

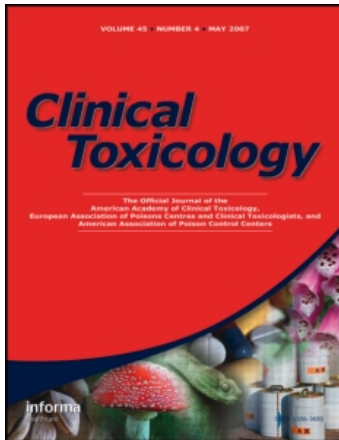
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Hypersensitivity Myocarditis Associated with Ephedra Use

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ABSTRACT

Background: Ephedrine has previously been described as a causative factor of vasculitis but myocarditis has not yet been associated with either ephedrine or its plant derivative ephedra. **Case Report:** A 39-year-old African American male with hypertension presented to Rush Presbyterian St. Luke's Medical Center with a 1-month history of progressive dyspnea on exertion, orthopnea, and dependent edema. He was taking Ma Huang (Herbalife) 1–3 tablets twice daily for 3 months along with other vitamin supplements, pravastatin, and furosemide. Physical examination revealed a male in mild respiratory distress. The lung fields had rales at both bases without audible wheezes. Internal jugular venous pulsations were 5 cm above the sternal notch. Medical therapy with intravenous furosemide and oral enalapril was initiated upon admission. Cardiac catheterization with coronary angiography revealed normal coronary arteries, a dilated left ventricle, moderate pulmonary hypertension, and a pulmonary capillary wedge pressure of 34 mm Hg. The patient had right ventricular biopsy performed demonstrating mild myocyte hypertrophy and an infiltrate consisting predominantly of lymphocytes with eosinophils present in significantly increased numbers. Treatment for myocarditis was initiated with azathioprine 200 mg daily and prednisone 60 mg per day with a tapering course over 6 months. Anticoagulation with warfarin and diuretics was initiated and angiotensin-converting enzyme inhibition was continued. Hydralazine was added later. One month into therapy, an echocardiogram demonstrated improved left ventricular function with only mild global hypokinesis. A repeat right ventricular biopsy 2 months after the first admission showed no evidence

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of myocarditis. At 6 months, left ventricular ejection fraction was normal (EFN 50%) and the patient asymptomatic. Conclusion: Ephedra (Ma Huang) is the suspected cause of hypersensitivity myocarditis in this patient due to the temporal course of disease and its propensity to induce vasculitis.

INTRODUCTION

Ephedra (Ma Huang) is a popular herbal product originating from China which contains from 0.5% to 2.5% sympathomimetic alkaloid (primarily ephedrine and pseudoephedrine). While cardiotoxicity is usually due to a dose-related alpha and beta receptor activity, vasculitis due to ephedrine and other sympathomimetics has been primarily limited to the cerebral arteries.¹⁻⁵ We describe a case of hypersensitivity myocarditis which appears to be attributable to ingestion of Ma Huang.

Case Report

A 39-year-old African American male with hypertension diagnosed 2 years prior to admission presented with a 1-month history of progressive dyspnea on exertion, dry cough, orthopnea, and dependent edema. He was thought to be in congestive heart failure secondary to hypertension and was admitted to initiate diuretic therapy with intravenous (IV) furosemide. After diuresis, the patient was discharged after a 23-hour admission. Outpatient echocardiography was scheduled but the patient was re-admitted 1 month after the first hospitalization with worsening symptoms which included palpitations and sharp, intermittent, left-sided chest pain. He denied weight loss, fevers, or chills. There were no known drug allergies. Admission medications are shown in Table 1. The patient took 1-3 of these tablets of each formulation daily for 3 months and was also taking pravastatin and furosemide 40 mg every morning.

The patient's past medical history was remarkable only for an injury to his left knee as a teenager and for an episode described as angioedema of uncertain cause in 1995. There was no history of rheumatic fever. His hypertension had never been treated. The patient denied alcohol intake, smoking, illicit drug use, or exposure to noxious chemicals. He had not traveled out of the Chicago area in the past year. His cardiac risk factors included only hypertension and recently diagnosed hypercholesterolemia. His father had died suddenly at the age of 47 years of uncertain cause.

Physical examination on the second admission revealed a well-nourished male who was cooperative and in mild respiratory distress. The temperature was 37.8°C with a respiratory rate 28/min, a heart rate 110 bpm, and

a blood pressure 120/86 mm Hg. The weight was 106 kg. Head and neck examination revealed normally reactive pupils and no lymphadenopathy. The lower lung field had rales without audible wheezes. Cardiovascular examination revealed internal jugular venous pulsations 5 cm above the sternal notch at 45° elevation. There were no carotid bruits. The precordium was hyperdynamic with a laterally displaced point of maximal impulse in the 6th intercostal interspace in the anterior axillary line. S₁ was normal in intensity and S₂ was normally split with a loud P₂ component. An S₃ gallop was present and a grade II/VI holosystolic murmur was maximal at the apex radiating to the axilla. Distal pulses were normal in the upper and lower extremities. The abdominal examination was benign without palpable masses and the liver span was approximately 10 cm. There was no edema of the extremities and neurologic examination was nonfocal.

An arterial blood gas on a flow of 2 L/min oxygen by nasal cannula revealed pH of 7.45, PCO₂ 34 mm Hg, PO₂ 81 mm Hg, and oxygen saturation 96%. Urinalysis was unremarkable and urine toxicology screen revealed no evidence of cocaine, opiates, or marijuana. Thyroid function studies, serum ferritin, and hemoglobin electrophoresis were normal. Westergren sedimentation rate was 8 mm/h. Two blood cultures from different sites were negative for growth. An electrocardiogram showed sinus tachycardia with left axis deviation, left atrial enlargement, and left ventricular hypertrophy. A chest X-ray demonstrated an enlarged cardiac silhouette with bilateral interstitial infiltrates consistent with congestive failure.

Medical therapy with IV furosemide and oral enalapril was initiated upon admission to the cardiac step-down unit. The day after admission, a two-dimensional echocardiogram showed mild left ventricular dilatation with global hypokinesis and an estimated ejection fraction of 15%. Left ventricular end-diastolic dimension was 60 mm and end-systolic dimension was 50 mm. There was mild to moderate mitral regurgitation and mild aortic and tricuspid insufficiency with structurally normal valves. Cardiac catheterization with coronary angiography revealed normal appearing coronary arteries and left ventriculography showed a dilated left ventricle (LV), pulmonary artery pressure 59/34 mm Hg, and a pulmonary capillary wedge pressure of 34 mm Hg. Estimated ejection fraction was 10-15%.

Several days into the hospital admission, the patient



Table 1

Herbalife Medications

Formula 1:	Papaya fruit	Capsicum
Fructose	Niacinamide	Chinese cruciferous concentrate
Soy protein	Zinc oxide	<i>Ligustrum lucidum</i>
Calcium carbonate	Copper gluconate	<i>Silybum marianum</i>
Caffeine	Vitamin A	<i>Rehmanina glutinosa</i>
Corn bran	Palmitate	Green Tablets:
Cellulose	Calcium pantothenate	Chinese Ma Huang—Extract
Guar gum	Papain	(approx 7 mg ephedrine alkaloid)
Potassium chloride	Bromelain	Yerba mate—(approx 10 mg
Canola oil	Pyridoxine hydrochloride	caffeine)
Soy	Thiamine	Valerian root
Oat fiber	Riboflavin	Purple willow
Dicalcium phosphate	Vitamin D3	Herbs
Carrageenan	Biotin	Papain
<i>dl</i> -Methionine	Cyanocobalamin	Bladderwrack
Magnesium oxide	Formula 2:	Beige Tablets:
Citrus pectin	Vitamins A, D, B-1, B-2, B-6,	Hawthorne berry
Psyllium seed husks	B-12, C, E	<i>Cascara sagrada</i>
Honey powder	Folacin	Uva ursi leaf
Ginger root	Biotin	Alfalfa
Ascorbic acid	Formula 3:	Cornsilk
Vitamin E acetate	Silica	Parsley
Ferrous fumarate	Boron	Marshmallow root
Licorice root	<i>Eleutherococcus senticosis</i>	Magnolia bark
Hawthorne berry	Molybdenum	Pan d'arco
Gotu kola	<i>Astragalus membranaceous</i>	<i>Pfaffia paniculata</i>
Dandelion root	<i>Ginkgo biloba</i>	Astragalus
Parsley	Fo-Ti	Fennel seed
	Shitake mushroom	Golden rod
	Bupleurum	Licorice

suffered an episode of hypotension requiring a reduction of the enalapril dose. Milrinone and dopamine IV were initiated. Six weeks after the first admission, the patient had right ventricular biopsy (Figure 1) performed demonstrating mild myocyte hypertrophy and an infiltrate consisting predominantly of lymphocytes. Eosinophils were also present, both mixed with the mononuclear cell infiltrate and in the myocardial interstitium in increased numbers. Congo red stains and iron stains were negative.

Treatment for myocarditis was initiated with azothioprine 200 mg/d and prednisone 60 mg/d with a tapering course over 6 months. Anticoagulation was begun with warfarin and diuretics and enalapril were con-

tinued. Hydralazine was subsequently added as to the outpatient therapy for hypertension. One month into therapy, an echocardiogram demonstrated markedly improved LV function with only mild global hypokinesis. A repeat right ventricular biopsy performed 5 months after the first admission showed no evidence of myocarditis. Right heart catheterization at this time revealed a pulmonary artery pressure 42/20 mm Hg and a pulmonary capillary wedge pressure 13 mm Hg. Cardiac output was 8.5 L/min. Repeat echocardiography revealed only mild global LV dysfunction with estimated ejection fraction of 50% and trivial mitral and tricuspid regurgitation. LV end-diastolic dimension was 50 mm and end-systolic



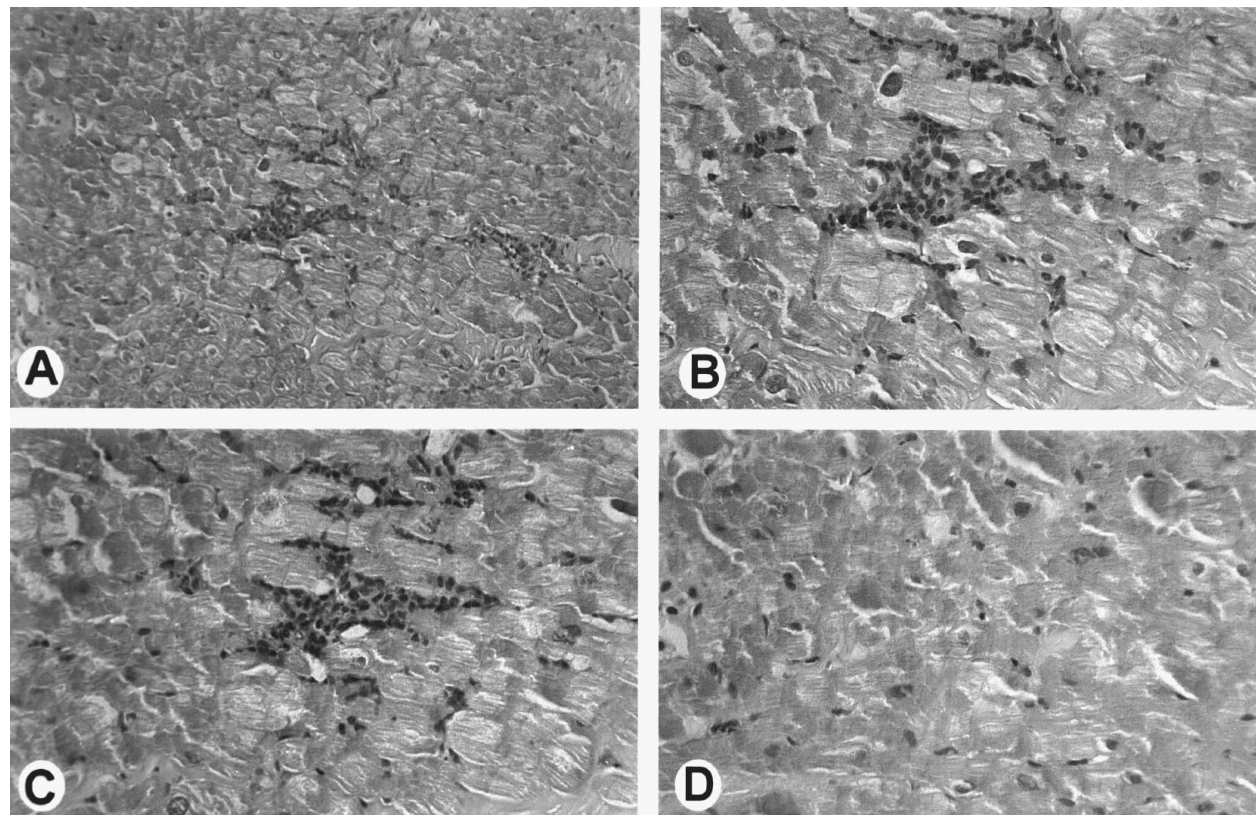


Figure 1. **A.** Endomyocardial biopsy showing a focus of mononuclear inflammatory cell infiltrate in the myocardium, expanding the interstitial space between the myocytes. The myocytes show mild hypertrophy and contraction band artifact. Hematoxylin and eosin ($\times 16$). **B.** Higher magnification shows myocyte damage with the formation of occasional large vacuoles adjacent to the inflammatory infiltrate. Note the presence of eosinophils surrounding the mononuclear infiltrate. Hematoxylin and eosin ($\times 40$). **C.** Deeper section of the same field shows a slightly more abundant eosinophilic infiltrate that is admixed with the lymphocytes. Hematoxylin and eosin ($\times 40$). **D.** Light micrograph of a different field of myocardium showing contraction band artifact and some eosinophils without evidence of mononuclear infiltrate. Hematoxylin and eosin ($\times 40$).

dimension was 38 mm. At 6-month follow-up, the LV function was normal, and the patient remained asymptomatic on pravastatin.

DISCUSSION

Hypersensitivity or eosinophilic myocarditis is rarely recognized clinically and usually found at autopsy. Methyldopa, the penicillins, sulfonamides, tetracycline, and antituberculous drugs are the pharmaceuticals most commonly associated with this entity (Table 2). Myocarditis has been described with sympathomimetics: primarily cocaine, *l*-norepinephrine, and phenylpropanolamine.⁶⁻¹⁴ The inflammatory infiltrate associated with cocaine-induced myocarditis is primarily lymphocytic and may be a

reaction of myocyte death or a hypersensitivity reaction.¹⁴ The other catecholamines usually produce a severe reversible dilated cardiomyopathy. It should be noted that other ingredients listed in Table 1 have not been associated with hypersensitivity myocarditis.

The ephedra species of plants (of which there are 40) consist of an upright evergreen (up to 6 feet in height) in which the sympathomimetic alkaloids are found in the green stems. While the ephedra species found in North and Central America are essentially devoid of these amine alkaloids, most Indian subcontinent and Chinese ephedras contain several alkaloids (including methylephedrine, methylpseudoephedrine, norepinephrine, and norepseudoephedrine) and thus can serve as the commercial source of ephedrine, and pseudoephedrine (although most ephedrine is produced by the reductive condensa-

Table 2
*Drug Causes of
Eosinophilic Myocarditis*

Acetazolamide
Amitriptyline
Amphotericin B
Ampicillin
Carbamazepine
Cefaclor
Chloramphenicol
Chlorthalidone
Desipramine
Hydrochlorothiazide
Indomethacin
Interleukin-4
Isoniazid
Methyldopa
Oxyphenylbutazone
Para-aminosalicylic acid
Penicillin
Phenindione
Phenobarbital
Phenylbutazone
Phenytoin
Spirolactone
Streptomycin
Sulfadiazine
Sulfisoxazole
Sulfononylureas
Tetanus toxoid
Tetracycline

tion of *L*-1-phenyl-1-acetylcarbinol with methylamine). As with any herbal product, it is difficult to determine the exact formulation of this ephedra product although total ephedrine in the green tablets (Herbalife) is estimated to be 7 mg.¹⁵

A case study described a patient with psychological dependence on ephedra, who developed a cardiomyopathy.¹⁶ She had ingested large quantities of the substance for over 10 years. Therapy with digoxin and diuretics and withdrawal of the ephedra resulted in resolution of her symptoms and a return to near normal left ventricular function. As with other sympathomimetic agents, ephedra appears to be the likely suspect causing myocarditis in this patient. Vasculitis has been documented with ephedrine use and the temporal nature along with the withdrawal of this substance and the subsequent clinical

improvement focuses on ephedra as the prime candidate. Furthermore, the other substances the patient was taking (including Yerba Mate or caffeine) have not been demonstrated to cause either vasculitis or myocarditis.

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