CASE REPORT

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Synephrine-containing dietary supplement precipitating apical ballooning syndrome in a young female

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Apical ballooning syndrome (ABS) is a unique reversible cardiomyopathy that is frequently precipitated by emotional or physical stress. In addition, the few drugs reported to precipitate ABS were either illegal or strictly controlled for medical use. This paper reports a case of ABS precipitated by a dietary supplement. Our case accentuates the potential risk of dietary supplements containing synephrine, which is uncontrolled and available to the general public. Therefore, the Korea Food and Drug Administration should regulate these dietary supplements, and warn healthcare workers and the general public of the potential hazards of the indiscriminate abuse of dietary supplements.

Keywords: Takotsubo cardiomyopathy; Dietary supplements; Synephrine

INTRODUCTION

Apical ballooning syndrome (ABS), also called stress-induced cardiomyopathy or Takotsubo cardiomyopathy, is characterized by transient akinesis from the apical to midventricular segments and hyperkinesis of the basal segments, with markedly reduced left ventricular systolic function [1]. ABS mimics acute coronary syndrome, since electrocardiography often reveals ST-segment elevation with mild elevation of cardiac biomarkers [2]. Generally, ABS is triggered by severe emotional or physical stress [3,4]. In addition, some drugs can precipitate the development of ABS. However, the drugs reported to trigger ABS were either illegal or strictly controlled for medical use [5,6]. By contrast, this paper reports a case of ABS precipitated by dietary supplements, which are not controlled and available to the general public.

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CASE REPORT

A 21-year-old female presented to the emergency room with disturbed consciousness and a seizure. She had no relevant medical history. She had been taking dietary supplements purchased via the internet for the proceeding week in order to lose weight. The supplements contained caffeine and synephrine. The physical examination revealed a blood pressure of 115/84 mmHg and pulse of 110 beats per minute. On auscultation, the lungs were clear and heart sounds normal, with no murmur or gallop. The 12-lead electrocardiograph revealed sinus tachycardia, T wave inversion in leads II, III, aVF, and V3-6, and a prolonged QTc interval of 537 ms (Fig. 1). Laboratory analysis revealed creatine kinase (CK) 374 U/L (normal range, 21 to 215), CK-MB 9.9 ng/mL (normal range, < 4.3), troponin I 0.59 ng/mL (normal range, < 0.07), brain natriuretic peptide 734 pg/mL (normal range, < 100), and C-reactive protein 3.6 mg/L (normal range, 0.1 to 6.0). The serum catecholamine levels measured 3 days after admission showed dopamine 6.03 ng/mL (normal range, 0.5 to 6.2), epinephrine 0.03 ng/mL (normal range, < 0.3), and norepinephrine 0.48 ng/mL (normal range, < 0.8). Transthoracic echocardiography (TTE) performed at the day of admission showed apical ballooning of the left ventricle due to akinesis from the apical to midventricular segments, and hyperkinesis of the basal segments, with a markedly reduced left ventricular ejection fraction of 28% (Fig. 2). The impairment extended across the coronary artery distribution. Cardiac magnetic resonance (CMR) was performed 2 days after admission. The cine CMR findings were consistent with TTE (Fig. 3A and 3B) and the late enhancement CMR revealed no late gadolinium enhancement (Fig. 3C). In addition, reconstructed CMR images of the coronary arteries revealed no significant stenosis (Fig. 3D and 3E). Under a working diagnosis of ABS, she was treated conservatively with a β-blocker, angiotensin converting enzyme inhibitor, and loop diuretics. Gradually, her symptoms improved. Another TTE performed 9 days after admission revealed a normal ejection fraction of 63%, with complete recovery of the apical and midventricular wall motion. While hospitalized, neurological evaluations including electroencephalography and brain magnetic resonance imaging were performed to determine whether epilepsy was the cause of her seizure. However, there was no definite evidence of epilepsy or other organic brain abnormalities. Therefore, she was not given any anti-

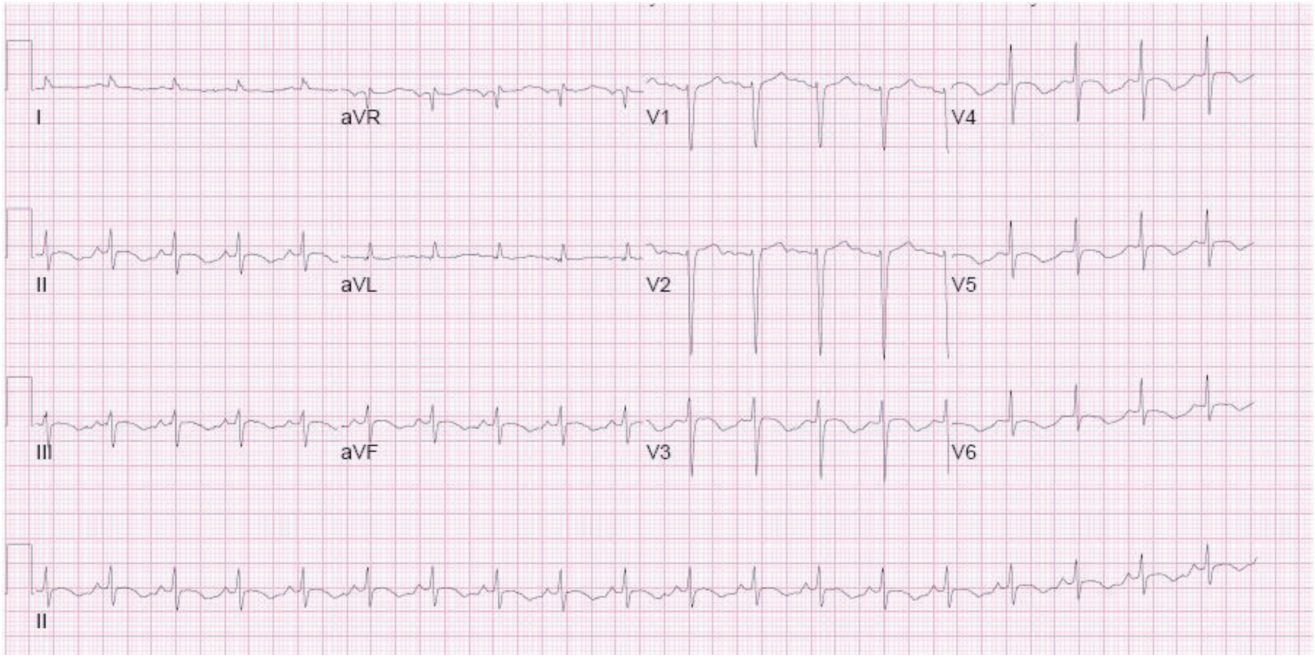

Figure 1. The 12-lead electrocardiograph on admission revealed sinus tachycardia, T wave inversion in leads II, III, aVF, and V3-6, and a prolonged QTc interval of 537 ms.

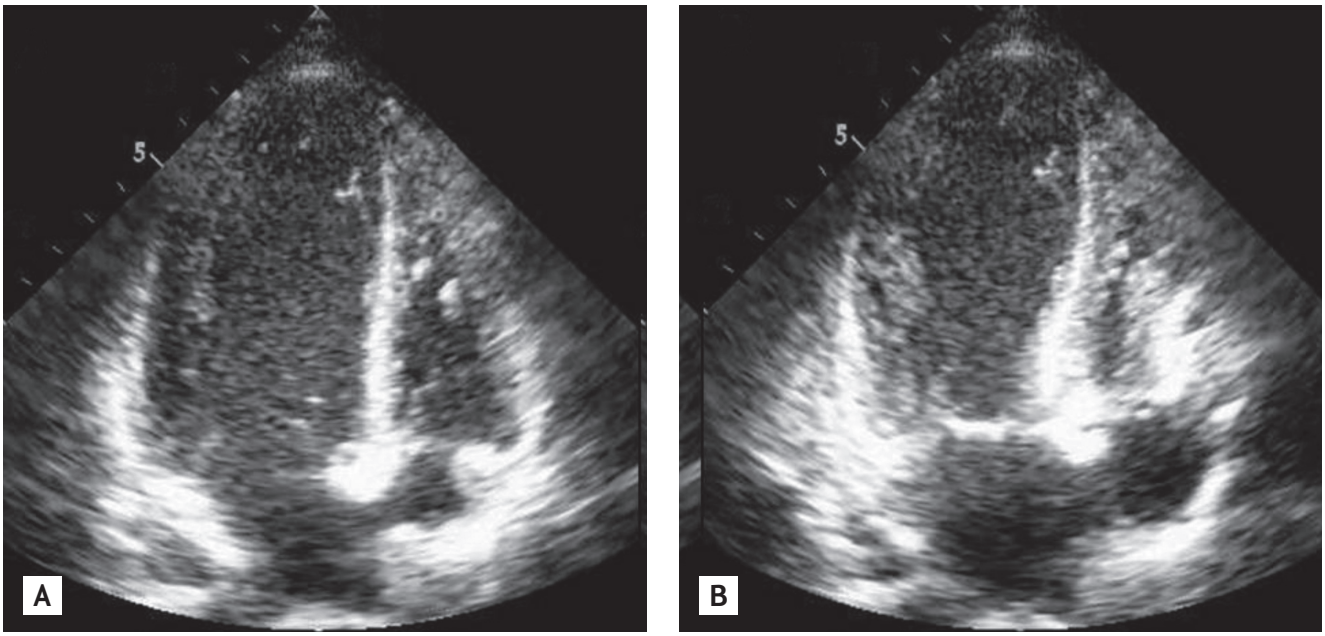

Figure 2. Apical four-chamber transthoracic echocardiography view during (A) diastole and (B) systole showing apical ballooning of the left ventricle due to akinesis from the apical to midventricular segments, and hyperkinesis of the basal segments with a markedly reduced left ventricular ejection fraction of 28%.

epileptic medication. She remained stable clinically and hemodynamically for 10 days of hospitalization and was discharged home without cardiological or neurological sequelae. In the year since, there has been no recurrence of ABS or seizures.

DISCUSSION

Besides severe emotional or physical stress, drugs can precipitate ABS. However, the drugs reported to trigger ABS, such as dobutamine, epinephrine, and amphetamine, are either illegal or strictly controlled for medical use in many countries [5,6]. In contrast, this paper reports a case of ABS precipitated by dietary supplements that are freely available to the general public.

In 2004, the United States Food and Drug Administration determined that ephedra and ephedrine-containing dietary supplements were unsafe for unregulated use and banned their sale. However, this ban does not preclude the use of other structurally related sympathomimetic amines in products for weight reduction. Consequently, synephrine has emerged as an alternative to ephedra in dietary supplements and is listed often as "extract of *Citrus aurantium*" or "extract of bitter orange." Synephrine is a sympathomimetic amine derived from *C. aurantium* and shares structural similarities with other sympathomimetic phenylethylamine drugs, such as ephedrine, amphetamine, and phenylpropanolamine. Although synephrine is considered safe compared to ephedra, the toxicity of this substance is largely unknown, especially in combination with caffeine, which potentiates the cardiovascular effects of other sympathomimetic agents. In addition, severe adverse cardiovascular side effects of synephrine-containing dietary supplements have been reported [7,8]. To our knowledge, this is the first report of ABS precipitated by synephrine-containing dietary supplements.

The pathophysiology of ABS remains poorly understood. Several hypotheses have been proposed as the mechanisms of ABS, including direct catecholamine-induced cardiomyocyte injury via intracellular calcium overload, and an indirect effect of a catecholamine surge resulting in epicardial spasm, microvascular dysfunction, or dynamic left ventricular outflow obstruction due to hyperkinesis of the basal segments [9]. Further studies are needed to clarify the pathophysiological mechanism of ABS.

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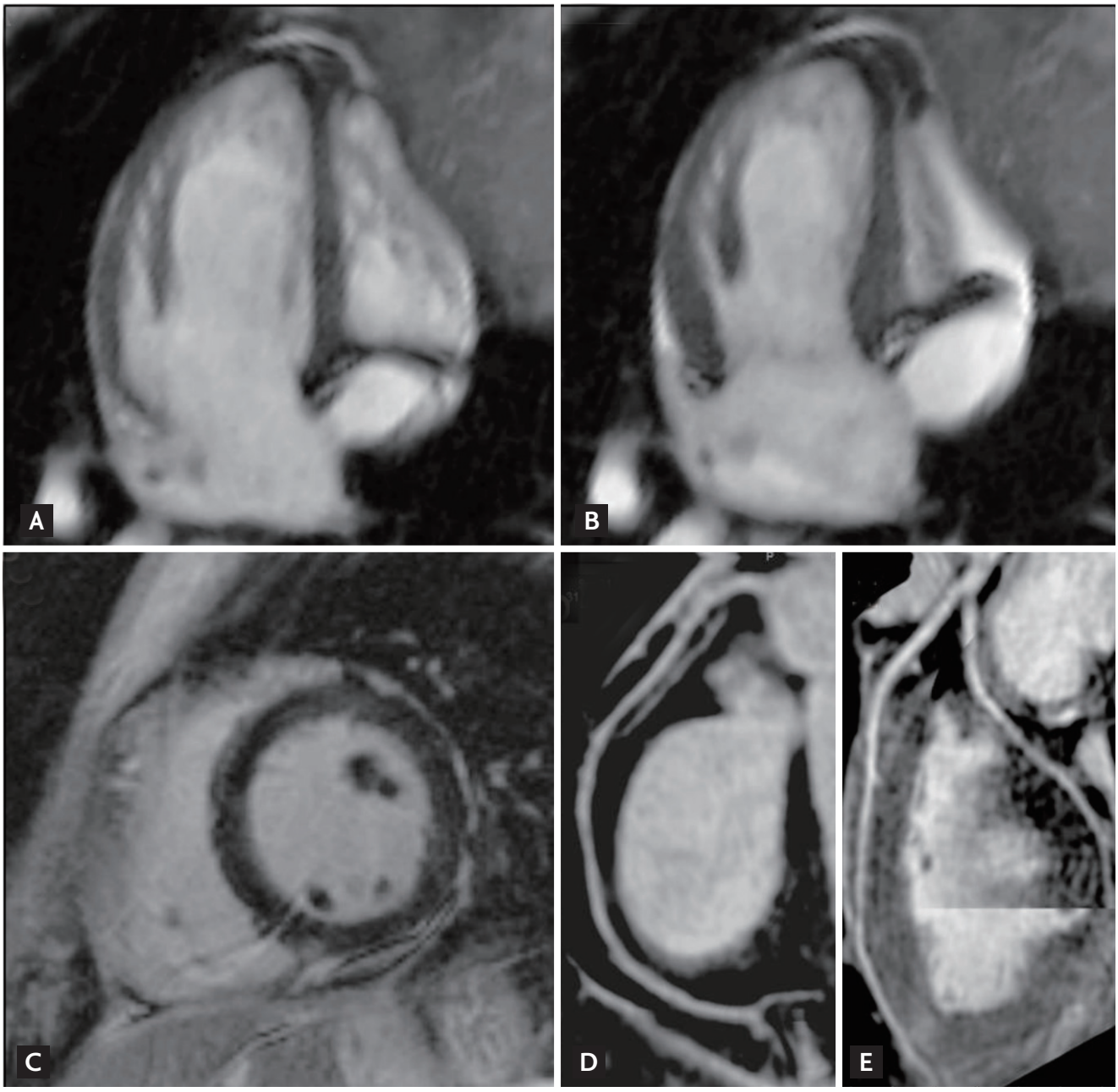

Figure 3. Cine cardiac magnetic resonance (CMR) images during (A) diastole and (B) systole were consistent with transthoracic echocardiography findings. (C) Late enhancement CMR revealed no late gadolinium enhancement. Reconstructed CMR image of the (D) right and (E) left coronary arteries revealed no significant stenosis.

In conclusion, our case accentuates the potential risk of dietary supplements containing synephrine, a sympathomimetic similar to ephedra. Currently, the use of these dietary supplements is uncontrolled and they are freely available to the general public. The Korea Food and Drug Administration should take a stronger position regarding the regulation of these dietary supplements, and warn healthcare workers and the general public to be aware of the potential hazard of the indiscriminate abuse of dietary supplements.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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