# **Cocaine-Associated Cerebral Vasculitis**

Peter A. Merkel, Walter J. Koroshetz, Michael C. Irizarry, and Merit E. Cudkowicz

Cocaine use is associated with a variety of serious neurological complications, including cerebral infarction, intracerebral and subarachnoid hemorrhage, transient ischemic attacks, migraines, and seizures. We report two cases of intracerebral hemorrhage with biopsy-proven cerebral vasculitis associated with the use of cocaine. The first case involved a 32-year-old man who presented with headache, left-sided hemiparesis, and severe hypertension and who was found to have a large right putaminal hemorrhage on cranial tomographic (CT) scan. Cerebral angiography did not show vasculitic changes, but brain tissue obtained during hematoma evacuation revealed a nonnecrotizing leukocytoclastic angiitis of the small vessels. The second case involved a 20-year-old man who presented with headache, agitation, and speech difficulty that progressed to disorientation and dysphasia. He had a large left temporoparietal hematoma seen on CT scan. Cerebral angiography was consistent with vasculitis, and brain tissue obtained during hematoma evacuation revealed a small vessel vasculitis. In both cases, thorough clinical and laboratory investigations found no evidence of systemic vasculitis or an etiologic agent other than cocaine. We also critically reviewed the previously reported cases of cocaineassociated cerebral vasculitis and the relevant medical literature to discuss the "cocaine-associated vasculitis syndrome" in the context of more established vasculitidies, including hypersensitivity vasculitis. In addition, we outline a diagnostic and therapeutic approach to patients with possible cocaineassociated vasculitis.

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INDEX WORDS: Vasculitis; cocaine; central nervous system; intracerebral hemorrhage.

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THE current epidemic of cocaine abuse has led to a greater understanding of the drug's many potential medical complications.<sup>1</sup> The use of cocaine by any route of administration can lead to serious neurological complications. Cocaine has been associated with cerebral infarction, intracerebral and subarachnoid hemorrhage, transient ischemic attacks, migraines, and seizures.<sup>2-7</sup> In recent years, there has been an alarming increase in the number of reported cases of cocaine-associated strokes.3,7 Proposed mechanisms for cocaine-induced stroke include hypertension with increased sympathetic drive, vasospasm, thrombosis, and cardiogenic embolus.<sup>6,8-11</sup> Six cases of cerebral vasculitis associated with cocaine use<sup>3,12-15</sup> have been reported. Four of these patients had encephalopathy or coma with pathological evidence of vasculitis.<sup>13-15</sup> In the other two cases, cerebral infarct and hemorrhage occurred in cocaine users and angiography showed arterial

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narrowing. Because of the scarcity of pathological and clinical correlation, the features of cocaine-associated vasculitis and its role in stroke is not clear.

We report two cases of intracerebral hemorrhage with biopsy-proven cerebral vasculitis associated with cocaine use. Case 1 has been previously reported in another format.<sup>16</sup> In addition, we critically review the previously reported cases and the relevant literature on vasculitis to discuss the "cocaine-associated vasculitis syndrome" in the context of more established vasculitidies.

### CASE 1

A 32-year-old right-handed man presented with headache and left-sided hemiparesis. He had a history of untreated hypertension and regular cocaine and alcohol use. He used intranasal cocaine on the day of admission and during the 2 previous days. On the day of admission he acutely developed a right temporal headache followed by left-sided weakness. In the emergency ward he complained of a severe right frontal and temporal headache and vomited. His blood pressure was 230/130 mm Hg, and he was treated with topical nitropaste, intravenous labetalol, and intravenous nitroprusside; medications were titrated to maintain systolic blood pressure between 160 and 180 mm Hg. Dexamethasone, 10 mg intravenously, was administered to control cerebral edema.

On examination the pulse rate was 92/min and regular and he was afebrile. There was a fourth heart sound and a grade II/VI systolic ejection murmur. He was somnolent but easily arousable and he answered questions appropriately with two- to three-word responses. Dysarthria, right gaze preference, left hemianopia, left flaccid hemiplegia, left hemianesthesia, left hyporeflexia, and left Babinski response were present. There was no papilledema and pupillary reflexes were normal. The rest of the physical examination was unremarkable.

On admission the hemoglobin level, leukocyte count, and platelet counts, as well as the renal and coagulation studies were normal. There was no eosinophilia. The electrolytes were normal except for a potassium value of 2.7 mEq/L. Liver enzyme concentrations were elevated initially with serum aspartate aminotransferase, 195 U (normal 10 to 40 U), lactic dehydrogenase, 348 U (normal 110-219 U), and alkaline phosphatase, 152 U (normal 45 to 115 U), but they normalized after 3 days. A Westergren erythrocyte sedimentation rate was 32 mm/h. Serum toxicology results were negative and urine toxicology screen results were positive for cocaine metabolites. An electrocardiogram showed a normal sinus rhythm at a rate of 78 with T wave inversions inferiorly. The chest radiograph revealed mild left ventricular prominence. A noncontrast cranial tomographic (CT) scan showed a  $5.0 \times 5.0 \times 4.5$  cm right putaminal hemorrhage with mass effect and a 0.5-cm midline shift to the left (Fig 1). Echocardiogram revealed mild concentric left ventricular hypertrophy but was otherwise unremarkable. Subsequent negative laboratory studies included screening for antibody to human immunodeficiency virus, antinuclear antibodies, antineutrophil cytoplasmic antibodies (ANCA; immunoflourescence staining and antibodies to myeloperoxidase and proteinase 3), rheumatoid factor, hepatitis B surface antibody, antigen,

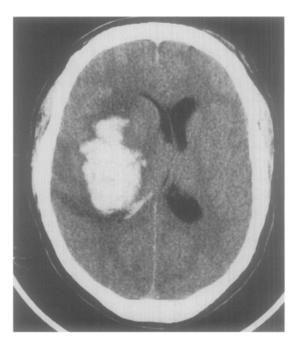


Fig 1: A noncontrast CT scan of the brain of case 1 showing a  $5.0 \times 5.0 \times 4.5$  cm right putaminal hemorrhage with surrounding low absorption consistent with edema. There is slight mass effect on the right lateral ventricle.

and core antibody, and anticardiolipin antibodies (immunoglobulin [Ig]G and IgM classes). Rapid plasma reagin test for syphilis was nonreactive. Urinalysis results, serum immune electrophoresis results, levels of the third and fourth complement components, and total complement were normal. Twenty-four urine collection for vanillymandelic acid and metanephrines was normal.

A four-vessel cerebral angiogram performed on hospital day 2 showed mass effect on the right middle cerebral carotid artery from the hemorrhage but no evidence of an aneurysm, arteriovenous shunting, or vasculitis. The next day the patient was more somnolent, with decreased upgaze and bilateral Babinski responses present. A noncontrast cranial CT scan revealed extension of hemorrhage into the right lateral ventricle with an 0.8-cm midline shift to the left. On the fourth hospital day the patient was more drowsy and only arousable to noxious stimuli. Another cranial CT scan revealed increased mass effect and a 1.5-cm midline shift to the left. He was intubated, hyperventilated, and given intravenous mannitol and dexamethasone. His level of consciousness continued to decline, and on the 5th day of hospitalization he underwent right parietal craniotomy with evacuation of the hematoma. The pathology revealed a nonnecrotizing leukocytoclastic angiitis (Fig 2). Several of the venules had transmural inflammatory cell infiltrates consisting of neutrophils and mononuclear cells. Special stains for microorganisms were negative.

After surgery the patient's mental status improved but he had a persistent severe left hemiparesis. The dexamethasone was tapered off within 1 week. He was treated with oral antihypertensive agents and discharged to a rehabilitation hospital. Three months after discharge a severe left hemiparesis remained but he had no new neurological sequelae.

#### CASE 2

A 20-year-old right-handed man presented to another hospital with a 2-day history of headache, increasing agitation, and speech difficulty. Evaluation included a normal noncontrast cranial CT scan and an unremarkable lumbar puncture. He was diagnosed as having a migraine headache. After 48 hours of waxing and

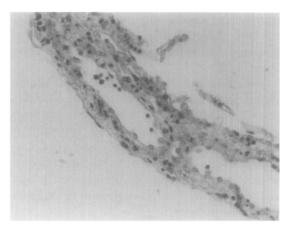


Fig 2: Pathological specimen from excavation of right parietal region of case 1. A small cerebral venule with a nonnecrotizing transmural inflammatory cell infiltrate consisting of polymorphonuclear cells, macrophages, and lymphocytes (H&E, original magnification  $25 \times$ ).

waning headache, the patient was acutely severely disoriented and dysphasic. A repeat CT scan revealed a left temporoparietal hemorrhage and he was transferred to our institution.

There was no history of hypertension. A drug history revealed daily marijuana and alcohol use and the use of cocaine within at least 6 months before admission. The patient denied recent amphetamine or cocaine use.

The patient's blood pressure was 122/70 mm Hg, his pulse rate was 80/min and regular, and he was afebrile. He was easily arousable and intermittently combative. There was a fluent aphasia characterized by impaired comprehension and nonsensical speech output with frequent paraphasic errors, a right hemianopia, and no papilledema. He moved all four extremities spontaneously, and deep tendon reflexes were symmetric and hyperreflexic. Bilateral Babinski responses were present. The remainder of the physical examination was unremarkable.

Normal admission laboratory values included hemoglobin level, leukocyte and platelet count, blood urea nitrogen concentration, serum creatinine level, serum electrolyte count, liver function tests, coagulation studies, and arterial blood gas level. There was no eosinophilia. The Westergren erythrocyte sedimentation rate was 20 mm/h. Serum toxicology screen was negative, and the urine drug screen was positive only for marijuana. An electrocardiogram and chest radiograph were unremarkable. A noncontrast head CT scan revealed a  $5.4 \times 3.0 \times 4.0$  cm left temporoparietal hematoma, with surrounding edema and subarachnoid blood within the adjacent cortical sulci and the ambient cistern (Fig 3). A left internal carotid and left vertebral artery angiogram revealed focal, segmental areas of narrowing in multiple branches of the left middle cerebral artery (MCA), and left anterior cerebral artery (ACA) (Fig 4A and B). There was no evidence of aneurysm or arterial venous shunting. Subsequent negative laboratory studies included screening for antibody to human immunodeficiency virus, antinuclear antibodies, anti-Ro antibodies, anti-La antibodies, antinative DNA antibodies. ANCA (immunoflourescence staining and antibodies to myeloperoxidase and proteinase 3), rheumatoid factor,

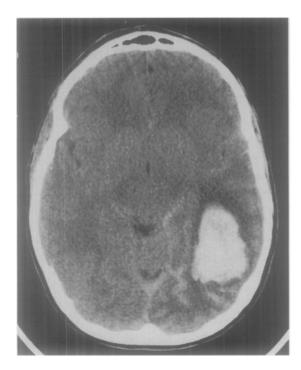


Fig 3: A noncontrast CT scan of the brain of case 2 showing a  $5.4 \times 3.0 \times 4.0$  cm left temporoparietal hematoma with surrounding low absorption consistent with edema. There is subarachnoid blood within the cortical sulci of the left temporal and parietal lobes.

anticardiolipin antibodies (IgG and IgM classes), lupus anticoagulant, rapid plasma reagin test for syphilis, urinalysis results, total complement level, and blood cultures.

The patient received intravenous dexamethasone, 4 mg, every 6 hours. During the subsequent 12 hours he became somnolent and hypertensive and underwent a left parietal craniotomy with evacuation of an intracerebral hematoma. Surgical pathology revealed small vessel vasculitis with neutrophil infiltration and fibrinoid degeneration of the walls of small arterioles and veins (Fig 5). In the adjacent parenchyma there was necrosis, neutrophil infiltration, hemorrhage, and edema. Special stains for microorganisms were negative.

After surgery the patient had a receptive aphasia and a right hemianopia. He was continued on high-dose dexamethasone, 4 mg, every 6 hours throughout his 17-day hospitalization. On the 13 hospital day a repeat angiogram of the left vertebral and bilateral common carotid arteries revealed multiple mild small segmental narrowings involving the middle-sized arteries and small branches of the left and right MCAs, the bilateral ACAs, and posterior cerebral arteries (PCA). The left MCA and left PCA were most affected. His neurological deficits cleared partially, and at discharge he had a residual right quadrantanopsia, a mild receptive aphasia, impaired short- and long-term memory, and difficulty with reading and writing.

Glucocorticoids were slowly tapered over 6 months. He developed a seizure disorder characterized by multiple episodes of olfactory hallucinations, fuguelike spells, loss of memory and frequent temper outbursts. A follow-up fourvessel cerebral angiogram performed 9 months after his initial event showed complete resolution of his prior abnormalities with no evidence of vasculitis. Eighteen months after his cerebral hemorrhage he had a residual right quadrantanopsia, alexia, and a mild receptive aphasia.

## DISCUSSION

The clinical and laboratory features of our two patients and the six previously reported cases of cerebral vasculitis associated with cocaine use<sup>3,12-15</sup> are summarized in Tables 1 and 2. In addition to these eight cases of cocaineassociated vasculitis, two cases of chronic co-

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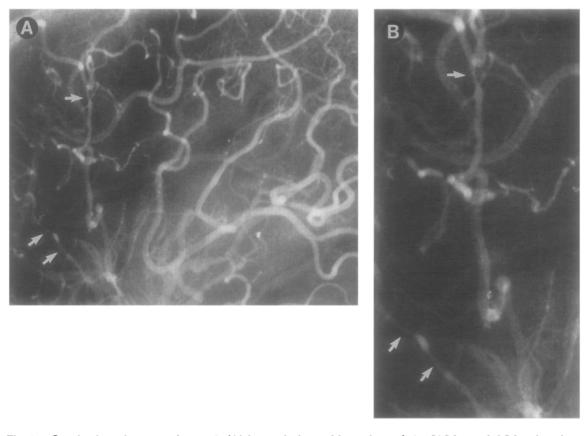


Fig 4: Cerebral angiogram of case 2. (A) Lateral view of branches of the MCAs and ACAs showing multiple areas of focal, segmental narrowing (arrows). (B) Close-up view of the branches of the left ACA showing several areas of focal narrowing (arrows).

caine abusers with transient ischemic attacks or strokes with angiograms showing "multifocal segmental stenoses" have been reported in abstract format.<sup>17</sup> A case of acute reversible renal failure, rhabdomyolysis, and leukocytoclastic vasculitis of the skin in a 34-year-old cocaine abuser has also been reported.<sup>18</sup> All eight welldescribed cases of cerebral vasculitis involved young people with a mean age of 28 years (range 22-36). The clinical presentations vary in several aspects. In one previously reported case, and in our two cases, patients suffered intracerebral hemorrhages. Our report is the first to document vasculitis by brain biopsy in cocainerelated intracerebral hemorrhage. Of the six previously reported cases, one suffered an ischemic stroke; the other five had encephalopathy and/or coma, one with superimposed focal findings. Only one case was associated with hypertension on clinical presentation. There

was no evidence of drug use other than with ethanol, marijuana, and cocaine, although polysubstance abuse cannot be excluded. In the six cases with tissue diagnosis, the time between the patient's last known cocaine use and the brain biopsy varied from hours to up to 6 months. All three of the usual forms of cocaine administration are mentioned in these case reports: nasal inhalation or "snorting," lung inhalation from smoking "crack," and intravenous use. Both neurological and cardiac events are known to occur with any of these routes of administration and with varying doses.<sup>2,4,5,19,20</sup> The possible contribution of other undisclosed drugs or contaminants to the development of vasculitis must be strongly considered as "street" drugs may contain multiple impurities and pharmacologically active additives.

Pathology specimens from the four previously reported cases with tissue diagnoses showed

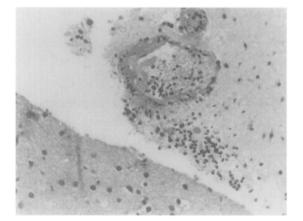


Fig 5: Pathological specimen from excavation of left parietal region of case 2. A small vessel showing fibrinoid degeneration and neutrophil infiltration of the vessel wall. There is necrosis, polymorphonuclear cell infiltration, and edema in the adjacent parenchyma (H&E, original magnification  $25 \times$ ).

acute and chronic small vessel inflammation.<sup>13-15</sup> In cases 4, 5, and 6 (as listed in Tables 1 and 2) there was predominantly lymphocytic infiltration of cerebral blood vessels, whereas in our cases 7 and 8, the walls and perivascular spaces of small arteries and veins contained mostly polymorphonuclear cells. Giant cells or granulomas were not seen in any of the six biopsy specimens. Necrosis of the arterial vessel wall was seen in case 8. In two of the biopsyproven cases and in the two cases without biopsy material, angiography showed focal narrowing in medium-sized arteries. Whether the vasculitis seen in small vessels also involved medium-sized arteries, accounting for the abnormal angiographic findings, is not clear. Autopsy material in case 4 did not show vasculitis in the medium and large vessels, but the angiogram in that case was normal.

The diagnoses of vasculitis in the first two published cases were based only on cerebral angiography. Reliance on imaging studies may cause clinicians to miss cases of small vessel disease.<sup>21,22</sup> The etiology of focal arterial narrowing seen by angiography in cases of cocaineassociated stroke is not definitively known. Cocaine has known vasoconstrictive properties in the coronary circulation<sup>23-32</sup> and vasospastic effects in cerebral vessels<sup>3,24,33</sup> with regional blood flow abnormalities demonstrable even 10 days after administration.<sup>24,25,33,34</sup> Cocaine-induced vasospasm is thought to be a contributing factor in some cases of stroke,6,8,9 myocardial infarction,<sup>31,32</sup> and fetal injury.<sup>26,27,35</sup> A case of central retinal artery occlusion related to cocaine use in a patient with a normal-appearing arterial system has been reported.<sup>11,36</sup> Hypertension, a well-known effect of cocaine use, has been independently shown to also induce vasospasm.<sup>37-41</sup> This effect has also been shown with methamphetamine.<sup>42,43</sup> It is difficult to know whether vasospasm or vasculitis is the cause of angiographic abnormalities in patients taking cocaine or catecholaminergics,44 and pathological study may be required. Nevertheless, the findings in the angiograms of patients with cocaine-associated vasculitis of "beading" are more consistent with vasculitis than with spasm. Segmental arterial narrowings that persist long after drug exposure, as in case 8, strongly favors a vasculitic etiology.

Vasculitis associated with drug abuse has been well described.45-54 Substances listed in these reports include methamphetamine, phenylephrine, ephedrine, heroin, barbiturates, dlysergic acid diethylamide (LSD), and cocaine. The polysubstance nature of drug abuse has often greatly complicated efforts to associate disease with an individual agent. However, methamphetamine and structurally related substances are known to cause necrotizing vasculitis.<sup>51-54</sup> A rhesus monkey model of methamphetamine-induced central nervous system (CNS) vasculitis has been described.<sup>42</sup> Angiographic and pathological studies in both humans and experimental animals show that vessels of all calibers can be involved in drugrelated vasculitis but that small vessel disease predominates.42,46,47,55 Most of these reports describe a necrotizing vasculitis similar to polyarteritis nardosa (PAN).<sup>42,46,47,53,55-60</sup> Less is known about the vascular pathology in cocaine abuse. Experimental evidence of direct cocaine-induced arterial injury was shown in rabbits given intravenous cocaine;61 collagen synthesis was altered and to the elastic media of arteries was damaged. Cocaine administration also releases chemical mediators that may be responsible for endothelial inflammation.<sup>62</sup> Cocaine use could

| Case<br>No. | Source                        | Patient<br>Age (yr)/<br>Gender | Route of<br>Cocaine<br>Use | CNS Event                          | Initial<br>Blood<br>Pressure<br>(mm/Hg) | Angiogram                        |
|-------------|-------------------------------|--------------------------------|----------------------------|------------------------------------|-----------------------------------------|----------------------------------|
| 1           | Kaye and Fainstat, 1987       | 22/M                           | Nasal                      | Infarct                            | 140/70                                  | Beading, occlusion,<br>narrowing |
| 2           | Kionoff et al, 1989           | 29/F                           | Inhalation                 | ICH                                | 120/80                                  | Beading, narrowing               |
| 3           | Krendel et al, 1990           | 36/M                           | Inhalation                 | Weakness, dysarthria,<br>confusion | 140/70                                  | Occlusion, narrowing             |
| 4           | Krendel et al, 1990           | 31/F                           | Inhalation,<br>IV          | Coma, cerebral<br>edema            | Not stated                              | Normal                           |
| 5           | Fredericks et al, 1991        | 32/M                           | Nasal, IV                  | Confusion, ataxia                  | "Normal"                                | Normal                           |
| 6           | Morrow and McQuillen,<br>1993 | 25/F                           | Nasal                      | Seizure, coma                      | Asystolic                               | Not done                         |
| 7           | Current Report, 1995          | 32/M                           | Nasal                      | ICH                                | 233/131                                 | Normal                           |
| 8           | Current Report, 1995          | 20/M                           | Nasal                      | ICH                                | 122/70                                  | Narrowing                        |

 
 Table 1: Clinical Characteristics of Reported Cases of CNS Vasculitis Associated With Cocaine Use

Abbreviations: CNS, central nervous system; IV, intravenous; ICH, intracerebral hemorrhage.

produce a cascade of cytokine release causing vasospasm and arteritis.

The pathogenesis of cocaine-associated cerebral vasculitis remains unknown. In all eight cases reviewed there is no evidence of a systemic vascular disease or an obvious etiologic agent for vasculitis other than cocaine. When reported, tests for human immunodeficiency virus, syphilis, and antinuclear antibodies were all negative. One patient<sup>14</sup> had a positive test for hepatitis B virus surface antigen but also had hepatitis B core antibody and no evidence for active hepatitis B infection. Hepatitis B virus surface antigen was not present in the other five patients for which adequate information was available. No cases of abnormal renal function were reported. Neither anticardiolipin antibodies (IgG and IgM classes)63-65 nor ANCA66,67 (cvtoplasmic and perinuclear types) were found in our two patients. The erythrocyte sedimentation rates reported for the cases of cocaine associated vasculitis varied widely (15-108 mm/ h). The necrotizing small vessel lesions seen in our patients are consistent with PAN. PAN usually affects medium-sized arteries and could, therefore, account for the angiographic abnormalities seen in four of the cases. However, the

confinement of vasculitis to the CNS, involvement of small vessels, and absence of P-ANCA (more specifically, antimveloperoxidase antibodies) are all inconsistent with PAN. Similarly, isolated CNS disease, absence of a granulomatous arteritis, and a negative test for C-ANCA (more specifically, antiproteinase 3 antibodies) make Wegener's granulomatosis very unlikely. The pathology of primary angiitis of the CNS (PACNS)<sup>17,21,68</sup> differs from that seen in our patients. PACNS involves infiltration of vessels with mononuclear, multinucleated, and plasma cells, and granuloma formation is common. The differences in histology and the rarity of PACNS make it unlikely that patients with cerebral vasculitis associated with cocaine represent a subset of cases of PACNS.

These eight cases only partially fit the usual pattern of drug-related vasculitis. Hypersensitivity vasculitis is a vague term encompassing vasculitis associated with medications,<sup>69</sup> serum sickness, malignancies, and infections. CNS involvement in hypersensitivity vasculitis including cerebral infarcts, focal brain lesions, or acute encephalopathy is uncommon, occurring in approximately 10% of cases.<sup>70</sup> Patients with hypersensitivity vasculitis almost always have

|                                     |                                                     |                                        | Clinical Outcome          |                                                        |  |
|-------------------------------------|-----------------------------------------------------|----------------------------------------|---------------------------|--------------------------------------------------------|--|
| Cerebral Artery<br>Biopsy/Pathology | Time Between<br>Cocaine Use and<br>Biopsy/Pathology | Treatment                              | Short Term<br>(d-wk)      | Long Term<br>(mo)                                      |  |
| Not done                            |                                                     | Glucocorticoids                        | No information            | Slow improvement                                       |  |
| Not done                            |                                                     | None                                   | Worsened                  | Stabilized after hema-<br>toma evacuation              |  |
| Small vessel angiitis               | 3.5 wk                                              | Glucocorticoids                        | Stabilized                | Gradual improvement                                    |  |
| Small vessel angiitis               | 42 d                                                | Glucocorticoids, cyclo-<br>phosphamide | Death                     |                                                        |  |
| Small vessel angiitis               | 13 d                                                | Glucocorticoids                        | Marginal improve-<br>ment | Gradual improvement                                    |  |
| Small vessel angiitis               | 5 d                                                 | None                                   | Death                     |                                                        |  |
| Small vessel angiitis               | 2 d                                                 | None                                   | Stabilized                | Gains in rehabilitation                                |  |
| Small vessel angiitis               | Within 6 mo                                         | Glucocorticoids                        | Partial recovery          | Residual quadrant<br>anopisa; seizures;<br>memory loss |  |

Table 1: (Cont'd)

skin lesions and eosinophilia and often have multiorgan involvement.<sup>69,71</sup> Hypersensitivity vasculitis was originally described as a necrotizing vasculitis,<sup>72-73</sup> but a more recent study questioned this observation and described a bland nonnecrotizing vasculitis.<sup>69</sup> Hypersensitivity vasculitis only affects small vessels, usually arterioles and venules with polymorphonuclear and mononuclear cells.<sup>69,71-73</sup> This is the pathological pattern seen in the six biopsy-proven cases in cocaine users. However, the cerebral angiograms in cases 1, 2, and especially 8 suggest that vasculitis may have affected medium-sized vessels as well. The time between antigen exposure and clinical manifestations can be quite variable in hypersensitivity vasculitis. Some pathological changes require an extended period of time to develop. All of the patients in the current series had exposure to cocaine beginning months to years before clinical presentation. In seven of eight cases, hospitalization followed cocaine use by hours. However, biopsy-proven vasculitis was

Table 2: Laboratory Results in Cases of CNS Vasculitis Associated With Cocaine Use

| Case<br>No. | Source                        | ANA      | ESR<br>(mm/hr) | BUN/<br>Creatinine | RPR or<br>MHATP | ANCA     | ACLA     |
|-------------|-------------------------------|----------|----------------|--------------------|-----------------|----------|----------|
| 1           | Kaye and Fainstat,<br>1987    | Negative | 15             | Normal chemistries | Negative        | NA       | NA       |
| 2           | Klonoff et al, 1989           | NA       | NA             | NA                 | NA              | NA       | NA       |
| 3           | Krendel et al, 1990           | Negative | 85             | Normal chemistries | Negative        | NA       | NA       |
| 4           | Krendel et al, 1990           | Negative | 108            | Normal chemistries | Negative        | NA       | NA       |
| 5           | Fredericks et al, 1991        | Negative | Normal         | NA                 | NA              | NA       | NA       |
| 6           | Morrow and<br>McQuillen, 1993 | NA       | NA             | Normal             | NA              | NA       | NA       |
| 7           | Current Report, 1995          | Negative | 32             | Normal             | Negative        | Negative | Negative |
| 8           | Current Report, 1995          | Negative | 2              | Normal             | Negative        | Negative | Negative |

Abbreviations: ANA, antinuclear antibody; ESR, erythrocyte sedimentation rate; BUN, blood urea nitrogen; RPR, rapid plasma reagin; MHATP, *Trepenema pallidum* hemagglutinayion assay; ANCA, antineutrophil cytoplasmic antibodies; ACLA, anti–cardiolipin antibodies; NA, no information available.

seen even after weeks of hospitalization and presumed abstinence from cocaine in cases 3, 4, 5, and 8. Similarly, hypersensitivity vasculitis can persist even after the responsible agent has been stopped.<sup>69,71</sup>

Drug-induced hypertension likely plays an important role in cocaine-associated stroke. Cocaine use can result in severe acute hypertension leading to intracerebral hemorrhage, subarachnoid hemorrhage, and infarction.<sup>2,4,8,9</sup> Only one of seven patients with cocaine-associated vasculitis for whom information was provided had elevated blood pressure on presentation. It is possible that acute elevations in blood pressure occurred at the time of the hemorrhage before the patients received medical attention. Hypertension may be particularly dangerous for patients with necrotizing vasculitis, causing hemorrhage of vessels that would not rupture in a normotensive state. The cause of patient 7's hemorrhage was thought to be hypertension in the setting of vasculitis. Patients 3, 4, and 5 had encephalopathy during periods of normal blood pressure. Patient 6 was in a coma after a period of seizure activity followed by an asystolic arrest. Patient 8 suffered an intracerebral hemorrhage, was not observed to be hypertensive, and had not used cocaine around the time of his hemorrhage. Therefore, hypertension is likely an important source of associated morbidity in cases of cocaine-associated vasculitis but not its cause.74-76

The medical treatments and clinical outcomes of the reported patients with cocaineassociated vasculitis varied greatly. One patient was treated with both glucocorticoids and cyclophosphamide, four were treated with glucocorticoids alone, and two received no long-term treatment. Clinical outcomes in these patients ranged from marked improvement to death. No patient had dramatic short-term improvement. Our patient 8 still had segmental narrowing angiographically after 2 weeks of glucocorticoid treatment, with angiographic resolution after 3 months of treatment. The small number of cases, varied regimens, and vastly different clinical situations make meaningful comparisons of these treatments impossible.

Treatment of patients with cocaine-associated vasculitis can, however, be guided by the

experience with patients with vasculitis of other etiologies.<sup>21,70,77-80</sup> The combination of highdose glucocorticoids and a cytotoxic agent such as cyclophosphamide is widely used for serious vasculitis, especially with CNS involvement, in a variety of well-defined vasculitides. The decision to begin immunosuppresive therapy should not be automatic in cases of vasculitis. The toxicities of glucocorticoids and cyclophosphamide need to be weighed against the potential and sometimes only theoretical benefits of therapy. Patients with hypersensitivity vasculitis may fully recover after discontinuation of the inciting agent and not require further therapy. When symptoms continue following removal of the involved antigen, glucocorticoids are very effective and are usually required only on a short-term basis. Additionally, the control of the hypertension that often accompanies vasculitis is considered an essential aspect of treatment.

Until both a greater understanding of the underlying etiology of cocaine-associated vasculitis is obtained and a larger series of patients are studied, therapy will continued to be made on a case-by-case process. Therefore, a conservative approach is proposed. After washout of the cocaine from the patient's system and careful control of hypertension, the clinical situation should be reappraised. If the patient is improving or not deteriorating from cerebrovascular complications temporally associated with cocaine use then close observation alone may be reasonable. If the patient has persistent angiographic signs consistent with vasculitis, a progressive clinical course, or if the neurological ictus is temporally removed from the last drug exposure, then glucocorticoids should be initiated. Ongoing deterioration or inability to taper glucocorticoids should prompt consideration of cyclophosphamide therapy. Neurosurgical consultation should be obtained on those patients with hemorrhagic stroke. In patients whose cerebral angiograms suggest vasculitis, serial studies may be worthwhile78,81 and may aid in tapering therapy. This approach was taken in our second case (8), in which the third angiogram after a 6-month course of steroids showed resolution of segmental narrowing. Given the previously mentioned diagnostic uncertainties regarding cerebral angiography, a strong case

can be made for brain biopsy in selected patients especially if cytotoxic therapy is being considered.

In summary, we feel that cocaine may be related to a unique type of cerebral vasculitis. This syndrome is still poorly understood both clinically and pathophysiologically. Cocaine use is believed to be an increasing risk factor for stroke in young people in the United States<sup>82</sup>

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