# Excessive oral amphetamine use as a possible cause of renal and splanchnic arterial aneurysms: A report of two cases

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***Introduction:*** **Multiple visceral aneurysms are uncommon and usually result from connective tissue diseases, systemic arteritis, or mycotic lesions. An association between multiple visceral aneurysms and excessive oral amphetamine use has not been reported.**
***Methods:*** **The clinical features of 2 patients at the University of Michigan Medical Center for treatment of multiple visceral aneurysms and amphetamine use were reviewed.**
***Results:*** **The patients had histories of excessive oral amphetamine use that ranged from 50 mg daily for 22 years to 200 mg daily for 2 years. No evidence was seen of systemic arteritis, connective tissue disorder, or an infectious process that may have caused the aneurysms. The arteriograms documented multiple splanchnic and renal artery aneurysms that involved both the large and the small arteries. The aneurysms of 1 patient were managed conservatively, and the patient has not had any clinical sequelae of the aneurysms during 14 years of follow-up. The second patient had hematobilia from a ruptured hepatic artery aneurysm that was treated with transcatheter embolic occlusion of the bleeding vessel. The patient had no recurrent gastrointestinal problems and continued to use amphetamines until his death from a cerebrovascular accident 6 years later.**
***Conclusion:*** **A possible association between excessive oral amphetamine use and multiple visceral aneurysms is reported for 2 patients in whom other risk factors were absent. The potential for chronic oral amphetamine use to cause multiple visceral aneurysms is an ill-defined but not unexpected complication of this substance that is known to contribute to arterial hypertension and to produce a form of necrotizing arteritis. (J Vasc Surg 1998;28:727-31.)**

Multiple visceral aneurysms are usually associated with a connective tissue disorder, systemic arteritis, or endocarditis with septic embolization that produces a distant arteritis with mycotic aneurysm formation.[1-4] Two patients with multiple visceral aneurysms have been encountered. These patients did not have the former illnesses but did have histories of excessive use of oral amphetamines. Both patients exhibited arteriographic patterns that were suggestive of a chronic arteritis affecting the large and the small arteries involved with aneurysmal changes. The clinical courses of these patients and a review of the literature that concerns amphetamine-associated vascular disease[5-13] support the tenet that a cause-effect association may exist between excessive oral consumption of amphetamines and these aneurysms.

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## CASE REPORTS

**Case 1.** A 35-year-old man had documented narcolepsy for which he had been taking 50 mg of D-amphetamine daily for 22 years. He was seen by his personal physician for intermittent episodes of abdominal pain, nausea, diarrhea, and gastrointestinal bleeding. The patient had insulin-dependent diabetes and hypertension and had had a previous splenectomy for trauma and a previous cholecystectomy. The patient had no history of alcohol abuse. He had an eosinophilia of unknown cause but no prior or existing clinical manifestations of connective tissue disease or systemic vasculitis. He also had no history of unusual febrile illnesses during childhood.

A computed tomography (CT) scan showed an aneurysm of the common hepatic artery that measured 4

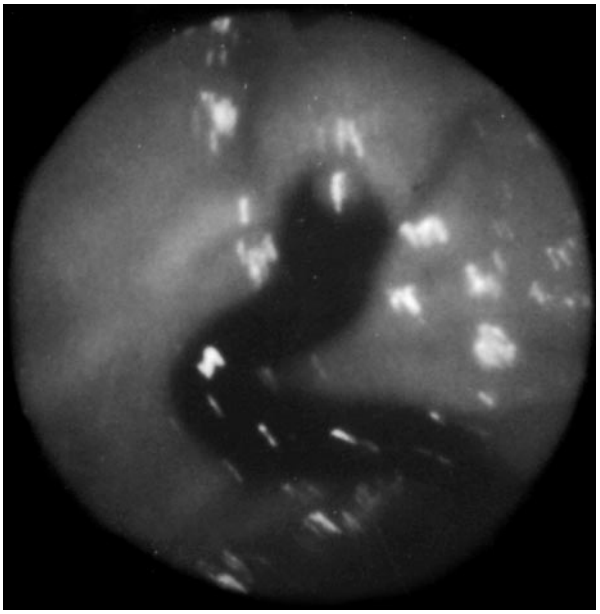

**Fig 1.** Case 1. Endoscopic demonstration of active bleeding *(arrow)* from ampulla of Vater (courtesy of Dr John D. Serini, Grand Rapids, Mich).

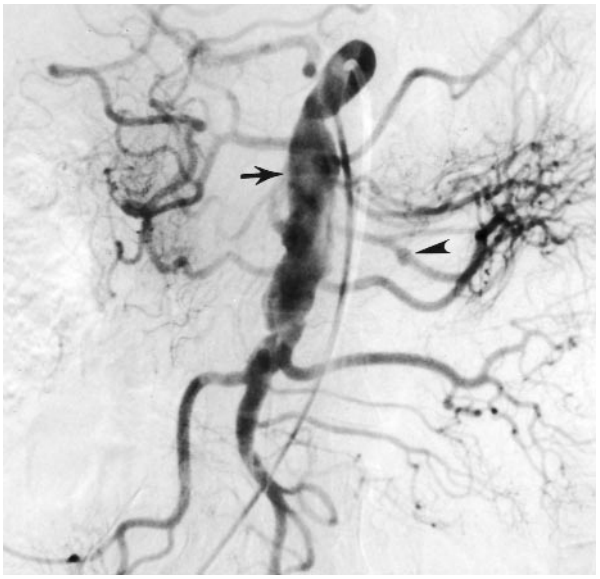

**Fig 3.** Case 1. Selective superior mesenteric arteriogram shows irregular-fusiform aneurysmal dilation of proximal artery *(arrow)* and small aneurysm of jejunal branch *(arrowhead)*.

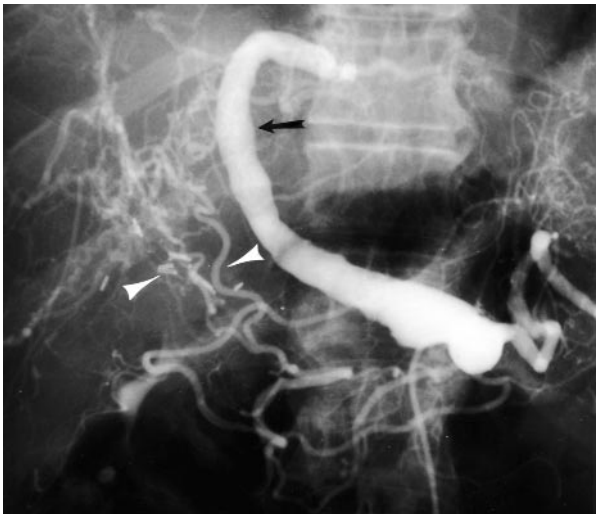

**Fig 2.** Case 1. Selective celiac arteriogram showing amorphous-fusiform aneurysm of common hepatic artery that extends into left hepatic artery *(arrow)*. Numerous biliary collateral vessels *(arrowheads)* are indicative of chronic occlusion of right hepatic artery.

cm in maximal diameter, with a lumen of 1.5 cm. The CT scan also revealed an aneurysmal superior mesenteric artery, hepatomegaly, and mildly dilated intrahepatic ducts. A technetium scan revealed bleeding in the right upper quadrant. An endoscopic evaluation revealed active bleeding from the ampulla of Vater (Fig 1).

The patient was stable hemodynamically, but the personal physician was concerned about the complexity of the cause for the bleeding, and the patient was transferred to the University of Michigan Medical Center. A physical examination did not reveal any vascular disease. The results of routine hematologic, coagulation, and liver function studies on admission were normal. Anti-DNA antibodies were absent. The results of rheumatoid factor titer, total protein, cryoglobin, and complement assay tests were normal. A hepatitis screen also had negative results. Echocardiography did not reveal any evidence of valvular vegetations.

An arteriogram revealed an amorphous-fusiform common hepatic artery aneurysm that extended into the left hepatic artery and a chronic occlusion of the right hepatic artery (Fig 2). Aneurysmal dilatation of the proximal superior mesenteric artery was also noted (Fig 3). Selective injection of the celiac artery revealed irregular thrombus within the hepatic artery aneurysm, but no active bleeding was evident. These aneurysms were not characteristic of periarteritis nodosa or other types of vasculitis. Because well-formed collateral vessels to the liver were present, it seemed reasonable and safe to occlude the common and left hepatic arteries with embolized Gianturco coils (Cook, Bloomington, Ind; Fig 4). The patient did well for the remaining years of his life and had no further episodes of gastrointestinal bleeding or abdominal pain. He continued to take amphetamines for narcolepsy. During the 6 years of follow-up, he exhibited no signs or symptoms of connective tissue disease or vasculitis. The patient died at the age of 41 years of a massive cerebrovascular accident. No autopsy was performed.

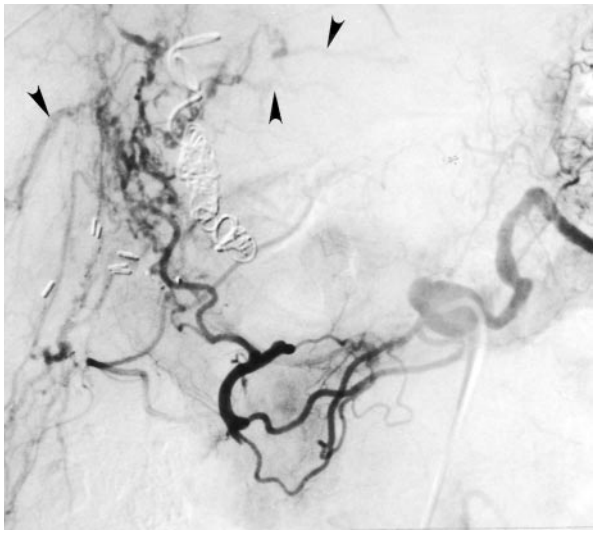

**Fig 4.** Case 1. Selective celiac arteriogram documents occlusion of common and left hepatic arteries with Gianturco (Cook, Bloomington, Ind) coils and reconstitution of right and left lobe intrahepatic branches *(arrowheads)* with biliary collateral vessels.

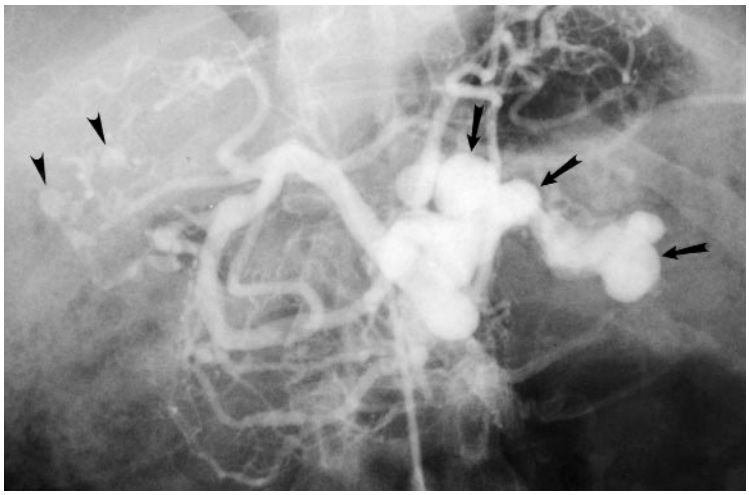

**Fig 5.** Case 2. Selective celiac arteriogram shows small hepatic artery aneurysms *(arrowheads)* and larger splenic artery aneurysms affecting proximal and middle portion of this vessel *(arrows)*.

**Case 2.** A 50-year-old man was admitted to the University of Michigan Medical Center for the evaluation of multiple calcifications that were consistent with the presence of multiple abdominal aneurysms and were identified on abdominal films. The patient previously had been morbidly obese and, 20 years before his admission, had consumed considerable amounts of D-amphetamine for more than 2 years, with ranges up to 200 mg a day. He had taken no amphetamines for at least 15 years before his admission. The patient had no prior or current manifestations of a collagen vascular disorder or systemic vasculitis. He had experienced no unusual childhood febrile illnesses. No evidence existed for hypertension or diabetes. He had a 25-year smoking history. The patient had experienced a myocardial infarction at 31 years of age during the time of his amphetamine use, but cardiac catheterization at that time did not document any coronary artery disease.

The results of the physical examination were unremarkable. The immunoglobulin levels and the erythrocyte sedimentation rates were normal. The test results for rheumatoid factor titers and antibodies for viral hepatitis were negative. Arteriography showed multiple macroarte-

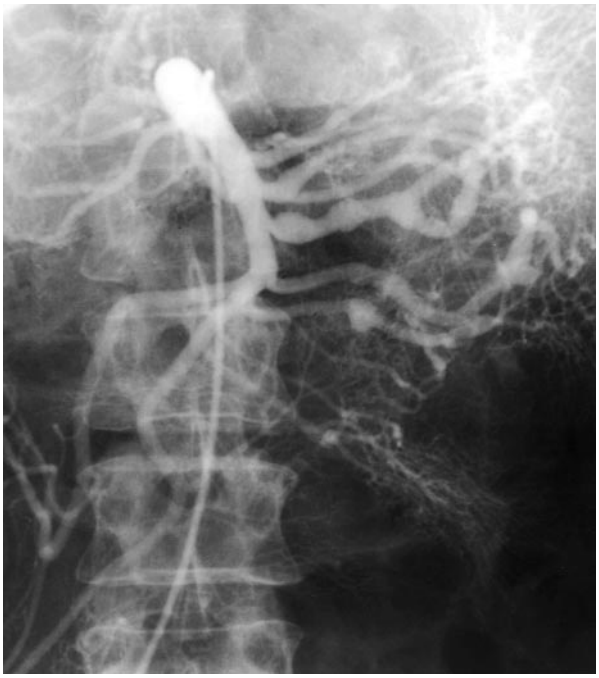

**Fig 6.** Case 2. Selective superior mesenteric artery arteriogram shows multiple proximal jejunal branch aneurysmal dilations.

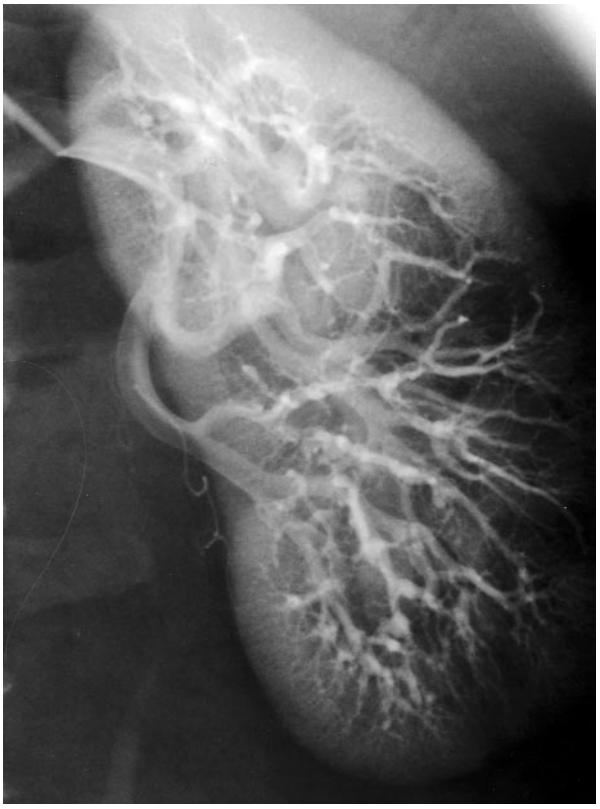

**Fig 7.** Case 2. Selective renal artery arteriogram exhibits irregular and tortuous vessels and microaneurysms consistent with arteritis.

rial aneurysms that involved the hepatic, splenic, and superior mesenteric arteries (Figs 5, 6). The branches of these vessels also were involved. Multiple microarterial aneurysms affected the intrarenal arteries (Fig 7). The larger aneurysms were not characteristic of common arteritis. The aneurysms were managed conservatively because the patient was asymptomatic. The patient has remained free of symptoms referable to his aneurysmal disease, and follow-up CT scan examinations have been unchanged for the past 14 years. During this follow-up period, the patient did not manifest signs or symptoms of connective tissue disease or vasculitis.

## DISCUSSION

Multiple visceral aneurysms of the splanchnic and renal arterial circulation are uncommon and usually are associated with collagen vascular diseases, systemic vasculitis disorders, or mycotic lesions that are usually associated with bacterial endocarditis, often as a result of illicit intravenous drug use.[1-4] The present cases had no evidence of the former conditions. Indeed, a feature common to both patients was the existence of chronic excessive oral amphetamine consumption.

Intravenous amphetamine abuse has been implicated as a cause for aneurysms in previously reported cases.[6-10] Many other confounding factors may have contributed to the aneurysms described in these earlier cases. For example, possible sepsis with subsequent mycotic aneurysm formation may have followed intravenous administration of multiple drugs in these patients. Arteriographic and histologic studies of tissues from patients with nonaneurysmal vascular complications attributed to amphetamines have revealed widespread mesenteric, renal, and cerebrovascular arterial disease.[5,6,8] The presence of lesions in medium-sized muscular arteries with involvement at bifurcations, where aneurysms often evolve, excludes most diseases other than the connective tissue disorders, which were not present in either of our patients.

Amphetamines are potent sympathomimetic amines with powerful central nervous system actions and peripheral $\alpha$ and $\beta$ adrenergic actions. They act by releasing catecholamines from interneuronal stores and by preventing their subsequent uptake. Whether chronic amphetamine use affected the intracranial arteries in our first patient who succumbed from a stroke was never determined.

However, amphetamines must be considered a possible contributor to arterial disease in this individual who died at the age of 41 years of a cerebrovascular accident. Similar events have been previously ascribed to amphetamines in both humans[5,9,13-15] and experimental animals.[12,13] Perhaps most revealing regarding the vascular effects of these substances was a report on deaths as results of ruptured intracranial berry aneurysms and ruptured aortic dissections among individuals with acute methamphetamine intoxication.[7] It is also reasonable to speculate that these sympathomimetic actions contributed to our second patient's myocardial infarction at the age of 31 years in the absence of anatomic coronary artery disease. Earlier reports have described cases of myocardial infarction attributed to coronary artery spasm in similar cases.[11,16,17]

The exact mechanism by which oral amphetamines cause multiple visceral aneurysms is unknown, but 2 acceptable hypotheses exist. First, the prolonged use of amphetamines may initiate chronic vasoconstriction of the affected arteries and thereby disrupt the blood flow through the vasa vasorum within the vessel wall. Mural ischemia as a result of such an event may cause an inflammatory injury or an actual vascular necrosis, with eventual aneurysmal dilatation. This may be the basis for the amphetamine-associated destructive necrotizing arteritis and the thrombus seen in previously reported cases.[5,6] Second, it is possible that the elevated blood pressures that accompany the chronic use of sympathomimetic amphetamines may lead to the accelerated weakening of vessels and of aneurysmal formation.

Amphetamine use for narcolepsy, lethargy, and attention deficit disorders recently has been on the rise, and abuse of this drug for recreational and weight-control purposes has been long recognized. The widespread use of amphetamines certainly may be curtailed by regulatory agencies. The State of Michigan had the highest rate of use of amphetamines among all states in 1983, but legal restrictions enacted in 1985 to limit prescriptions for these agents resulted in the decreased use of these drugs to the lowest level among all 50 states. However, the abuse and illicit diversion of these agents continues in many other populations.[18] A potential relationship between excessive oral amphetamine use and macrovascular visceral artery aneurysmal disease of the type encountered in the 2 reported cases should, in the absence of other common explanations, be considered when these 2 conditions are seen simultaneously.

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