coronary syndrome (3). It is predicted that norepinephrine may trigger coronary vasospasm by stimulating alpha1-receptor in coronary blood vessels. Meanwhile, norepinephrine-mediated beta1-receptor stimulation may trigger hyperdy-
### Table 2. Reported Cases of Asthmatic Attack Accompanied by Takotsubo Cardiomyopathy.

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Age</th>
<th>Sex</th>
<th>Symptom</th>
<th>Time Lag</th>
<th>ST elevation</th>
<th>ECG</th>
<th>Onset</th>
<th>Severity of Asthmatic Attack</th>
<th>Pulmonary Support</th>
<th>EF(%)</th>
<th>Cardiac Support</th>
<th>Recovery Time of EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>27</td>
<td>F</td>
<td>+</td>
<td>1 week</td>
<td>I, aVL</td>
<td>I, aVL</td>
<td>SABA</td>
<td>Severe</td>
<td>MV</td>
<td>34</td>
<td>IABP</td>
<td>ND</td>
</tr>
<tr>
<td>14</td>
<td>42</td>
<td>F</td>
<td>+</td>
<td>1 week</td>
<td>inferior lateral wall</td>
<td></td>
<td>SABA</td>
<td>Severe</td>
<td>MV</td>
<td>11</td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td>14</td>
<td>45</td>
<td>F</td>
<td>+</td>
<td>several weeks</td>
<td></td>
<td></td>
<td>SABA</td>
<td>Severe</td>
<td>MV</td>
<td>31</td>
<td>IABP</td>
<td>ND</td>
</tr>
<tr>
<td>15</td>
<td>69</td>
<td>F</td>
<td>+</td>
<td>4 months</td>
<td>I, II, aVL, V1-6</td>
<td></td>
<td>SABA</td>
<td>Mild</td>
<td>ND</td>
<td>54</td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td>16</td>
<td>79</td>
<td>F</td>
<td>+</td>
<td>2 weeks</td>
<td>II, III, aVF, V4-6</td>
<td>II, III, aVF</td>
<td>SABA</td>
<td>Mild</td>
<td>ND</td>
<td>14 days</td>
<td></td>
<td>ND</td>
</tr>
<tr>
<td>17</td>
<td>78</td>
<td>F</td>
<td>+</td>
<td>1 day</td>
<td>I, II, III, aVF, V2-6</td>
<td></td>
<td>Emotional stress</td>
<td>Mild</td>
<td>ND</td>
<td>14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>62</td>
<td>M</td>
<td>+</td>
<td>same time</td>
<td>II, III, aVF, V1-6</td>
<td></td>
<td>Epinephrine</td>
<td>Severe</td>
<td>ND</td>
<td>7 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>62</td>
<td>M</td>
<td>+</td>
<td>3 days</td>
<td>V1-6</td>
<td></td>
<td>Epinephrine</td>
<td>Severe</td>
<td>MV</td>
<td>ND</td>
<td>PCPS</td>
<td>7 days</td>
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<tr>
<td>20</td>
<td>64</td>
<td>M</td>
<td>+</td>
<td>7 days</td>
<td>V2-6</td>
<td></td>
<td>Severe</td>
<td>ND</td>
<td>32</td>
<td>IABP</td>
<td>3 days</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>67</td>
<td>F</td>
<td>+</td>
<td>same time</td>
<td>I, aVL, V1-2</td>
<td></td>
<td>SABA</td>
<td>Severe</td>
<td>ND</td>
<td>8 days</td>
<td></td>
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<tr>
<td>21</td>
<td>74</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>II, III, aVF, V3-6</td>
<td></td>
<td>Severe</td>
<td>ND</td>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>80</td>
<td>F</td>
<td>+</td>
<td>same time</td>
<td>Anesthesia machine trouble</td>
<td></td>
<td>Severe</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>F</td>
<td>+</td>
<td>3 weeks</td>
<td>II, III, aVF, V5, V6</td>
<td></td>
<td>Epinephrine, Ketamine</td>
<td>Severe</td>
<td>MV</td>
<td>10</td>
<td>IABP</td>
<td>3 days</td>
</tr>
<tr>
<td>23</td>
<td>51</td>
<td>F</td>
<td>+</td>
<td>4 days</td>
<td>II, III, aVF, V2-6</td>
<td>V3-6</td>
<td>Intubation</td>
<td>Severe</td>
<td>MV</td>
<td>66</td>
<td>ND</td>
<td>7 days</td>
</tr>
<tr>
<td>24</td>
<td>71</td>
<td>M</td>
<td>+</td>
<td>+</td>
<td>V1-4</td>
<td></td>
<td>Intubation</td>
<td>Severe</td>
<td>MV</td>
<td>ND</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>66</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>V1-4</td>
<td></td>
<td>SABA</td>
<td>Severe</td>
<td>ND</td>
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<td></td>
</tr>
<tr>
<td>26</td>
<td>71</td>
<td>F</td>
<td>+</td>
<td>same time</td>
<td>V2, V3</td>
<td></td>
<td>SABA</td>
<td>Severe</td>
<td>MV</td>
<td>35</td>
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<td>27</td>
<td>72</td>
<td>M</td>
<td>+</td>
<td>same time</td>
<td>anterior wall</td>
<td></td>
<td>Drug allergy</td>
<td>Moderate</td>
<td>ND</td>
<td>37</td>
<td>6 days</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>70</td>
<td>F</td>
<td>+</td>
<td>same time</td>
<td>anterior wall</td>
<td></td>
<td>Drug allergy</td>
<td>Mild</td>
<td>ND</td>
<td>25</td>
<td>vasopressor</td>
<td>7 days</td>
</tr>
<tr>
<td>our case</td>
<td>63</td>
<td>M</td>
<td>+</td>
<td>1 day</td>
<td>V2-5</td>
<td></td>
<td>ICS/LABA</td>
<td>Severe</td>
<td>NIV</td>
<td>49</td>
<td>ND</td>
<td></td>
</tr>
</tbody>
</table>

namic basal contraction because there are more sympathetic nerve endings and norepinephrine in the basal myocardium (2).

The clinical features are similar to those of acute coronary syndrome. The major symptom is chest pain (7, 8), the major clinical presentation is electrocardiographic changes (ST elevation in the acute phase and a negative T wave in the subacute phase) (9, 10), with minimal myocardial enzyme release. It is known to be reversible; however, it often presents with cardiac complications during the acute phase, such as life-threatening ventricular arrhythmias, pump failure, cardiac rupture and systemic embolism (11); hospital mortality is reportedly 1.7-6% (12, 13).

We reviewed all 20 cases reported in the previous literature in which Takotsubo cardiomyopathy was associated with an asthmatic attack, including our case (6, 14-28) (Table 2). The patients were mainly women suffering from severe attacks. Sixteen cases (75%) had only dyspnea and only four cases (25%) had chest pain. Regarding the duration between the onset of the asthmatic attack and the diagnosis of Takotsubo cardiomyopathy, in 16 cases (80%), it was within a week. The ECG revealed an ST elevation; eight cases each in the chest and limb leads. Regarding the severity of the attack, 14 cases (70%) involved status asthmaticus and 10 cases required mechanical ventilation. With regard to the EF, the average EF was 34.1% and four cases required mechanical cardiac support. The average duration of the recovery time of the EF was 7.1 days. At onset, an epinephrine injection overdose or the inhalation of an excessive amount of short-acting beta2-adrenoceptor agonist (SABA) have been reported (5, 6), although the asthmatic attack itself was the trigger in 35%.

This is the first reported case in which Takotsubo cardiomyopathy developed just after an ICS/LABA inhalation overdose. An ICS/LABA inhalation overdose may be one of the triggers. There have been some reports regarding the effects of inhaled beta2 agonists on cardiovascular function (29) and stress cardiomyopathy precipitated by the intravenous administration of catecholamines and beta-receptor agonists (5). Moreover, Shao et al. used a rat model to support the hypothesis of circulating catecholamines as initiators of stress-induced cardiomyopathy and the importance of beta-adrenoceptors (30).

The asthma attack itself could also be a trigger. Barnes et al. demonstrated the elevation of catecholamines in acute asthma compared with that in a normal status (31, 32). It may simply have induced Takotsubo cardiomyopathy by increasing the plasma concentration of catecholamine. Moreover, intravenous epinephrine and inhaled beta-adrenoceptor agonists may increase the risk of Takotsubo cardiomyopathy.

We think that this is an instructive case regarding both the treatment and education for patients with asthma.

Around 50% of patients do not take controller medications as prescribed (33). We should teach patients carefully about the importance of regular controller treatment and the cardiac risks of not only a SABA, but also an ICS/LABA overdose.

Although epinephrine and beta-adrenoceptor agonists are essential, we should use them carefully. Once Takotsubo cardiomyopathy is diagnosed, we need to treat the asthma attack itself by paying special attention to the hemodynamics.

The authors state that they have no Conflict of Interest (COI).

Nayuta Saito and Manabu Suzuki contributed equally to this work.

References