



Case Report

Hypertensive heart disease associated with methamphetamine abuse

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ABSTRACT

In Japan, methamphetamine accounts for the majority of illicit drug use and dependence is becoming a critical issue. Methamphetamine abuse induces cardiovascular complications, such as cardiomyopathy and heart failure. However, methamphetamine-associated cardiovascular complications are not common in Japan. We report the case of a young patient with hypertensive heart disease associated with habitual methamphetamine abuse. A 37-year-old man was admitted with congestive heart failure. He was a habitual methamphetamine abuser and developed chronic hypertension after he started methamphetamine abuse. His echocardiogram demonstrated left ventricular concentric hypertrophy with diffuse hypokinesis. An endomyocardial biopsy revealed histological evidence of a hypertensive heart. This case shows that habitual methamphetamine use may cause hypertensive heart disease because of chronic hypertension.

<Learning objective: Methamphetamine-associated cardiomyopathy and congestive heart failure are uncommon in Japan. However, habitual methamphetamine abuse can be a potential cause of hypertensive heart disease due to chronic hypertension and congestive heart failure associated with hypertrophy.>

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Introduction

Methamphetamine is a central nervous system stimulant and its abuse is widespread and increasing in many countries. A report published by a tertiary care medical center in Hawaii suggested that 40% of young patients with cardiomyopathy are methamphetamine abusers [1]. Methamphetamine abuse induces cardiovascular complications, such as hypertension, tachycardia, acute coronary syndrome, pulmonary arterial hypertension, cardiomyopathy, and heart failure [1,2]. Previous studies have demonstrated that 5% of patients admitted for congestive heart failure in the USA have a history of illicit stimulant drug abuse [3], and also that the prevalence of methamphetamine-associated congestive heart failure is significantly increasing [4]. In Japan, although the lifetime exposure to illicit drugs is low compared with European and American countries, methamphetamine accounts for the majority of illicit drug use. The number of people arrested for

abusing methamphetamine has not decreased in recent years. Moreover, the rate of repeat offenders of methamphetamine abuse has been increasing and drug dependence is becoming a critical issue. There are several reports of methamphetamine causing dilated cardiomyopathy [2,5]. However, few papers have reported abuse of methamphetamine causing hypertensive heart disease and heart failure in Japan.

We report the case of a young patient with hypertensive heart disease associated with methamphetamine abuse.

Case report

A 37-year-old man presented to our hospital with dyspnea on exertion and pedal edema for 3 months. He had been abusing intravenous methamphetamine since the age of 17 years. He reported a history of hypertension since the time he started abusing methamphetamine. His systolic blood pressure (BP) was 150–170 mmHg, but he was not on any hypertension medication. Interestingly, his BP was less than 140 mmHg on the two occasions he was in prison for illegal drug abuse. His family history was unremarkable. His body weight was 72.8 kg on admission, but had increased by 6 kg in 3 months. On arrival, his BP was 170/

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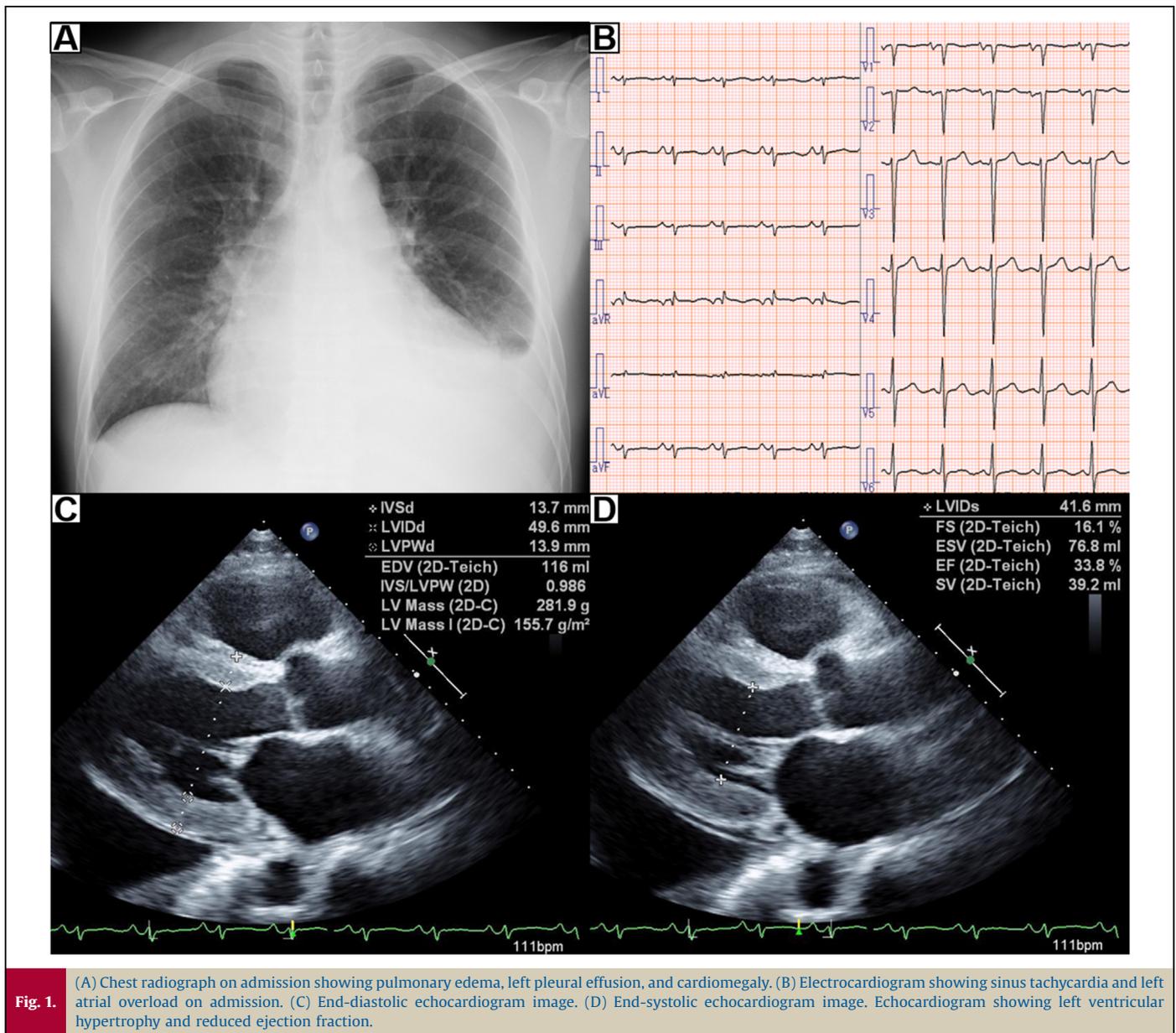
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102 mmHg, and his heart rate was 109 bpm. His temperature was 36.5 °C, and his peripheral blood oxygen saturation was 84% in room air. A jugular venous pulsation was observed in sitting position and suggested heart failure. His respiratory sounds were clear, and his heart sounds showed a gallop rhythm. Chest radiography revealed pulmonary edema, left pleural effusion, and cardiomegaly (Fig. 1A). Electrocardiography revealed sinus tachycardia and left atrial enlargement (Fig. 1B). A urine drug test for methamphetamine was negative because he had not used methamphetamine for several weeks prior to admission. Laboratory investigations before treatment are shown in Table 1. No tumor or thrombosis was detected on thin-slice chest and abdominal computed tomography. Causes of secondary hypertension, such as aldosteronism, pheochromocytoma, Cushing's syndrome, renovascular hypertension, and hyperthyroidism, were ruled out. Echocardiography demonstrated left ventricular hypertrophy (LVH) with diffuse hypokinesia (Fig. 1C, D). The ejection fraction was 43% (modified Simpson method). Moderate tricuspid regurgitation was observed with a pressure gradient of 45 mmHg, suggesting pulmonary hypertension. No hypertensive changes

Table 1 Laboratory and urinary findings.

Na	139	mEq/L	NT-pro BNP	2667	pg/mL
K	3.9	mEq/L	Noradrenalin	1312	pg/mL
BUN	14	mg/dL	Adrenalin	143	pg/mL
Cr	0.95	mg/dL	Dopamine	24	pg/mL
AST	126	IU/L	ACTH	24.5	μg/dL
ALT	237	IU/L	Serum aldosterone	377	pg/mL
LDH	437	IU/L	Plasma renin activity	1.4	ng/mL
ALP	509	IU/L	Aldosterone-renin ratio	269	
γ-GTP	527	IU/L	ACE	18.2	U/L
T-Bil	2.5	mg/dL	Urine methamphetamine	(-)	
FDP	1.8	μg/mL	Urine metanephrine	0.145	μg/mg Cre
D-dimer	1.2	μg/mL	Urine normetanephrine	0.47	μg/mg Cre

Na: sodium, K: potassium, BUN: blood urea nitrogen, Cr: creatinine, AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, T-Bil: total bilirubin, FDP: fibrinogen and fibrin degradation products, NT-pro BNP: N-terminal pro-brain natriuretic peptide, ACTH: adrenocorticotropic hormone, ACE: Angiotensin-converting enzyme.



were observed in the retina, kidney, or carotid, cerebral, and peripheral arteries. Based on these findings, he was diagnosed with congestive heart failure. In general, treatment for congestive heart failure includes vasodilators and diuretics to reduce cardiac afterload and volume overload. On hospital day 1, he received nasal oxygen (2 L), intravenous nitroglycerin (1 μ g/kg/min), and bolus furosemide (20 mg). On day 2, intravenous furosemide was switched to oral furosemide (40 mg), and spironolactone (25 mg), perindopril (4 mg), and amlodipine (5 mg) were initiated. On day 6, pedal edema and pulmonary edema improved. He then underwent cardiac catheterization and endomyocardial biopsy. Coronary angiography revealed normal coronary arteries. Right heart catheterization showed a pulmonary capillary wedge pressure of 17 mmHg, pulmonary artery systolic/diastolic/mean pressure of 47/27/35 mmHg, right ventricular systolic/diastolic/end-diastolic pressure of 44/7/16 mmHg, mean right atrial pressure of 11 mmHg, and cardiac index of 2.24 L/min/m² (Fick method).

An endomyocardial biopsy was taken from the left ventricular wall. Hematoxylin and eosin staining revealed myocyte hypertrophy, vacuolization, and large and abnormal nuclei (Fig. 2A–C). Masson's trichrome staining demonstrated perivascular and interstitial fibrosis (Fig. 2D). Necrotic myocardium, disarray, and amyloid deposition were not detected. On day 8, carvedilol was initiated at a dose of 1.25 mg and doubled every 5 days while confirming that heart failure did not worsen. Carvedilol was titrated to 5.0 mg until discharge. On day 21, he was discharged from the hospital. His symptoms had improved and his BP had decreased to 140/98 mmHg. Chest radiography no longer showed evidence of pulmonary edema, pleural effusion, or cardiomegaly. The N-terminal pro B-type natriuretic peptide (NT-proBNP) level had decreased to 251 pg/mL. Four months after discharge, his NT-proBNP level was still 152 pg/mL, without signs of heart failure.

Discussion

Methamphetamine abuse is widespread in many countries, including Japan. As a potent central and peripheral nervous system stimulant, methamphetamine causes release and blocks reuptake of dopamine, epinephrine, norepinephrine, and serotonin at neuronal synapses. Hypertension and tachycardia increase with methamphetamine use in a dose-dependent manner because of adrenergic stimulation. Methamphetamine can also induce arrhythmias, vasospasm, atherosclerosis, acute coronary syndrome, aortic dissection, cardiomyopathy, and sudden cardiac death.

Dilated, hypertrophic, and stress cardiomyopathy are associated with methamphetamine use. Dilated cardiomyopathy is thought to reflect direct toxicity of methamphetamine on cardiac myocytes. Hypertrophic cardiomyopathy is thought to reflect the effect of severe hypertension caused by activation of peripheral alpha (α)- and beta (β)-adrenergic receptors. Stress cardiomyopathy is due to the acute effect of catecholamines on adrenergic receptors in the myocardium. Among these, dilated cardiomyopathy is the most common type of cardiomyopathy associated with methamphetamine abuse [2]. However, it is not yet clear why patients may develop different manifestations of methamphetamine-associated cardiomyopathy. Ventricular hypertrophy usually occurs in response to sustained pressure overload as seen in hypertension. In habitual methamphetamine abusers, increased BP can lead to sustained hypertension [2]. Because our patient developed hypertension after starting methamphetamine abuse 17 years previously, habitual abuse potentially contributed to his hypertension and led to cardiac remodeling represented by concentric hypertrophy [2,6]. His electrocardiograph did not show typical findings of LVH, but it met the Cornell product criteria as a marker of LVH [7].

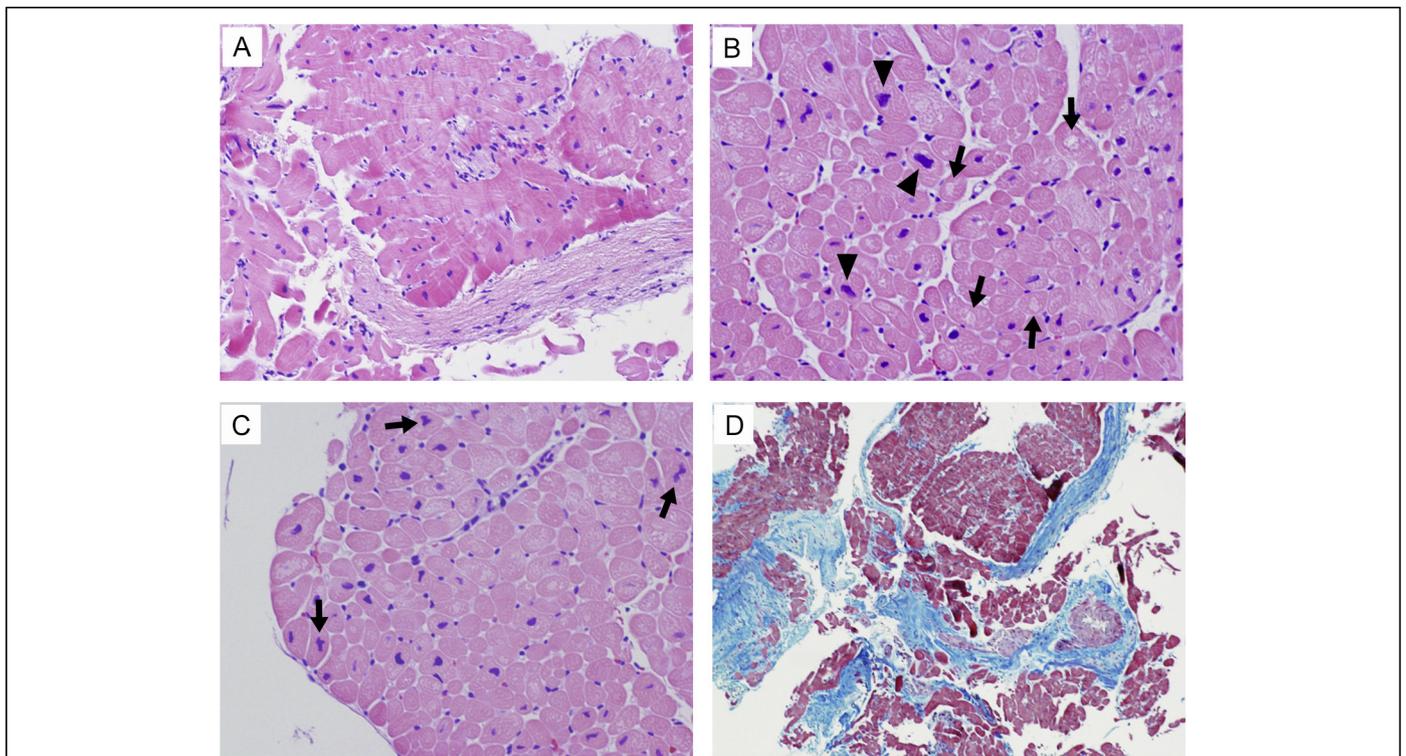


Fig. 2.

(A) Moderate hypertrophy of cardiac myocytes (hematoxylin and eosin staining, $\times 100$ original magnification). (B) Myocyte vacuolization (arrows) and large nuclei (arrowheads) (hematoxylin and eosin staining, $\times 100$ original magnification). (C) Abnormal nuclei (arrows) (hematoxylin and eosin staining, $\times 100$ original magnification). (D) Perivascular fibrosis surrounding the artery and interstitial fibrosis (Masson's trichrome stain, $\times 40$ original magnification).

Methamphetamine is the cause of abnormal histological changes in cardiac tissue. The histopathological changes in the heart in habitual methamphetamine abusers include necrosis, myocardial hypertrophy, and perivascular and/or interstitial fibrosis [6]. Most of these features overlap with abnormalities of myocardial tissue observed in hypertensive heart disease and correspond to the results of endomyocardial biopsy in our case. In a previous report, histological evidence of a hypertensive heart was observed in 32.7% of methamphetamine-related death cases [8]. These histological changes were induced by the effect of hypertension as well as by the direct effect of methamphetamine on cardiac myocytes [9]. Myocyte vacuolization and nuclear atypia in cardiac myocytes have often been observed in patients with cardiomyopathy. Hypertrophy, myocyte vacuolization, and nuclear atypia were identified in the hearts of methamphetamine abusers [10]. Our patient showed evidence of both myocyte vacuolization and nuclear atypia in cardiac myocytes. Hypertrophic cardiomyopathy, Fabry disease, amyloidosis, sarcoidosis, and hemochromatosis were excluded by echocardiography, laboratory testing, cardiac biopsy, and cardiovascular magnetic resonance imaging. Habitual methamphetamine abuse probably contributed to his hypertension and LVH. Therefore, our patient was diagnosed as a case of hypertensive heart disease associated with methamphetamine abuse.

There are currently no evidence-based recommendations in the context of methamphetamine-associated cardiomyopathy, but the literature on pheochromocytoma suggests that 14 days of α -antagonist therapy is adequate to facilitate safe introduction of β -antagonists. However, we initially administered carvedilol because our patient had not used methamphetamine for several weeks prior to admission. Carvedilol is both a nonselective β -adrenergic receptor blocker (β_1 , β_2) and an α -adrenergic receptor blocker (α_1). It reversibly binds to β -adrenergic receptors on cardiac myocytes. Inhibition of these receptors prevents a response to the sympathetic nervous system, leading to decreased heart rate and contractility. This action is beneficial in heart failure patients in whom the sympathetic nervous system is activated as not only a compensatory mechanism but also by methamphetamine stimulation. Carvedilol blockade of α_1 receptors causes vasodilation of blood vessels. This inhibition leads to decreased peripheral vascular resistance and an antihypertensive effect. Reflex tachycardia due to carvedilol blockade of β_1 receptors does not occur.

As in our case, patients with methamphetamine-associated cardiomyopathy have hypertensive hearts. Endomyocardial biopsy is useful for diagnosis, keeping in mind that habitual methamphetamine use may cause hypertensive heart disease because of chronic hypertension. Recognition of cardiomyopathy and acute heart failure as a complication associated with methamphetamine abuse is necessary to treat patients presenting with hypertensive heart disease.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgments

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