Report of Two Cases: Rattlesnake Venom-Induced Thrombocytopenia

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Abstract. We report 2 patients who presented with vasomotor symptoms and severe thrombocytopenia following rattlesnake bites. These symptoms persisted in spite of treatment with antivenin and transfusion of multiple doses of platelets. Thrombocytopenia is a common occurrence in moderate to severe crotaline envenomation. Algorithms suggested for the treatment of rattlesnake envenomation with crotaline-specific antivenin may not reverse the associated thrombocytopenia. The precise mechanism of venom-induced thrombocytopenia (VIT), even in the absence of significant coagulopathy, is unknown. Our experience suggests that, unless spontaneous bleeding occurs, repeated transfusion of fresh frozen plasma and/or platelets may not be indicated. (received 28 June 2004, accepted 1 August 2004)

Keywords: thrombocytopenia, rattlesnake envenomation, Cro-Fab™, antivenin, platelet transfusion

Introduction

Poisonous snake bites in the United States predominantly involve the crotalid snakes: copperheads, cottonmouths, and rattlesnakes. These snakes have a complex venom system with multiple components ranging from small metal complexes and peptides to complex proteins with molecular weights in excess of 100 kDa [1]. These venoms have been described by Nicole and Raphael as a “mosaic of antigens” [2]. For many years, the mainstay of pit viper envenomation treatment has been a horse serum-based whole-antibody preparation, Antivenin (Crotalidae) Polyvalent,™ (ACP; Wyeth, Marietta, PA). Recently, the use of Fab-based sheep-derived preparations (CroFab™, Protheris, Nashville, TN) has become widely used as an alternative to whole IgG immunotherapy for snakebites, largely in order to minimize the risks of immediate hypersensitivity and delayed serum sickness. Aggressive treatment with crotaline-specific antivenin often leads to resolution of coagulopathy and thrombocytopenia. However, cases have been reported in which thrombocytopenia persists in the absence of significant coagulopathy [3].

Case Reports

Case 1. A 22-yr-old man was transferred to the University of Virginia Medical Center after he sustained a bite to the dorsal surface of the metacarpophalangeal joint of the left index finger while handling a rattlesnake (species unknown) that he believed to be dead. The patient had a medical history of asthma, controlled by albuterol inhalation. At presentation, his vital signs were: blood pressure, 107/61 mm Hg; pulse, 102 beats/min; respiratory rate, 17/min; temperature, 36.1°C; hemoglobin oxygen saturation, 100%. He was diaphoretic, and his left upper extremity was severely swollen and ecchymotic up to the middle of the upper arm, The left arm was larger in circumference than the right arm; radial pulses were palpable in both arms. There were 2 puncture wounds on the dorsal surface of the left index finger just distal to the metacarpophalangeal joint, with blood oozing from each. The patient was drowsy, but responded to commands. X-ray studies revealed only soft tissue swelling. Significant pain was elicited by passive flexion and extension of the fingers. Upon hospital admission, the laboratory test results were remarkable only for
a platelet count of 10 x 10^9/L. Other laboratory results were within the reference ranges, including: prothrombin time (PT), 15.2 sec (reference, 12.2-15.3 sec) with INR 1.1; partial thromboplastin time (PTT), 30.3 sec (reference 24.1-33.7 sec). Liver function tests and serum electrolyte and urea concentrations were normal.

Therapy was begun with morphine, 2 mg iv, 2 doses; a total of 10 whole blood-derived units of platelets; and 6 vials of crotaline polyvalent immune Fab-ovine (CroFab™, Protheris, Nashville, TN). Two hr later, the posttransfusion platelet count was 38 x 10^9/L, and reevaluation of local symptoms revealed progression of arm swelling and ecchymoses that had spread to include the upper arm. The platelet count steadily fell to a low of 15 x 10^9/L 23 hr later. Two vials of CroFab™ were given and 3 doses (total of 18 whole blood derived units) of platelets were transfused on the second hospital day; however, postransfusion platelet counts were 12-16 x 10^9/L range. Due to the spread of ecchymoses and the lack of response to platelet transfusions, 2 vials of CroFab™ were again administered. An orthopedic consultation confirmed that there was no evidence of compartment syndrome. A culture of the wound grew multiple Gram-positive and Gram-negative cocci. In the next 12 hr, 12 vials of CroFab™ were administered along with oxycodone and fentanyl for pain. Clindamycin therapy was instituted, and the arm was kept elevated. Thrombocytopenia persisted on the third hospital day despite the transfusion of 3 doses (total of 18 whole blood-derived units) of platelets, with a postransfusion count of 10 x 10^9/L.

The patient developed a febrile, non-hemolytic reaction to a unit of platelets; culture of the unit of platelets was negative. Platelet serology studies did not reveal any evidence of alloimmunization. In spite of the transfusion of 11 doses of platelets (total of 66 whole blood-derived units) within the next 2 hospital days, the platelet counts never achieved a level >23 x 10^9/L and the PT, INR, and fibrinogen levels remained within normal limits. Further platelet transfusions were withheld. The patient left the hospital against medical advice on the ninth hospital day, with a platelet count of 44 x 10^9/L, and he never returned for visits in the outpatient clinic.

**Case 2.** A 39-year-old man with a history of delirium tremens was transferred to the University of Virginia Medical Center following a bite by a black diamond rattlesnake to the left index finger and left inner biceps. He presented with tongue, oropharyngeal, and mouth swelling, and extensive petechiae and ecchymoses of the arm. Ensuing periglottic edema and respiratory compromise necessitated intubation and respiratory support. He had received 15 vials of CroFab™ while en route to the hospital. A platelet count done at the transferring hospital was 33 x 10^9/L; transfusion with 1 dose (6 whole blood-derived units) of platelets was completed, and a postransfusion count of 206 x 10^9/L was recorded. Laboratory test results on arrival at the university hospital were notable for a PT of 62.1 sec (reference 11.8-14.6 sec) with INR 7.0, and a PTT of 51.0 sec (reference 24.1 - 33.7 sec). Vital signs on admission were: blood pressure, 148/93 mm Hg; respiratory rate, 16/min; pulse, 136 beats/min, with palpable extremity pulses. There were teeth marks on the left inner biceps with bruising, and a bite mark on the left index finger.

The patient was treated with 4 more vials of CroFab™. The coagulation parameters were corrected by the second hospital day, but the platelet count dropped to <10 x 10^9/L. The patient was transfused with 1 dose of platelets (total of 5 whole blood-derived units) and the platelet count increased to 24 x 10^9/L. He was then transfused with 2 doses (total of 10 whole blood-derived units and 1 single-donor unit) of platelets as the platelet count again dropped to <10 x 10^9/L. The platelet count increased to 22 x 10^9/L, but then promptly fell to <10 x 10^9/L within the ensuing 9 hr. He was started on Ativan, po, prn, and the Clinical Institute Withdrawal Assessment for Alcohol Scale protocol was instituted, because of his history of alcohol abuse and delirium tremens. His respiration improved; he was extubated and transferred to the general medicine unit. In the morning of the third hospital day, his INR increased to 10.0; the platelet count diminished to <10 x 10^9/L by that evening, and he was again transfused with 2 doses (total of 10 whole blood-derived units) of platelets. Because the INR increased to greater than 12.0 by the fourth hospital day, with a platelet count of <10 x 10^9/L, the patient was transfused with 6
units of fresh frozen plasma, 1 dose of platelets (5 whole blood-derived units) and 10 vials of CroFab™ over a 12-hr period. The posttransfusion platelet count was 92 x 10⁹/L, which fell to 44 x 10⁹/L when the patient was discharged after 8 days of hospital stay.

Discussion

Envenomation by the crotalus and agkistrodon species causes a decrease in circulating platelets in both humans and experimental animals [4]. Wingert et al [4] suggested that, without treatment, resolution of VIT usually can be expected within 72 hr, but longer durations have been observed. Following injection of the venom into rabbits, there is a 3-phase platelet response: an initial drop followed by a rise at 36 hr, a subsequent overshoot, and a return toward normal levels at 144-282 hr (6 to 12 days). Because this effect appears to be time- and dose-related, it may serve as an index to determine the level of poisoning following bites by these snakes, and may thus be of value in determining antivenin dosing. The loss of circulating platelets may be due to: (a) toxin-induced damage to platelet precursors in the bone marrow; (b) platelet consumption during disseminated intravascular coagulation (DIC) or destruction during the intravascular coagulation initiated by the direct action of the venom (eg, crotalocytin); (c) aggregation or peripheral sequestration of platelets at the wound site [5]; or (d) a combination of these factors [4,6].

A unique protein component of timber rattlesnake venom, crotalocytin, has the ability to cause platelet aggregation and independently to induce platelet ATP release [6,7]. This protein may be the venom component responsible for the immediate depression of platelets after a bite. Examinations of the bone marrow of patients after rattlesnake envenomation showed normal maturation progression of myelocytic cells from myeloblast to mature polymorphonuclear, even though there was a shift from the normal 2:1 ratio to 8:10:1 [4,8]. Megakaryocyte precursors were normal in number and appeared morphologically unchanged. There was little nuclear division, no vacuolization or hyaline infiltration of the cell borders, and no platelet fragmentation; hence there was no evidence of toxin-induced damage to platelet precursors in the bone marrow [4,8].

Rao et al [9] commented that an antibody to crotalocytin may be the antivenin of choice, but this may be commercially unfeasible. To explain the prolonged thrombocytopenia that occurs after the initial drop (the delayed phase), Simon and Grace [10] examined platelet migration in venom-injected rabbits and noted platelet sequestration near the site of injection. Offerman [11] reported a patient who presented with biphasic venom-induced thrombocytopenia, of which only the first phase responded to antivenin therapy. The second phase was refractory to both crotaline Fab and traditional antivenin (crotaline) polyvalent therapy. Boyer et al [12] suggested possible explanations for the recurrence of local and coagulopathic effects of envenomation, which include (a) pharmacokinetic and pharmacodynamic mismatch between venom and antivenin; (b) separation of the circulating venom/antivenin complex after initial effective binding; (c) late onset of effects of venom components different from those initially active; and (d) the development of host anti-antivenin immune response.

Rattlesnake VIT can occur in the absence of significantly abnormal coagulation studies. Tallon [5] described a 24-yr-old man bitten in the hand by a timber rattlesnake who presented with hematemesis, gross hematuria, and gingival bleeding, with a platelet count of 2 x 10⁹/L, but normal PT and PTT. Even though the plasma fibrinogen level was slightly depressed, and fibrinogen degradation products (FDP) were elevated, the peripheral blood smear did not show red cell fragmentation to indicate DIC. In our report, the second patient had an increase in FDP, with a fall in fibrinogen and elevated PT and INR, without evidence of DIC in the peripheral blood smear. Most coagulation parameters were promptly corrected with transfusion of FFP and antivenin, although in this case repeated antivenin therapy did not reverse the thrombocytopenia. Of 31 patients with rattlesnake bites who have been transferred to our university hospital during the years 2002 to 2004, only the 2 cases described here presented with prolonged thrombo-
Evidently coagulation defects and thrombocytopenia do not always occur together following rattlesnake envenomation; when they do, the fact that the coagulation defects respond to antivenin therapy, while the thrombocytopenia does not, suggests that these may be independent effects of the venom.

The course of thrombocytopenia after rattlesnake envenomation is an ongoing topic of study. One snake venom toxin, crotalocytin, causes immediate effects that seem to be corrected by antivenin [10]; however, the persistent thrombocytopenia induced by the timber rattlesnake seems to be resistant to antivenin. A possible explanation is that a different venom component, which is responsible for the delayed platelet effects, is not neutralized by antivenin. The failure of platelet transfusion to produce a sustained increase in platelet count is consistent with this hypothesis. Many components of timber rattlesnake venom could possess antigenic determinants that would not allow antivenin to bind and neutralize them, as timber rattlesnake venom is not a component of the current antivenin preparation [13,14]. Alternatively, the antibody binding may be much less specific, implying that larger amounts of antivenin may be useful, although this cannot be confirmed given the retrospective nature of these reports. Our case studies do not support the use of large quantities of antivenin for the sole purpose of reversing delayed thrombocytopenia. Lastly, venom may continue to “leak” from the soft tissue wound into the damaged local microcirculation for several days, depending on the venom dose delivered by the snake, and the wound location. The venom has a circulating half-life greater than that of CroFab™. Therefore, providing regular dosing with CroFab™ following an initial bolus may mitigate the effects of venom persistence.

In conclusion, envenomation by the timber rattlesnake may produce prolonged thrombocytopenia. In our cases, the administration of CroFab™ was associated with improvement in PT and INR. In contrast, thrombocytopenia responded poorly to antivenin therapy and produced only transient increases in platelets (in the absence of alloimmunization). Drawing from our observations and those of others, the most important and practical therapeutic option may be to let this self-limiting platelet disorder run its course while the patient is protected from potential trauma-induced hemorrhage by measures ranging from strict hospital bed rest to discharge instructions to avoid contact sports. This conservative approach also reduces the risk of transfusion reaction (as occurred in our first case), anaphylaxis, transfusion-related infectious agents, or serum sickness.

References