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HEMOLYTIC UREMIC SYNDROME FOLLOWING TAIPAN ENVENOMATION WITH RESPONSE TO PLASMAPHERESIS

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Summary

We report a case of hemolytic uremic syndrome (HUS) in a 33 year old male who was bitten by a taipan, with apparent massive envenomation. The microangiopathic hemolytic anemia (MAHA) and thrombocytopenic aspects of his HUS appeared to respond to plasmapheresis, but his anuric renal failure persisted. He also had prolonged severe muscular paralysis which gradually began to resolve over the course of two weeks. At this point he suffered a cardiac arrest sustaining severe and subsequently fatal hypoxic brain injury.

This case raises the possibility that the taipan venom may have induced HUS by damaging the renal endothelium. His cardiac arrest was not apparently related to his HUS.

Key words: Hemolytic uremic syndrome, taipan envenomation, plasmapheresis.

Abbreviations: aPTT, activated partial thomboplastin time; DIC, disseminated intravascular coagulation; HUS, hemolytic uremic syndrome; MAHA, microangiopathic hemolytic anemia; PT Prothrombic time; TTP, thrombotic thrombocytopenic purpura.

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INTRODUCTION

Venom from the taipan (*Oxyuranus scutellatus*) has procoagulant, neurotoxic and myotoxic effects, mediated by a mixture of toxins including: taipoxin, a phospholipase A_2 presynaptic toxin and myotoxin; taicatoxin, a calcium channel blocker; and a prothrombin activator.[1] This latter component causes rapid defibrination with variable thrombocytopenia, prolongation of the PT and aPTT from clotting factor consumption and a rapid rise in D Dimer. These effects are relatively short-lived following treatment with antivenom, with substantial correction occurring within the first 12 hours.[2] The neurotoxic component predominantly affects pre-synaptic function of peripheral nerves inducing a widespread flaccid paralysis that may last weeks.[2] The venom has also been shown to directly alter RBC membranes, possibly via its phospholipase activity, inducing sphero-echinocytic changes with fragmentation.[3] There is a much weaker myotoxic effect. Hemolytic uremic syndrome (HUS) has been described with snake envenomation, although in the Australian reports from the 1970s it was not labelled as such but it appeared to fit this syndrome.[4] More extensive experience of HUS following bites of Russell's viper in India, has been reported, but little clinical detail was included.[5]

One probable mechanism of HUS is related to excessive leakage into the blood of unusually large von Willebrand factor (ULvWVF) multimers following damage to the vascular endothelium by toxins, such as shiga toxins and shiga like toxins produced by *Shigella dysenteriae* and *E. coli* organisms.[6] It is possible, but at present hypothetical, that the massive envenomation which occurred in this patient caused similar damage to the renal endothelium.

CASE REPORT

A 33-yr-old Caucasian male was bitten twice on the left knee by a taipan (*Oxyuranus scutellatus*). Symptoms of envenomation occurred almost immediately including ascending leg pain and vomiting. A crepe bandage and splint was applied to the whole leg. On arrival at the local hospital, approximately 45 mins later, partial removal of the bandage to allow swabbing of the site and to identify the venom, resulted soon afterwards in a widespread muscular paralysis involving both intra- and extra-ocular movements, bulbar function, chest and limb muscles, but without loss of

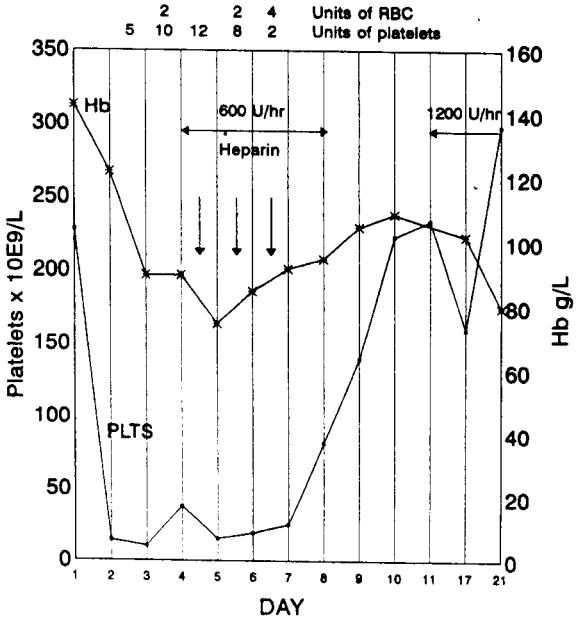

Fig. 1 This shows the relationship between the plasmapheresis, depicted as the three downward pointing arrows, and the patient's platelets and hemoglobin. D Dimer test became negative on d 4 and red blood cell fragmentation finally disappeared around d 14. Urine volume progressively fell to zero by d 10. The numbers of units of red blood cells and platelets transfused are shown at the top of the figure. The horizontal arrows represent the time span of intravenous heparin therapy.

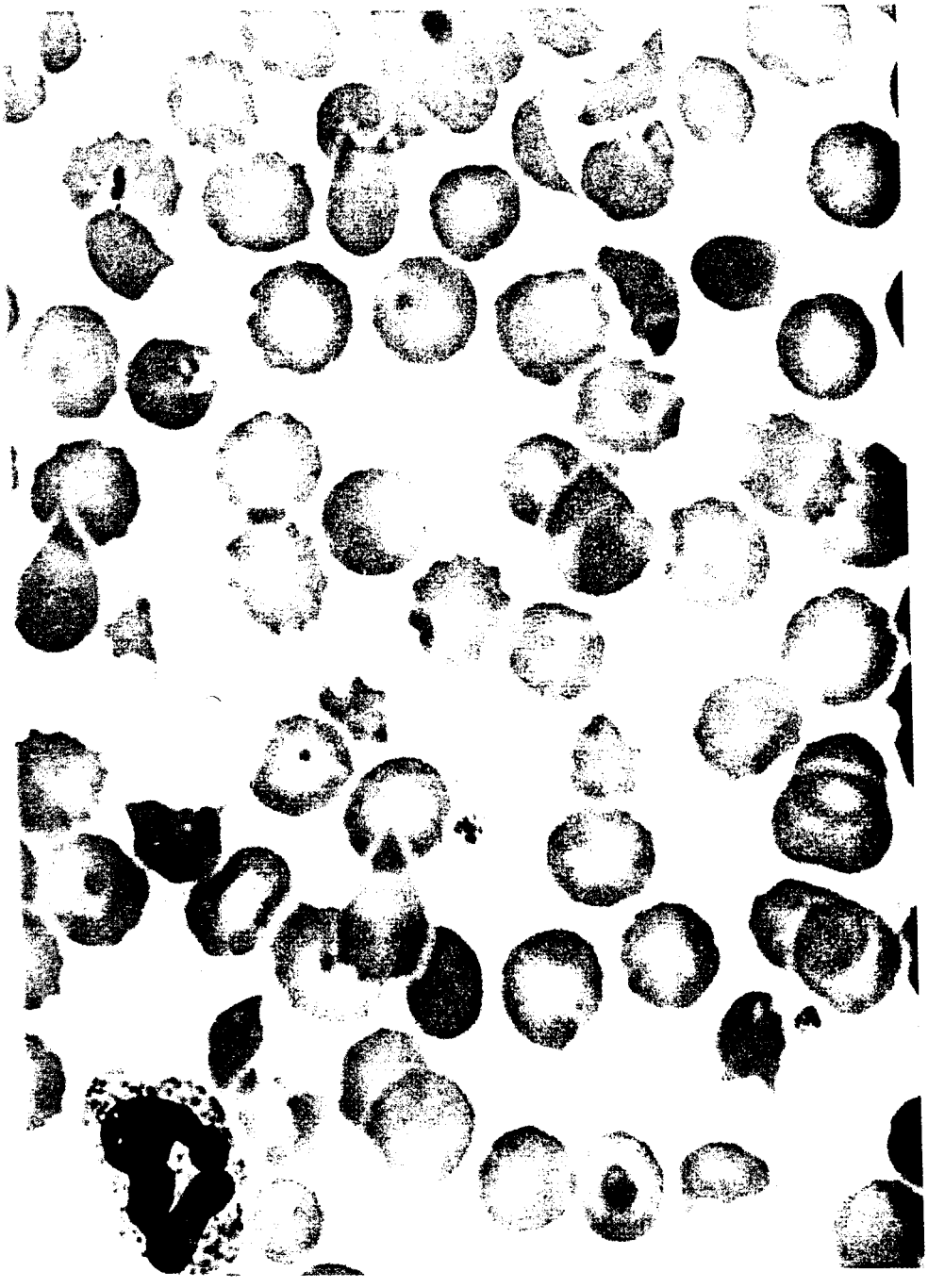

Fig. 2 Photomicrograph of the patient's initial blood film showing sphero-echinocytosis and fragmented red blood cells. (Wright's oil, original magnification × 100).

consciousness. The bandage was rapidly reapplied but antivenom was withheld until venom identification was completed, around one h following admission. Initially 2 doses of 12,000 units of taipan specific antivenom with 0.25 ml of 1:1000 s/c adrenalin and intravenous steroids were given, followed by a dose of polyvalent antivenom when the bandage was removed.

Seven and a half h after being bitten, the patient was transferred to Princess Alexandra Hospital (PAH) Intensive Care for ventilatory support. At this stage there was no clinically significant bleeding, the patient was hemodynamically stable but was very oliguric. Over the first 12 h he received 5 doses of 12,000 units of specific taipan antivenom.

At the local hospital his initial blood film had shown marked sphero-echinocytosis with fragmented red cells (Fig. 2), and his coagulation screen had been normal. However, on arrival at PAH his coagulation screen showed marked deterioration with a PT 17 s (reference range 12 ± 3 s), aPTT 62 s (25 to 38), D Dimer titre >8 (<1) and fibrinogen 0.8 g/l (1.5 to 4). His platelet count was normal at 175×10^9/l (150–400). While his PT, aPTT and fibrinogen returned to normal 15 h after envenomation, his platelet count continued to fall rapidly, reaching 14×10^9/l by 30 h (Fig. 3). Over the next 5 d his platelet count remained less than 50×10^9/l despite extensive platelet support. During this time his D Dimer level progressively fell and on d 4 became negative, suggesting that the thrombocytopenia was not due to disseminated intravascular coagulation (DIC) and further supported by the rapid return to normal of his PT, aPTT and fibrinogen.

The red cell fragmentation remained a prominent feature with a progressive fall in hemoglobin levels initially 142 g/l (130–170) but then falling to 72 g/l on the d 3, despite having received 2 units of packed cells. This drop was felt to be due to a microangiopathic hemolytic anemia as there had never been obvious bleeding. Concurrently, despite

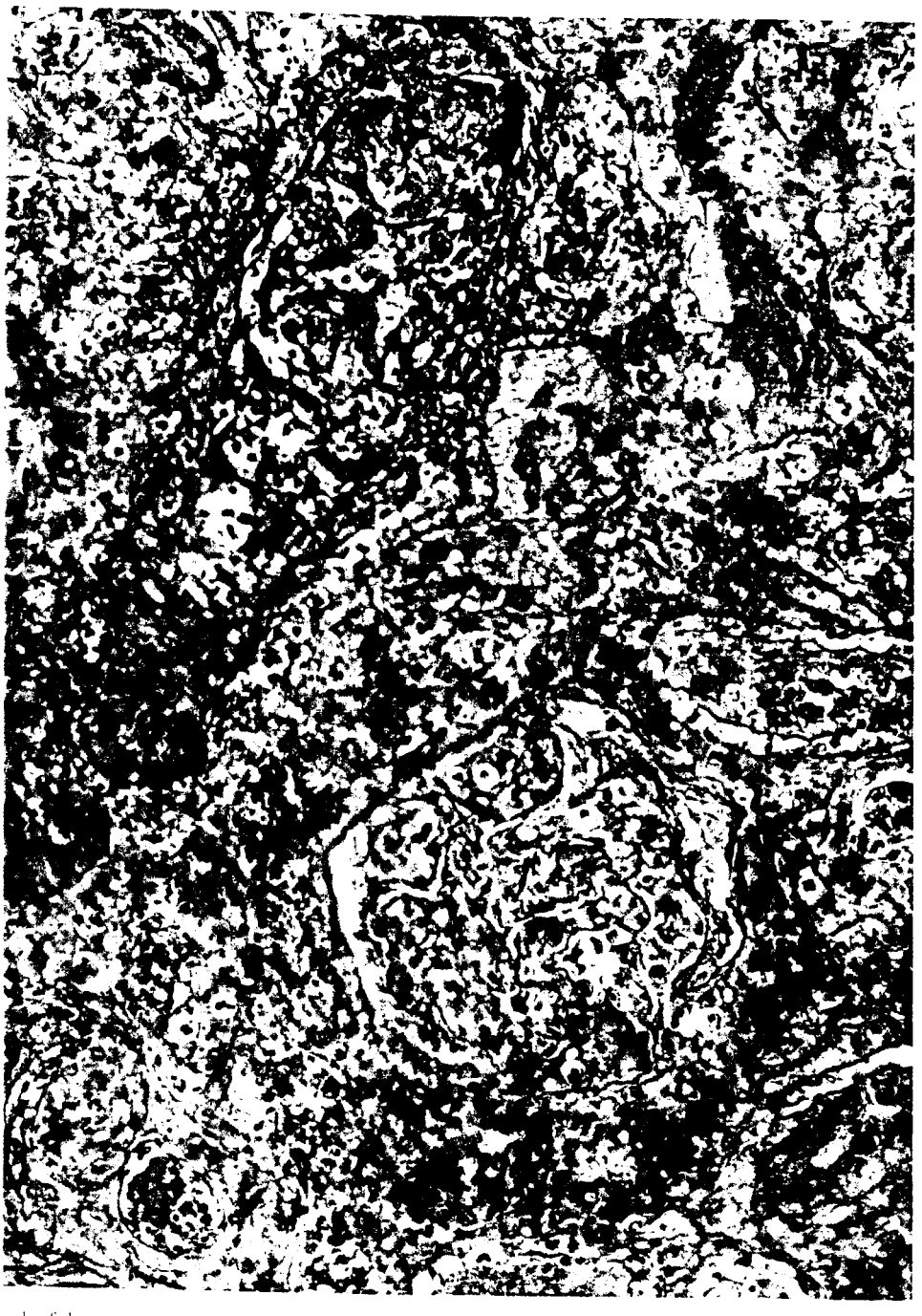

Fig. 3 Photomicrograph of the post mortem renal histology using Mallory's trichrome stain. The section shows an interlobular artery containing a red staining fibrin clot and a glomerulus with scanty red staining fibrin. (Original magnification ×40).

an initial response to fluid load. he became progressively more oliguric and was virtually anuric by d 4. While he had transient evidence of rhabdomyolysis, gross myoglobinuria was not present, and it was felt that this was not a significant factor in his acute renal failure.

On assessment on d 3 it was felt that the patient had a HUS-like condition, since he had thrombocytopenia without other coagulation abnormalities, microangiopathic hemolytic anemia and acute renal failure. He did not appear to have underlying neurological dysfunction, but this was difficult to assess because of his sedation while being ventilated. He subsequently received 3 of 3 l plasma exchanges over the next 3 d using fresh frozen plasma (FFP) as a replacement fluid. Intravenous heparin infusion was started simultaneously at 5000 units/24 h. Apheresis was stopped because of apparent lack of response, but within 36 h of his first apheresis, his platelet count began to rise and returned to normal within 3 d. Likewise, his microangiopathic hemolytic anemia also abated, the final blood transfusion coinciding with the final apheresis and red cell fragmentation no longer being visible by d 14.

His paralysis slowly improved and by d 11 he was weaned from the ventilator. On d 14 he was re-intubated because of fatigue. He then suffered an asystolic cardiac arrest from which he was resuscitated without prolonged hypotension or hypoxia. Unfortunately, during this arrest he sustained a massive brain injury from which he never recovered. Further ventilatory support was ceased on d 21 and the patient died shortly afterwards. His renal function never recovered and he continued to have marked muscle weakness up until his death.

Post mortem examination showed fibrin thrombi in the interlobular arteries of the kidneys (Fig. 3), small arteries of the spleen and in the pulmonary arterioles and small arteries. There were infarcts in the spleen and a single small infarct of the left kidney. There was no evidence of rhabdomyolysis. The liver, heart and skin appeared relatively normal. The

cerebral cortex showed widespread hypoxic-ischemic damage with a gliomesodermal reaction of around 10 d duration. Other areas of the brain, including the cerebellum, showed multifocal patchy necrosis. Overall the brain showed changes in the end arterial territories and boundary zone regions indicative of hypotensive injury of an age coinciding with his cardiac arrest.

DISCUSSION

Rapid defibrination with equally rapid recovery of normal blood coagulation is a well recognised feature of envenomation by many of the elapid snakes, of which the taipan is a member. There is a variable, but usually not severe, associated thrombocytopenia which also recovers rapidly.[2] While our patient's defibrination and recovery followed the usual course, his severe and persistent thrombocytopenia with associated microangiopathic hemolytic anemia and acute renal failure were unusual complications suggesting HUS. The very closely related syndrome of thrombotic thrombocytopenic purpura (TTP) was also possible but seemed less likely since he did not really show typical TTP central nervous system involvement, taking into account that his extensive muscular paralysis and sedation for ventilation made neurological assessment difficult. HUS or HUS-like changes have been reported from snake bites of the gwadar (*Demansia nuchalis nuchalis*), the dugite (*Demansia nuchalis affinis*) in Western Australia[4] and Russell's viper (*Vipera russelli*) in India.[5] TTP has been described following bee stings and spider and dog bites. The distinction between HUS and TTP is somewhat artificial as there is considerable overlap between the two and they are probably best regarded as a continuum of a similar disease process.[6]

DIC was considered as a cause for his thrombocytopenia, renal failure and MAHA, but was rejected on the grounds that:

1. D Dimer levels returned to normal despite continuing thrombocytopenia;
2. his other coagulation parameters remained normal; and
3. he did not appear to have other major organ dysfunction frequently seen in DIC.

The response to plasma exchange with FFP, while initially felt to be not effective, seemed in retrospect most impressive. His thrombocytopenia and hemolytic anemia rapidly abated in the course of a few days (Fig. 1), but unfortunately his severe renal impairment remained unchanged. Permanent renal damage is not uncommon in adult primary and secondary diarrheal or viral types of HUS, with around 20% requiring long term dialysis or transplant.[8]

The post mortem findings in the kidney were in keeping with HUS, showing fibrin containing thrombi in the pre-glomerular small arteries and arterioles. There are a number of histological changes that can be seen ranging from glomerular capillary wall and basement membrane thickening, to occasionally membrano-proliferative glomerulonephritis, to changes in the pre-glomerular arterioles and arteries with intimal myxoid hyperplasia or fibrinoid necrosis.[7] The amorphous hyaline material which may occlude the glomerular capillaries in TTP and DIC was not seen.[7] Because of the time between the initial renal insult and death, as well as the recovery and the MAHA/thrombocytopenia, many of the features listed above are likely to have changed considerably as the body's healing processes continued and chronic renal failure progressed.

The pathological process in the kidney leading to a HUS-like picture in snake bite, has to our knowledge not been investigated. It is possible that high circulating levels of snake venom could damage the renal endothelium in a manner similar to that produced by shiga toxin or shiga-like toxins, but this remains speculative.

Post mortem appeared to confirm that our patient's severe brain injury was related to the period of hypotension from his asystolic cardiac arrest, which occurred 12 days after the taipan bite. The cause of his arrest remains uncertain but did not appear to be related to microvascular changes such as those seen in his kidneys or spleen, as his heart was microscopically normal at post mortem. Cardiac dysfunction has been reported within the first 24 hours of envenomation causing bradycardia and T wave inversion, but delayed cardiac events have not been reported.[1]

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