Case Report: Fatal Diffuse Thrombotic Microangiopathy after a Bite by the “Fer-de-Lance” Pit Viper (Bothrops lanceolatus) of Martinique

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Abstract. In Martinique, a man bitten two days earlier by a pit viper (Bothrops lanceolatus) was hospitalized with impaired consciousness and tetraplegia. Investigations confirmed cerebral and myocardial infarctions. Resolving thrombocytopoiesis was associated with virtually normal blood prothrombin time/activated partial thromboplastin time but increasing hyperfibrinogenemia. Despite specific antivenom treatment, he developed fatal left ventricular failure six days after the bite. At autopsy, multiple cerebral, myocardial and mesenteric infarctions were found. Rupture of mitral chordae tendinae was the likely cause of death. Histopathologic examination showed multi-focal thrombotic microangiopathy with intimal-medial dissection by thrombi extending from foci of endothelial damage in small cerebral, myocardial, pulmonary, mesenteric, and interlobular renal arteries and arterioles. These findings were the causes of infarctions. There was intense angiogenesis in organizing cerebral infarcts. Immunohistochemical analysis showed platelet aggregates and endothelial cells within microthrombi. Viperidae venoms contain vascular endothelial toxins, notably metalloproteinase hemorrhagins, but von Willebrand factor activators or vascular endothelial growth factor–type factors are more likely to have been implicated in this case.

Bothrops lanceolatus, the notorious “Fer-de-Lance” pit viper (Serpentes-Crotalinae), is endemic to Martinique, one of the Windward Islands of the Caribbean.1 As reported previously,2,3 envenomation from this snake leads to local symptoms such as pain, bleeding from the fang punctures, small ecchymoses, and swelling. Local envenomation may increase over time, resulting in serious local complications such as blistering, local necrosis, abscess, and extensive swelling involving the whole bitten limb and the trunk. Severe envenomation by this snake is regularly associated with systemic multifocal thrombotic complications, a phenomenon unique to victims of this species and the closely related B. caribbaeus on the neighboring island of St. Lucia.4 Thromboses usually occur within two days after the bite and may develop in patients who initially have signs of only moderate envenomation associated with normal results of blood coagulation tests apart from decreased platelet counts. Thromboses usually involve cerebral, myocardial, and pulmonary arteries, which lead to death or major functional sequelae in approximately 25% of cases. The reintroduction in 1993 of an effective specific antivenom (Bothrofav®, Sanofi-Pasteur, Lyon, France) resulted in a dramatic improvement in the prognosis of this envenomation.5

Cases of snake bite–induced vascular occlusion have been reported rarely and inconsistently in victims of other species of Viperidae.6–15 including the Southern Pacific rattlesnake (Crotalus oreganus helleri).16 However, B. lanceolatus and B. caribbaeus are the only snakes that cause multiple arterial thromboses in 30–40% of envenomed patients.17 The exact mechanism responsible for these vascular obstructions is not known and may have implications for more familiar forms of arterial disease encountered in general internal medicine. We report the first case of B. lanceolatus envenomation in which multiple systemic infarctions could be studied histopathologically.

CASE REPORT

A 74-year-old previously healthy man was bitten by a “fer-de-lance” snake on the left elbow while working in his garden in Morne Rouge in northern Martinique. He did not seek immediate medical attention but applied local dressings soaked in lemon juice, a popular traditional treatment of snake bites in Martinique. However, two days later, he was found unconscious by his family and was taken to the emergency room of the country’s largest hospital in the capital (Fort-de-France). The clinical findings on admission were fang puncture marks 20 mm apart, swelling of the bitten limb, impaired consciousness, and tetraplegia. Breathing, arterial blood pressure, urine output, and laboratory test results of blood coagulation were normal (Table 1). The platelet count was 93 × 10^9/L. Specific antivenom therapy (80 mL of Bothrofav® intravenously) was initiated without any reaction. A Magnetic resonance imaging (MRI) diffusion weighted scan showed multiple cerebral infarcts (Figure 1). Results of an angio-MRI were normal. Myocardial infarction was diagnosed by characteristic electrocardiographic changes and elevated serum troponin-1c levels. Results of coronary angiography were normal.

The patient was subsequently treated in the Stroke Unit but showed no signs of neurologic improvement. Table 1 shows the evolution of cardiac enzymes and results of other blood tests. Six days after the bite, he developed atrial fibrillation and left ventricular failure. Echocardiography showed rupture of the mitral valve. He did not respond to intensive care and died 10 days after the bite. His family gave consent to an autopsy.

Autopsy findings. An autopsy was performed 30 hours after death. Serous effusions were found in the peritoneal (50 mL) and pleural (approximately 500 mL) cavities. The lungs were not collapsed but were edematous and congested and weighed 800 g. No blood clot or thrombus was found in the pulmonary arteries or superior and inferior vein cavae. The pericardial cavity contained a serous effusion (50 mL) (Figure 2A) and was lined with a thick, white deposit. The increased heart weight (600 g) was attributable to left ventricular hy-
pertrophy. The heart contained many *peri mortem* agonal clots. The myocardium showed patchy fibermegaly and nucleomegaly with fibrosis indicative of pre-existing ischemic heart disease. A section of the heart showed infarcts of different ages and sizes (Figure 2B). The largest infarct was 35 mm in diameter and involved the septum and the posterior wall of the left ventricle. Two chordae tendinae of the posterior leaflet of the mitral valve had ruptured. There was no visible thrombosis of the coronary vessels. However, several atheromatous deposits were found, leading to focal stenosis of ap-

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day after bite</th>
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<tbody>
<tr>
<td>Hemoglobin (g/dL) [13–17]</td>
<td>15.9 14.3 13.5 13.1 11.6 10.7</td>
</tr>
<tr>
<td>Platelets (× 10^9/L) [&gt; 140]</td>
<td>93 86 103 109 127 207</td>
</tr>
<tr>
<td>Prothrombin (%) [70–100]</td>
<td>71 72 68 71 61 58</td>
</tr>
<tr>
<td>APTT (sec) [25–40]</td>
<td>31 35 32 29 35 35</td>
</tr>
<tr>
<td>Fibrinogen (g/L) [2–4]</td>
<td>NA 5.6 7.1 11.3 11.2 12.1</td>
</tr>
<tr>
<td>CRP (mg/L) [0–10]</td>
<td>68 106 148 NA 256 279</td>
</tr>
<tr>
<td>Troponin-1c (μg/L) [0.5–1]</td>
<td>79.4 103 103 37.1 NA</td>
</tr>
<tr>
<td>CK (U/L) [&lt; 190]</td>
<td>1,844 1,520 NA NA NA 130</td>
</tr>
<tr>
<td>LDH (U/L) [219–439]</td>
<td>2,972 2,201 NA NA NA 944</td>
</tr>
<tr>
<td>Bilirubin (μmol/L) [0–17]</td>
<td>26 21 23 31 24 26</td>
</tr>
<tr>
<td>Creatinine (μmol/L) [30–115]</td>
<td>123 109 107 98 119 135</td>
</tr>
</tbody>
</table>

* Values in brackets are normal ranges or values. APTT = activated partial thromboplastin time; NA = not available; CRP = C-reactive protein; CK = creatine kinase; LDH = lactate dehydrogenase.

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**FIGURE 1.** Magnetic resonance imaging of the brain (diffusion weighted scans) of the patient showing multiple cerebral infarctions with a typical junctional distribution.
proximately 50%. The liver was increased in weight (1,800 g) but showed no specific pathologic features. The appearance of one intestinal loop suggested necrosis and both kidneys appeared sclerotic. There was no extradural hemorrhage. The brain and cerebellum weighed 1,200 g and appeared edematous with sparse petechiae covering their surfaces (Figure 2C). The other organs appeared normal.

**Histopathologic examination.** Organs removed at autopsy were examined after fixation for three weeks in 4% formaldehyde solution. Microscopic examination showed fibrinous pericarditis with a polymorphic inflammatory infiltrate and scattered ischemic foci in the left ventricle. These foci consisted of acidophilic myocytes surrounded by polymorphonuclear neutrophils with or without fibroblast activation depending on the stage of organization. It was established that some of these changes had occurred within 24 hours before death. The mural myocardial infarcts did not correspond to thromboses of the epicardial coronary vessels but rather with occlusion of the lumen of intra-mural arteries. In each case, a fibrinous thrombus was visible invading the lumen (Figure 3A).

**Figure 2.** Macroscopic aspects of an autopsy specimen of the patient. **A**, Pericardium; **B**, transversal section of the heart; **C**, temporal cortex; **D**, transversal section of the cerebellum.

**Figure 3.** Vascular occlusions in the patient associated with fibrinous thrombi and clogging endothelial cellular debris. **A**, Intra-mural artery of myocardium (original magnification × 400). **B**, Small artery of the sub-arachnoidal space (original magnification × 200). **C**, Small pulmonary artery of inter-alveolar septum (original magnification × 400). **D**, Small renal inter-lobular artery (original magnification × 400). (Hematoxylin and eosin stained.)
This thrombus was anchored to a breach in the previously intact endothelium, with its expansion leading to dissection between the media and intima (endothelium). There was no thickening or inflammation of the vascular wall. On histologic examination, hemorrhagic disruption of the myocardial fibers of the posterior papillary muscle of the mitral valve was found; no vegetation or other evidence of endocarditis was present.

Cerebral tissue showed ischemic changes similar to those in the heart, but in the older lesions granulomatous organization, phagocytosis, glial activation, and unusually intense angiogenesis were visible. These findings are intriguing given the time that had elapsed before death. These lesions, 5–30 mm in diameter, were bilateral and often symmetrical (Figure 2D). Anteriorly, they were visible on the left frontal, parietal, right temporal, and occipital lobes, as well as on the cerebellar cortex and the lentiform nucleus (right putamen; right and left thalamus). The thrombotic lesions (Figure 3B), which were confined to the sub-arachnoid space, were similar to those observed in cardiac tissue. The same thrombotic process in small vessels was also observed within the small pulmonary arteries and the capillaries of the inter-alveolar septa (Figure 3C), within the small renal inter-lobular vessels (but with no glomerular involvement) (Figure 3D) and, to a localized extent, in the small intestine and colon.

All vascular occlusions consisted of fibrinous thrombi and endothelial cellular debris. No platelet aggregates were visible with hematoxylin-eosin-saffron staining. Remarkably, there was no vasculitis, perivascularitis, or perivascular hemorrhage and no evidence of embolic phenomena. These appearances are best described as diffuse thrombotic microangiopathy.

Immunohistochemical examination. Automated immunohistochemical analysis was performed with avidin-biotin-peroxidase complex (Benchmark XT; Vetnana, Tucson, AZ). The following antibodies were used: anti-von Willebrand (vWF) polyclonal rabbit anti-human A0082 (Dako, Glostrup, Denmark) diluted 1:2,000, anti-CD 31 monoclonal mouse anti-human clone JC/70 A M 0823 (Dako) diluted 1:30, and anti-CD 42b monoclonal mouse anti-human, clone 42 CO1 MS-1174 (Microm Inc., Eden Prairie, MN), diluted 1:10. Antigen retrieval (EDTA) was used for these antibodies.

Specific staining for anti-vWF (Figure 4A) and anti-CD 31 (Figure 4B) confirmed the dissection of endothelium from media in vessels that were otherwise normal in thickness and showed no complete rupture of their walls. Staining with anti-vWF and CD31 for endothelium and CD42 for platelets (Figure 4C) showed that the occlusive thrombi were composed of endothelial cells, platelets, and fibrin.

DISCUSSION

Our patient was hospitalized in a comatose state two days after being bitten by *B. lanceolatus*. Cerebral and myocardial infarctions were diagnosed clinically in the emergency room. However, mesenteric infarction was not observed until an autopsy was conducted. The likely cause of death was cardiogenic shock resulting from massive myocardial infarction and rupture of the posterior papillary muscle of the mitral valve. Our previous experience suggests that this fatal outcome might have been prevented by early antivenom therapy.2

The patient’s blood coagulation profile (Table 1), which showed thrombocytopenia, minimally reduced prothrombin with normal activated partial thromboplastin time (APTT), and elevated fibrinogen concentration, was typical of victims of *B. lanceolatus* envenomation who develop thromboses.2 The fact that many of these patients show no evidence of coagulopathy apart from thrombocytopenia suggests that thrombosis is not a direct procoagulant effect of the venom but is more likely to be vasculopathic in origin.17 The increasing fibrinogen concentrations (Table 1), presumably part of the hepatic acute-phase response, might have contributed to a hypercoagulable state.18

The most significant histopathologic finding was the asso-
cipation of the infarctions with diffuse thrombotic microangiopathy involving small arteries and arterioles of brain, heart, lungs, intestine, and kidneys. Although occlusion of small blood vessels and rarely even of single major arteries has been described in fatal envenoming by Viperidae,6–16 the lesions found in our patient were most unusual in being multi-focal in individual organs and diffusely present in five major organs. The vessel wall changes distinguish these lesions from the mere deposition of platelet thrombi in microvasculature associated with disseminated intravascular coagulation.19,20 Histopathologic studies excluded the possibility of multiple emboli, for example of endocardial origin, and established the pathogenesis as being primarily vasculitic. There was no inflammation of the walls of vessels and no inflammation around the vessels but obvious foci of endothelial damage from which the thrombi had arisen, dissecting the endothelial lining of the blood vessels (tunica intima) from their muscular coat, the tunica media, occluding the vessel’s lumen to produce ischemic damage in the tissue that they supplied, with fatal consequences. Specifically, destruction of one of the papillary muscles supporting the mitral valve led to cardiogenic shock in a man who was previously healthy.

In patients envenomed by Viperidae, vascular endothelial damage is usually caused by venom haemorrhagins that are metalloproteinases,21,22 one of which has been found in B. lanceolatus venom.23 However, venom metalloproteinases do not cause the histopathologic changes in medium/small arteries and arterioles observed in our patient. Another possibility would be a kinase insert domain–containing receptor–binding vascular endothelial growth factor (VEGF)–type factor of the kind demonstrated in several Viperidae venoms.24 These factors stimulate angiogenesis that was a prominent and unexpected feature of the organizing cerebral infarcts that had occurred several days before the patient’s death.

Endothelial activation can release (vWF), which is thought to play a central role in the pathogenesis of inherited thrombotic thrombocytopenic purpura (TPP) and hemolytic uremic syndrome (HUS).25,26 conditions associated with thrombotic angiopathy. Thrombotic thrombocytopenic purpura is caused by the persistence of highly reactive high molecular weight antiplatelet (vWF) antibodies against vWF-CP, whereas homozygous or compound heterozygous mutations of ADAMTS13 are responsible for recessively inherited TTP. Histopathologic changes in TPP that resemble those in our patient are capillary obstructions by platelets aggregates that cause diffuse thrombotic microangiopathy involving various tissues including the myocardium.30,31 Hemolytic uremic syndrome, most often caused by Escherichia coli O157:H7 or Shigella dysenteriae infections, is characterized by vascular endothelial damage attributable to shiga/shiga-like toxins (verotoxins), which leads to microangiopathic hemolysis and acute renal failure with histopathologic evidence of severe renal ischemia associated with extreme thickening of vascular walls.25 Our patient lacked the glomerular lesions (glomerulolysis, hypercellularity), cryoglobulin deposition, and other renal vascular abnormalities described in TPP and HUS.32

Thrombotic angiopathy has been described in a number of other conditions including malignant disease, organ transplantation with graft versus host reactions, stem cell transplanted, and catastrophic antiphospholipid syndrome. Catastrophic antiphospholipid syndrome occurs in patients with systemic lupus erythematosus or lupus-like syndromes.34 It is characterized by simultaneous thromboses affecting major organs, especially the brain and kidneys. Typically, there are venous thromboses and, more rarely, fibrin thrombi in small muscular arteries seen in our patient. However, the APTT of our patient remained normal (Table 1), making the presence of antibodies to phospholipids most unlikely.35–37

On the basis of these comparisons with other medical conditions in which there is diffuse thrombotic microangiopathy, it seems most likely that in B. lanceolatus (and probably B. caribbaeus) envenomation there is activation of vascular endothelium, either as in diarrhea-associated HUS, with release of immature forms of vWF expressing adherent surfaces for platelet agglutination or by a VEGF-type factor. Further understanding of the extraordinary clinical features of B. lanceolatus envenoming in humans must await detailed studies of the venom. It is possible that these studies may improve our understanding of the pathogenesis of other vasculopathies.

Received November 27, 2007. Accepted for publication January 18, 2008.

Acknowledgments: We thank Aura Kamiguti, Paul L. F. Giangrande, and Gareth Turner for helpful comments and discussions.

Financial support: This study was supported by Centre Hospitalier Universitaire de Fort-de-France

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