Case Reports

Thrombotic microangiopathy in two tiger snake envenomations

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SUMMARY

Thrombotic microangiopathies are a rare group of disorders with features such as microangiopathic haemolytic anaemia, thrombocytopenia and renal failure. Thrombotic microangiopathy has been previously reported in association with envenomation from a number of snake species. We present the first two reported cases of thrombotic microangiopathy caused by envenomation from the common tiger snake (Notechis scutatus). Both patients had classical features of thrombotic microangiopathy with microangiopathic haemolytic anaemia, thrombocytopenia and renal failure commencing in the first 48 hours after envenomation. The presentations and recovery were similar to case presentations of other snakebite envenomation associated thrombotic microangiopathies. Normal ADAMTS13 activity suggests that plasmapheresis may not be beneficial, although this needs further investigation.

Key Words: thrombotic microangiopathy, tiger snake, envenomation

Thrombotic microangiopathy is an uncommon complication of snake envenomation. It is characterised by microangiopathic haemolytic anaemia, thrombocytopenia and acute renal failure. It has previously been associated with venom from a number of different species including Australian brown snakes (Pseudechis spp.) and the Coastal Taipan (Oxyuranus scutellatus). We present the first two reported cases of this complication in confirmed common tiger snake (Notechis scutatus) envenomation and discuss thrombotic microangiopathy associated snake envenomation. Consent was obtained from both patients to allow their cases to be presented in this article.

CASE HISTORIES

Case one

A 55-year-old woman with a past medical history of hypertension and smoking stepped on a snake on the verandah of her rural house and was bitten once on her left little toe. She had no first aid measures at home and her family drove her to the local regional hospital where she arrived 15 minutes after the bite.

A pressure bandage was applied, her leg was immobilised and she was transferred to a metropolitan hospital. Her initial symptoms were headache, nausea and a single vomit with no neurological signs of envenomation. A bite site swab was sent for testing with a snake venom detection kit and was positive for tiger snake. Other investigations revealed elevated activated partial thromboplastin time, decreased fibrinogen and normal creatine kinase.

She was treated with two vials of tiger snake antivenom intravenously approximately three hours post-bite and was transferred to the intensive care unit. Her international normalised ratio was unmeasurable nine hours post-bite with undetectable fibrinogen levels. These improved back to normal 19 hours post-bite. Over the next two days she developed anaemia, thrombocytopenia and non-oliguric renal failure (Figure 1). Her blood film showed fragmented red cells, which suggested the diagnosis of microangiopathic haemolytic anaemia. She was transferred to a tertiary hospital for plasma exchange therapy. She had plasma exchange with cryo-deplete fresh frozen plasma, alternating with intermittent haemodialysis for the next 13 days. She was discharged from hospital on day 19 with improving renal function (Figure 1). At her last outpatient review, she had no residual renal
dysfunction. Enzyme-linked immunosorbent assay detected 1.3 ng/ml of tiger snake venom in serum prior to antivenom (limit of detection 0.2 ng/ml). ADAMTS13 activity (a metalloprotease enzyme) was reported to be 85% (normal range 40 to 130%) and no venom was detected in serum after the administration of antivenom, indicating that sufficient antivenom had been administered.

Case two

A 46-year-old man with a past medical history of smoking and hypertension was bitten while handling his pet tiger snake. The man picked up a sack containing the snake and was bitten on the right thumb through the bag. The snake reportedly ‘held on’ to his thumb for several seconds before letting go. The man had a crepe bandage applied to his arm immediately and presented to his regional hospital. His initial symptoms were headache, nausea and a single vomit. He had further vomiting when the bandage was removed on presentation to hospital and this was reapplied. A snake venom detection kit for the bite site was positive for tiger snake.

Three hours after presentation he had persistent vomiting and laboratory investigations suggestive of envenomation, with an associated raised activated partial thromboplastin time, international normalised ratio and decreased fibrinogen. He had two vials of tiger snake antivenom approximately four hours post-bite. His symptoms resolved soon after. His international normalised ratio peaked at 2.0, nine hours post-bite with a fibrinogen <0.5 g/l, which returned to 1.2 g/l, 17 hours post-bite. The enzyme-linked immunosorbent assay detected 13 ng/ml of tiger snake venom in serum prior to antivenom.

Over the next two days, he developed non-oliguric then oliguric renal failure and thrombocytopenia (Figure 1). Fragmented red cells were present on blood film on day 3. He received continuous renal replacement therapy from day 4 until day 10 and then intermittent haemodialysis for seven weeks. He did not receive plasma exchange therapy.

![Figure 1: Plots of laboratory results versus time for both patients including haemoglobin and platelet count [A,C] and creatinine and lactate dehydrogenase (LDH) [B,D].](image-url)
At last review three months after envenomation, his creatinine was 150 μmol/l. ADAMTS13 activity was not tested.

DISCUSSION

We present two patients who were bitten by a common tiger snake (N. scutatus), confirmed by enzyme-linked immunosorbent assay testing of serum, who developed clinical and laboratory evidence of envenomation, which included venom induced consumption coagulopathy (VICC), although this was only partial in the second case6. This was despite appropriate first aid measures and relatively rapid administration of antivenom. There were improvements in their symptoms and laboratory abnormalities within 48 hours. Both patients subsequently developed renal failure with associated anaemia, thrombocytopenia and red cell fragmentation consistent with microangiopathic haemolytic anaemia. The clinical pictures were consistent with thrombotic microangiopathy and are the first reported cases of tiger snake envenomation associated thrombotic microangiopathy.

Thrombotic microangiopathies are a rare group of disorders associated with a number of symptoms, signs and laboratory abnormalities including fever, thrombocytopenia, microangiopathic haemolytic anaemia, renal failure and central nervous system involvement. Thrombotic microangiopathies can be classified according to their cause6. The two most common forms are thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome.

The pathogenesis of thrombotic thrombocytopenic purpura is thought to be related to decreased activity of ADAMTS13. ADAMTS13 is a metalloprotease enzyme that cleaves the large von Willebrand factor, an important step in the inhibition of spontaneous platelet aggregation in flowing blood6. Lack of ADAMTS13 activity promotes von Willebrand factor induced platelet aggregation and microangiopathic haemolytic anaemia. Idiopathic or autoimmune is the most common form of thrombotic thrombocytopenic purpura, reportedly representing 40 to 77% of all cases8,10. Acquired autoantibodies inhibit the proteolytic activity of ADAMTS13. Risk factors include female gender, middle age (30 to 50 years) and HIV infection. Treatment is plasma exchange to remove autoantibodies and increase ADAMTS13 activity8 and this has shown to reduce mortality. Other rarer causes of thrombotic thrombocytopenic purpura include a hereditary form of ADAMTS13 deficiency, drugs including ticlopidine and chemotherapeutic agents, pregnancy and certain collagen vascular diseases. Some of these conditions are associated with normal ADAMTS13 activity.

Haemolytic uraemic syndrome typically presents with acute renal failure, microangiopathic haemolytic anaemia and thrombocytopenia, is more common in children and is associated with a diarrhoeal illness in 80 to 90% of cases. Most cases are caused by toxin producing serotypes of E. coli or Shigella species and are associated with a normal ADAMTS13 activity. Atypical haemolytic uraemic syndrome is associated with complement dysfunction and occurs more commonly in adults8.

Thrombotic microangiopathy and snakebite

A syndrome consistent with thrombotic microangiopathy has been described after snakebite for many years, but only recently has the syndrome been recognised as thrombotic microangiopathy. Reported cases include Australian elapidae such as Australian brown snake (Pseudonaja spp.), coastal taipan (O. scutellatus), rough scale snake (Tropidechis carinatus) and a number of viperidae including the Saharan horned viper (Cerastes cerastes) and Russell’s viper (Daboia spp.)13.

The cases presented here are the first two cases describing thrombotic microangiopathy following envenomation with tiger snakes (N. scutatus). The common tiger snake is native to the south eastern corner of Australia. There were a number of features of thrombotic microangiopathy present in both patients. Both had evidence of microvascular haemolysis with anaemia, increased bilirubin, increased lactate dehydrogenase and fragmented red cells on microscopy. Both patients developed rapidly progressive renal failure in the first 48 hours after envenomation, yet had only mildly elevated creatine kinase levels, excluding rhabdomyolysis as the cause. Finally, both patients developed thrombocytopenia with lowest platelet counts of 10×10^9/l on day five and 45×10^9/l on day three, respectively.

The coagulopathy associated with snakebite envenomation has been referred to as disseminated intravascular coagulation (DIC) because it shares common features. However, the term venom-induced consumption coagulopathy (VICC) has been introduced because it better describes the clinical features and the absence of other features of DIC. There are a number of major differences described between DIC and VICC1.

First, VICC is characterised by bleeding without obvious fibrin deposition, microvascular thrombotic obstruction or non-renal end organ failure, whereas DIC is characterised by bleeding and multi-organ
failure. Second, VICC occurs within hours of the envenomation and resolves within 24 to 48 hours. In contrast, DIC continues while the precipitating disorder is present. Third, the pathogenesis of VICC is due to the action of a snake procoagulant toxin at one point in the coagulation pathway, not the tissue factor/factor VIIa pathway thought to be important in DIC. Finally, the mortality from DIC is significantly higher than VICC, but this is probably more related to the underlying cause of the DIC rather than DIC itself.

Both our patients had deranged coagulation profiles that improved within 24 hours of antivenom therapy consistent with VICC and the subsequent clinical pictures were consistent with thrombotic microangiopathy.

The exact mechanism of thrombotic microangiopathy in snake envenomation is not known. ADAMTS13 activity was available only in case one and was within the normal range prior to plasmapheresis. This suggests that ADAMTS13 is unlikely to be a major factor in the pathogenesis of snakebite associated thrombotic microangiopathy, although measurement of ADAMTS13 levels in further cases including other species will be important.

The presence of normal ADAMTS13 activity has implications regarding the use of plasmapheresis and plasma replacement in snakebite associated thrombotic microangiopathy. Plasma replacement aims to increase ADAMTS13 levels and plasmapheresis aims to remove antibodies to ADAMTS13, neither of which is likely to be beneficial in snakebite associated thrombotic microangiopathy. Both treatments have their own inherit risks including fresh frozen plasma associated transfusion related lung injury. It is possible that the plasmapheresis therapy will remove any free circulating antivenom, therefore making the patient potentially susceptible to re-envenomation. Plasmapheresis has been used in snakebite associated thrombotic microangiopathy, because of the similarities of this condition with thrombotic thrombocytopenic purpura, but its use did not appear to change the course of the syndrome compared to untreated cases. Further research is required to confirm whether plasmapheresis improves outcomes in snakebite-associated thrombotic microangiopathy and whether it can be recommended as standard practice.

In conclusion, we present two cases of thrombotic microangiopathy associated with tiger snake envenomation. Both patients had classical features of thrombotic microangiopathy with microangiopathic haemolytic anaemia, thrombocytopenia and renal failure commencing in the first 48 hours after envenomation. The presentations and recovery were similar to case presentations of other snakebite envenomation associated thrombotic microangiopathies. Normal ADAMTS13 activity suggests that plasmapheresis may not be beneficial, although this needs further investigation.

REFERENCES
