# CASE REPORT

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# Cerebral Vasculitis Associated with Cocaine Abuse

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**ABSTRACT:** A variety of central nervous system pathology has been associated with cocaine abuse, including cerebral vasculitis. We report a case of a 25-year-old woman who died of hypoxic encephalopathy following cardiac arrest due to cocaine abuse. Autopsy revealed a distinctive cerebral vasculitis with features characteristic of hypersensitivity drug included vasculitis. The significance of cerebral vasculitis associated with cocaine is reviewed.

**KEYWORDS:** pathology and biology, cocaine, cerebral vasculitis

With the increase in cocaine abuse in the United States during the 1980s, a variety of vascular pathology associated with cocaine, including cerebral vascular complications, has been observed [*1,2*]. Hemorrhagic and nonhemorrhagic strokes, as well as transient ischemic attacks, have been described in association with both cocaine hydrochloride and alkaloidal cocaine [*1–3*]. In many cases of hemorrhagic stroke, underlying vascular lesions such as berry aneurysms and arteriovenous malformations have been observed; however, in others, despite extensive study, no apparent underlying vascular pathology has been described [*4*]. Recently, vasculitis associated with cocaine abuse has been reported [*5,6*]. We report here a third case of microscopically confirmed cerebral vasculitis associated with cocaine, and review the pathologic features of drug associated cerebral vasculitis.

## Case Report

A 25-year-old woman was brought by her boyfriend to the Emergency Room in cardiorespiratory arrest. Two or three hours earlier they had been stopped by the police for a minor motor vehicle violation. The police had become suspicious of drug abuse and had taken the boyfriend to the station for further questioning, leaving the woman in the car. When he returned after about two hours, he found her unconscious and seizing ("frothing at the mouth, breathing rapidly and shaking all over"). He drove immediately to the emergency room. She stopped breathing en route.

Initial EKG revealed asystole, and resuscitation was begun immediately. After administration of several doses of epinephrine and defibrillation, normal sinus rhythm was

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regained with a pulse of 80 and blood pressure of 140/80. Initial blood gasses (on Ambu bag) revealed pH – 6.65, pO2 – 274 mmHG, pCO2 – 38 mmHG and bicarbonate – 4.1 meq/L. pH was rapidly corrected with bicarbonate administration, although she continued to have evidence of a metabolic lactic acidosis (blood lactate – 9.6 mmol/L). She was transferred to the intensive care unit on a ventilator, unresponsive with fixed and dilated pupils.

There was a history of cocaine and alcohol abuse. Initial serum drug screen was negative for ethanol and other volatiles, and sedative hypnotics including barbiturates (amobarbital, butabarbital, secobarbital, pentobarbital and phenobarbital), benzodiazepines (chlordiazepoxide, diazepam, oxazepam), carisoprodol, ethchlorvynol, glutethimide, meprobamate, methaqualone, methylprylon, and phenytoin. Urine drug screen was positive for cocaine metabolite (benzoylecgonine) but negative for amphetamines, barbiturates, benzodiazepines methadone, methaqualone, opiates, phencyclidine, propoxyphene and tricyclics.

Neurologic evaluation revealed no response to voice or other stimulation. Pupils were 6 mm, equal, and fixed. There was no consensual response or gag reflex. However, roving conjugate eye movements with doll's head maneuver were noted. Motor exam revealed frequent, but intermittent, decerebrate posturing. There was some jerking, thought to be most consistent with myoclonus. Muscle tone was markedly increased. Drug therapy with propranolol, phenytoin, and phenobarbital was initiated. Postresuscitation EKG revealed right bundle branch block and evidence of inferior and anterior myocardial ischemic injury. Blood CPK levels were elevated (5940 μ/L the day following admission and 1932 μ/L two days after admission). AST (SGOT) and LDH were elevated five days after admission (97 IU/L and 410 IU/L, respectively). With the exception of an elevated white blood count (16 000 upon admission), the remainder of her laboratory studies including CBC, electrolytes, liver function tests (bilirubin, ALT or SGPT and alkaline phosphatase), triglycerides, cholesterol, total protein, uric acid, BUN, creatinine, and urinalysis were unremarkable.

Her clinical status remained unchanged. Two days after admission an EEG was markedly abnormal with a burst suppression pattern. Three days later a repeat EEG revealed no cerebral activity. Following a third EEG study, she was pronounced dead five days after admission.

Subsequent investigation revealed that the night before admission the patient and her boyfriend had been up most of the night using cocaine. When they were stopped by the police, the boyfriend had somewhat less than two grams of cocaine, which he gave to the patient. Apparently, she took the cocaine while he was at the police station. According to medical history given by friends and relatives, the patient had been a regular user of cocaine by nasal route for several years and drank alcohol, but was not known to use other drugs or take cocaine by the intravenous route or in the form of crack.

Autopsy revealed a well developed, young adult woman with no evidence of traumatic injuries or needle track scars. The heart, liver, spleen, and kidneys had been removed for organ donation. HIV antibody and hepatitis B antigen screening tests were negative before organ donation. Both kidneys and liver were successfully transplanted. One renal transplant patient died of a gastrointestinal hemorrhage approximately 10 months later. The other kidney recipient and the liver recipient remain well after approximately two and a half years.

The lungs were atelectatic and revealed microscopic reactive changes consistent with the five day course on a ventilator. There was no evidence of lymphadenopathy, and abnormalities of the pancreas, GI tract, or internal genitalia were not observed. There was no histologic evidence of vasculitis other than in the central nervous system described below.

The brain weighed 1575 g. It was soft and swollen. The ventral brainstem was flattened

and the hippocampal unci were prominent, especially on the left. There was distinct softening and some liquefactive change of the left infero-lateral temporal and occipital lobes in the distribution of the posterior cerebral artery.

Microscopically, there was diffuse encephalomalacia and edema, characterized by widespread, acute neuronal necrosis, and vacuolation of the neuropil. In addition, there was focal hemorrhage and disintegration of the cerebellar tonsils consistent with herniation. An acute infarct with liquefactive necrosis and sparse polymorph response was noted in the left occipital cortex.

There was a rather striking, focal but widespread vasculitis in the cortex and brainstem (Fig. 1), characterized by infiltration of vessel walls by lymphocytes and occasional polymorphs, and distinct cuffs of small lymphocytes in perivascular spaces of small parenchymal blood vessels. Areas of acute necrosis with a few polymorphs were seen in the pons and medulla, characteristic of acute infarcts. A single microglial nodule was noted in the medulla adjacent to one of these areas. These foci of acute infarction of the brainstem were often associated with the vasculitis. On the other hand, vasculitis was not particularly associated with infarction in the frontal, occipital and hippocampal cortex.

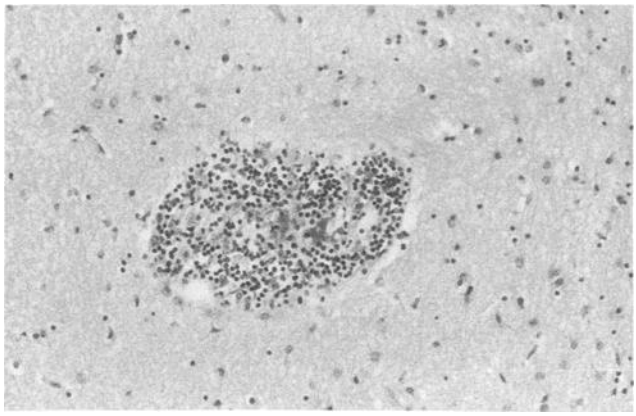

FIG. 1—*Small cerebral vessel with infiltration of wall by inflammatory cells and distinct perivascular cuff of lymphocytes.*

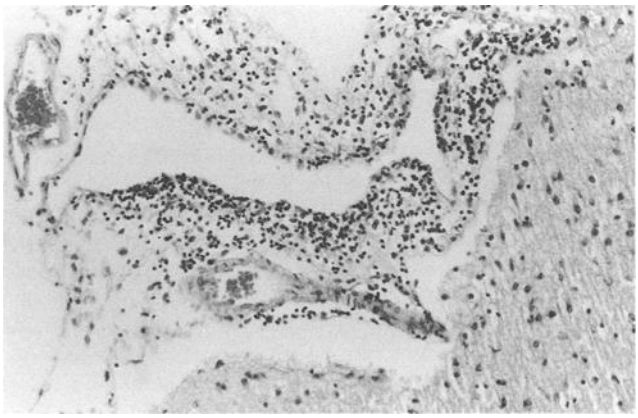

FIG. 2—*Leptomeningeal venule with mixed polymorphonuclear and lymphocytic vasculitis.*

Larger blood vessels did not appear involved; however, there was distinct inflammation of the venules of the meninges (Fig. 2) and a rather sparse lymphocytosis of the subarachnoid space. Rarely, hemosiderin-laden macrophages were noted in the subarachnoid and perivascular spaces. Wallerian degeneration and focal demyelination (by luxol fast blue stain) were noted in the pyramids of the medulla and lateral columns of the spinal cord. Giant cells were not observed.

In summary, the central nervous system showed diffuse hypoxic injury with cerebral edema, swelling and herniation with infarction in the distribution of the left posterior cerebral artery. There was widespread, focal, predominantly lymphocytic vasculitis of the small vessels of the brain that was associated with acute infarcts in the brainstem but not in the cortex. Vasculitis also involved venules of the leptomeninges, specifically.

Postmortem analysis of vitreous humor revealed 10 mcg/mL phenobarbital (therapeutic drug administered during hospitalization). Cocaine and its metabolites were not detected in the postmortem brain tissue or brain blood postmortem. Because the original serum drug screen did not include cocaine, the emergency room sample was reanalyzed two days after death (one week after it was obtained). Although cocaine was not detected, benzoylecgonine was detected at 3820 ng/mL concentration (GCMS, Pacific Toxicology Laboratories, Los Angeles, CA).

## Discussion

Zeek [*7*] was the first to separate hypersensitivity vasculitis from other forms of necrotizing vasculitis. Hypersensitivity vasculitis, she observed, was characterized by involvement of small arteries, arterioles, capillaries and veins as opposed to the polyarteritis type of vasculitis that involved medium sized and sometimes small sized arteries. Although drug reactions were included in Zeek's hypersensitivity vasculitis, other conditions have been included in this category, including bacterial and protozoal infections, influenza, serum sickness and some of the collagen vascular disorders [*8*].

In 1970 Citron et al. [*9*] reported on 14 drug abusers with a necrotizing periarteritis, clinically indistinguishable from periarteritis nodosa. Although vasculitis was defined angiographically, they reported in detail on the pathology of four cases that came to autopsy. In these patients they observed lesions in medium and small arteries in most organs and in the arterioles of the brain, characterized by fibrinoid necrosis of the media and intima with a mixed inflammatory infiltrate in the acute phase, and by intimal proliferation with subsequent fibrosis and lumenal narrowing in subacute and old lesions. Although their patients abused multiple drugs including narcotics, hallucinogens, stimulants and sedatives, intravenous amphetamine abuse was common to 12 of the 14 patients and they suggested that amphetamine may be the offending agent.

In 1979, Mullick and workers [*10*] described the pathologic features of drug related vasculitis in 30 patients. They observed a vasculitis of arterioles, capillaries, venules and small veins, and occasional small arteries but with sparing of larger vessels (elastic and muscular arteries and large veins). There was mixed infiltrate with a large lymphocytic component and oftentimes prominent eosinophilic component that sometimes spread to parenchymal organs. The pattern is similar to that described by Zeek, except that necrosis was not a feature. Clinically, their patients divided into two groups. Cases with skin involvement only resolved upon withdrawal of drug. On the other hand, many of those with systemic involvement died of their vasculitis. Aside from the skin, vasculitis was most commonly observed in the heart, liver and kidneys, although CNS involvement was documented.

Thus, there appear to be two major pathologic patterns of drug associated vasculitis: necrotizing ("toxic") and nonnecrotizing ("hypersensitivity") types [*8*]. Necrotizing vasculitis is characterized by arterial involvement in the pattern described by Citron et al.

[9], while the nonnecrotizing type is characterized by the pathologic features described by Mullick et al. [10]. Central nervous system involvement was observed in both series.

There have been a number of reports of vasculitis of the nervous system specifically associated with drugs and drug abuse [11–21]. However, many of these cases [16–21] are documented only by radiologic or angiographic methods and pathological confirmation is lacking. It has been pointed out by several investigators [22,23] that angiographic findings may be nonspecific and can be accounted for by mechanisms other than vasculitis, such as vasospasm induced by hemorrhage or the pharmacologic effects of drugs themselves. Nevertheless, pathological confirmation of cerebral vasculitis diagnosed angiographically has been reported in some cases [11–15].

Weiss et al. [11] reported two cases of intracerebral hemorrhage following the use of methamphetamine. In the pathologic material of one case they confirmed infiltration of the walls of small cerebral vessels by lymphocytes, histiocytes and a few neutrophils. Compound granular (gitter) cells were also noted, indicative of an old infarct as well as edema suggesting a more recent infarct. The second case revealed recent focal hemorrhage and mild gliosis of the white matter. The vessels were considered normal.

Rumbaugh et al. [12] reported on 19 patients who had abused multiple drugs including amphetamines (8 cases), barbiturates (9 cases), alcohol (7 cases) and heroin (6 cases), in whom they observed small arterial occlusive changes on cerebral angiograms. Pathologic findings were noted in two of the cases. These included changes involving the smaller arterioles and capillary segments of the cerebral vessels. Histiocytes and round cells were noted associated with arterioles and venules as well as perivascular reactive glial cells, microcystic degeneration and edema. In an accompanying article [34], they demonstrated cerebral vascular pathology in monkeys induced by the intravenous administration of amphetamine. The pathologic lesions in this animal model were characterized by focal ischemia and infarction, diffuse edema and ischemic cell injury, and hemorrhagic lesions centered around small sized vessels. Perivascular cuffs of lymphocytes were present in at least one animal.

Stafford et al. [13] observed a necrotizing angiitis of medium and small arteries, arterioles and veins on the nerve biopsy of a multidrug abuser (barbiturates, LSD, methamphetamines) suffering from systemic disease including mononeuropathy multiplex. Pathologic features included segmental fibrinoid necrosis with a pleomorphic infiltrate of polys, lymphoid cells, eosinophils and plasma cells in and around vessel walls. Kessler et al. [14] described a 22-year-old intravenous drug abuser of heroin, cocaine and amphetamine with classic angiographic changes of vasculitis. Cerebral biopsy revealed subarachnoid hemorrhage, fibrillar eosinophilic changes of vessel walls and variable leukocytic infiltrate in leptomeningeal and penetrating cortical arterioles.

In 1981, Bostwick [15] described the autopsy findings in a 39-year-old drug abuser of heroin, cocaine and amphetamines, who had vasculitic changes on cerebral angiography. He observed destructive arterial lesions in coronary, renal, periadrenal, mesenteric, brainstem and cerebral arteries consistent with the pattern described by Citron [9]. Thus, cerebral vasculitis associated with drug abuse of both necrotizing and nonnecrotizing types have been described.

Wooten et al. [16] described a 20-year-old man who developed subarachnoid hemorrhage confirmed by CT and lumbar puncture following the ingestion of ersatz "speed" (ephedrine). Initial angiogram was normal, but during a second angiogram seven days later he developed transient right hemiparesis and aphasia associated with angiographic changes in the distribution of the left carotid artery considered characteristic of vasculitis. A skin biopsy revealed finely granular deposits of IgM and C3 about small dermal blood vessels. Although inflammation was not seen in dermal blood vessels and pathologic confirmation of cerebral vasculitis was lacking, making other interpretations of the case possible [24], the finding of immune complexes in dermal blood vessels is intriguing since

it has been hypothesized that drug-associated hypersensitivity vasculitis is mediated by immune-complexes [7].

The first report of vasculitis related specifically to cocaine was made in 1987 by Kay and Fainstadt [5]. Their diagnosis, however, was based solely on angiography and no pathology was reported. Some workers [25] have questioned whether their findings might be accounted for by vasospasm due to subarachnoid hemorrhage. Volkow et al. [26] reported on abnormalities of cerebral blood flow in chronic cocaine abusers using positron emission tomography. They hypothesized that these changes could reflect vasospasm in cerebral arteries exposed chronically to the sympathomimetic actions of cocaine, although vasculitis might also account for the findings in at least some of these cases.

In 1990, Krendel et al. [6] reported pathological descriptions of vasculitis associated with cocaine abuse. Cerebral biopsy three weeks after the onset of neurologic symptoms associated with the smoking of crack cocaine in their first patient revealed acute and chronic inflammatory cells infiltrating the walls of small cortical vessels and an area of necrosis consistent with infarction. Their second patient was autopsied 42 days after admission for neurologic signs and symptoms associated with smoking of crack cocaine. The brain showed multiple, cystic, necrotic and gliotic areas in the white matter of the frontal lobes and right hemisphere and a lymphocytic infiltrate of small vessels. Neither of these patients demonstrated the classic "beading" on angiography considered to be characteristic of vasculitis, although the first patient did have an occlusive lesion of the right middle cerebral artery and a tapering occlusion of the basilar artery. Multinucleated giant cells were observed in the neuropil of both of these patients; however, their significance was uncertain in light of the lack of evidence of an infection that might produce them. We did not observe such cells in our case, but we did note a microglial nodule, apparently associated with an area of infarction in the medulla. As in Krendel's patients we found no evidence of infection including no clinical, pathologic or laboratory evidence for HIV or hepatitis B, specifically.

In our case, death was due to complications of cerebral hypoxia caused by seizures and cardiorespiratory arrest as a result of massive cocaine ingestion. It seems unlikely, however, that the vasculitis can be accounted for by global cerebral hypoxia. It is not clear that the five day clinical course is sufficient to develop a lymphocytic perivasculitis of this type. More importantly, we have not observed vasculitis as part of the pathologic picture of patients who die of global cerebral hypoxia caused by cardiorespiratory arrest due to drug overdose or other causes, nor are we aware of descriptions of vasculitis associated global hypoxic cerebral injury. An interesting point is that in our patient, although the vasculitis did not correlate with infarcts in the cortex, brainstem infarcts did correlate relatively well with vasculitic lesions. Could pre-exisiting vasculitis have contributed to the seizures and cardiac arrest in this patient?

Finally, the distinct vasculitis seen in this patient corresponds with the known morphologic patterns of drug reactions, especially of the nonnecrotizing, hypersensitivity variety. The distribution in leptomeningeal and small cortical vessels is strikingly similar to that described in Kessler's patient, and many of the pathologic features are reminiscent of the reports of Krendel et al. [6], Weiss [11] and Mullick et al. [10]. On the other hand, large vessel lesions such as those described by Bostwick [15] and Citron et al. [9] were not observed. Thus, cocaine associated vasculitis observed in our case, as well as those of Krendel et al. [6], is of the small vessel, hypersensitivity type. The role that such a vasculitis might play in the development of cocaine associated strokes or other neurologic conditions has yet to be determined.

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