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Neurotoxicity with persistent unilateral ophthalmoplegia from envenoming by a wild inland taipan (*Oxyuranus microlepidotus*, Elapidae) in remote outback South Australia.

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Abstract

Introduction

A case of life threatening envenoming by a wild specimen of the inland taipan, *Oxyuranus microlepidotus*, is described. There have been 11 previously well-documented envenomings by *O. microlepidotus*, but only 2 were inflicted by wild snakes. Envenomed patients have presented predominantly with defibrinating coagulopathy and neurotoxicity.

Case Report

The victim was seeking to observe members of an isolated population of this species and was envenomed while attempting to photograph an approximately 1.5 m specimen. He reported feeling “drowsiness” and blurred vision that
progressed to ptosis; he later developed dysphagia and dysarthria. The patient was treated with 1 vial of polyvalent antivenom, which was later followed with an additional two vials of taipan monovalent. He was intubated during retrieval, and recovered after 3 days of intensive care. He had a right ophthalmoplegia that persisted for approximately 1 week post-envenoming. Despite a positive 20-minute whole blood clotting test, defibrination coagulopathy was absent, and there was no myotoxicity, or acute kidney injury.

Discussion

Physicians presented with a patient envenomed by *O. microlepidotus* should remain cognizant of the possible variability of medically important venom toxins in some populations of this species. Some patients seriously envenomed by this species may develop persistent cranial nerve palsies. When clinically indicated, prompt provision of adequate antivenom is the cornerstone of managing *O. microlepidotus* envenoming. Rapid application of pressure-bandage immobilization and efficient retrieval of victims envenomed in remote locales, preferably by medically well-equipped aircraft, probably improves the likelihood of a positive outcome.

Introduction

The genus *Oxyuranus* contains 3 species of highly venomous elapid snakes. Of these, the coastal taipan (*O. scutellatus*) has been most medically important, although in comparison to the early Twentieth Century, is now a less common cause of serious envenoming in Australia. However, the Papuan taipan, *O. s. canni*, has major medical importance in Papua New Guinea. It is noteworthy that some authors consider *O. s. canni* synonymous with *O. scutellatus*, but this
impression is probably based on a single study (Wüster et al. 2005) that investigated several mitochondrial DNA sequences derived from a single specimen of *O. scutellatus*, and from two specimens of *O. s. canni*. Wüster et al. (2005) appropriately indicated that for several reasons (e.g. the limited sample size), further investigation would be necessary in order to confirm synonymy of *O. s. canni* with *O. scutellatus*. We agree, and although their synonymy may soon be confirmed, we prefer to reference the subspecies until further supporting evidence is published.

There have not yet been any documented envenomings by the newly discovered western desert taipan, *O. temporalis*. The inland taipan, *Oxyuranus microlepidotus*, attains an average adult length of 1.5 m, and occurs in remote inland regions of channel country (south-western Queensland with extension into sections of north-eastern South Australia and north-western New South Wales) and surrounding areas of dunes, as well as gibber plains (or, ‘stony downs’, flat, pebble/stone-covered plains) near the junction of Queensland, New South Wales and South Australia (Mirtschin et al., 2017). *Oxyuranus microlepidotus* venom is well known for having the so far highest experimental lethal potency (subcutaneous LD$_{50}$ 0.025 mg/kg; Broad et al., 1979) of any tested snake venom. However, experimental venom lethal potency tested in mice doesn’t reliably predict medical risk, and there have been no fatalities among the handful of patients seriously envenomed by *O. microlepidotus* (Mirtschin et al., 2017). Most patients envenomed by *O. microlepidotus* have presented with defibrinating coagulopathy and neurotoxicity.

We report here a case of an *O. microlepidotus* envenoming that caused progressive and persistent neurotoxicity without defibrinating coagulopathy.
The case also highlights some of the difficulties that may be encountered when assessing a victim bitten by a highly venomous snake in a remote location.

Clinical Record

A 28 yr old male professional snake catcher sought to photograph a specimen of inland taipan (*O. microlepidotus*) in a location (north of Coober Pedy, South Australia; 526 miles north of Adelaide; general regional coordinates: 29.0139° South, 134.7533° East) known to have a possibly isolated population of this species. An approximately 1.5 m specimen of *O. microlepidotus* was found (photographs of the specimen have been reviewed and the taxon verified by the senior author) in late afternoon (at about 1730 hours), and carefully positioned for photography by the victim. The snake moved away from the selected site, and the victim gently pulled the snake back by the tail. The snake ‘looped’ backwards, and the victim re-positioned it by turning it while maintaining the grip on its tail. As the victim’s companion prepared to take the photo, the victim noted that he was bleeding from the right forearm, and understood that he had been grazed or ‘raked’ by a glancing bite or single fang scratch. Within a few minutes he felt nauseated, light-headed and stated that he felt “drowsy”; he and his companion promptly applied a pressure-bandage immobilization (PBI) then sought help at a nearby hospital. It should be noted that the area is serviced by community and family physicians, and has no intensive care facilities. Critically ill patients are moved by a statewide specialist medical retrieval service to a tertiary referral hospital in the state’s capital city (a 2hr flight to the south).

The victim was evaluated approximately 45 minutes after the bite, and the treating physician consulted with the South Australian retrieval service
(MedSTAR) who then contacted the on-call toxinologist (SAW). At approximately one hour post-envenoming, the patient began vomiting, and reported increasingly blurred vision; early bilateral ptosis and slurred speech were noted, but there was no evidence of respiratory compromise. Given the local unavailability of formal laboratory services, a 20-minute whole blood clotting test (20WBCT) was performed in a glass tube and remained non-clotted after 25+ minutes, a ‘positive’ result suggesting the presence of coagulopathy. Because of the limited clinical personnel in the Coober Pedy local hospital, urgency of the patient’s condition and process of arranging retrieval, a blood sample from a healthy volunteer was not tested as a 20WBCT control sample. Two hours after the envenoming, one vial of Polyvalent snake antivenom (Seqirus®, Melbourne, VIC, Australia; contains 12000 \textit{in vitro} neutralizing units for \textit{O. scutellatus} venom; this is equal to the neutralizing capacity of monospecific taipan antivenom) was administered IV to the patient, and a two-stage air retrieval from Coober Pedy was arranged. The Polyvalent antivenom infusion was completed, and the patient departed with the first aircraft 3.5 hours after the 'bite'. In order to slow the uptake of any possible sequestered venom, the PBI was intentionally left in place during the entire retrieval process. As the patient was transferred from the first to the second aircraft mid-retrieval (5 hours after the envenoming), his vital signs remained within normal limits, but he was unable to significantly crease his forehead, exhibited progressive dysarthria, dysphagia with increasing drooling, and severe ptosis. In light of this progression, the patient was given rocuronium, intubated, ventilated and provided with an additional two vials of Taipan antivenom (Seqirus®, Melbourne, VIC, Australia; as noted previously, each vial also contains 12000 \textit{in
vitro neutralizing units for *O. scutellatus* venom), 5.5 hours post-bite. The retrieval was further complicated by an aircraft malfunction necessitating transfer to a third aircraft.

After arrival at the tertiary medical center, 10.3 hours post-bite, formal laboratory investigations revealed no evidence of coagulopathy including an absence of elevated D-dimer. Aside from a transiently elevated C-reactive protein (60 mg/L, peaked approximately 40-42 hr post-envenoming; likely related to moderate local inflammation at the wound site), all laboratory investigations remained within normal limits, as did the patient's vital signs. He remained intubated for 48 hours, and exhibited ptosis, as well as ophthalmoplegia post-extubation. Deep tendon reflexes were reduced (1+) in upper and lower extremities. Both pupils reacted sluggishly, but his right pupil appeared qualitatively more so; the patient was unable to tolerate comprehensive testing of his right eye, and exhibited right-sided photophobia. He complained of nausea and growing ocular fatigue with further attempted examination/testing. He was discharged five days after admission with a persistent right ophthalmoplegia; ophthalmological and neurological examination prior to discharge was otherwise unremarkable. The patient reported a full recovery 7 days after the envenoming.

Discussion

Approximately 11 bites and/or envenomings by *O. microlepidotus* have been reported (only 2/11 were inflicted by wild specimens) (Trinca, 1969; Mirtschin et al., 1984; Covacevitch et al., 1995; White et al., 1992; Smith and Ambikapathy, 1992; Johnston et al., 2017), and a number of formally undocumented bites by
this species have also occurred. Almost all of the previously documented patients presented with defibrination coagulopathy, most also had paralysis, and at least one had myotoxicity. Our patient only developed neurotoxicity, that manifested as delayed descending flaccid paralysis commencing with cranial nerve involvement about 1 hour post-bite, then progressing approximately 4-5 hours post-bite.

The results of a 20WBCT suggested coagulopathy, but instrumented testing about 9 hours later did not find any fibrin-split products, and the aPTT and INR were normal. Relevantly, Smith and Ambikapathy (1992) reported an *O. microlepidotus* envenoming that featured persistent neurotoxicity with a prolonged aPTT, thrombocytopenia and giant platelets. Their patient received one vial of Polyvalent antivenom, and the aPTT returned to normal 4 hours later; the fibrin split products remained within normal limits, but the thrombocytopenia remained abnormal for 10 days. They did not specifically mention the INR, or fibrinogen, although omission of the INR may have been due to the mixed use of the term at that time because ‘INR’ was standardized after reassessment of the International Sensitivity Index (ISI) in 1983 (WHO, 1983), and for several years thereafter its standardization was discussed or reviewed by several authors (e.g. see Hirsh et al., 1989). Thus, the report by Smith and Ambikapathy (1992) is difficult to interpret because it could suggest a possible transient anticoagulant coagulopathy with thrombocytopenia and altered platelet morphology. In a recent study of 33 patients systemically envenomed by *Oxyuranus* spp., 31 (93%) developed defibrinating coagulopathy and the median time for the INR to decrease to less than 2.0 was 12.3 hours (IQR: 12.3–18.7 hours; range 8.5–42 hours; Johnston et al., 2017). Recent investigation suggests
that D-dimer has a half-life of approximately 15 hours (Rühl et al., 2015). Smith and Ambikapathy (1992) speculated that the venom had a “direct marrow effect”, but their report contains no further information to support their hypothesis. Therefore, the possibility that our patient developed a transient anticoagulant coagulopathy cannot be excluded. However, given the clinical evidence in our case and other well-documented *O. microlepidotus* envenoming, in our opinion a false positive 20WBCT is more likely. The 20WBCT is commonly used globally in the rural tropics where medical laboratories may be difficult to access, and has certainly been a useful test in a variety of clinical settings (e.g. see Sano-Martins et al., 1994; Gaus et al. 2013; Iliyasu et al., 2015). However, the assay has variable sensitivity and specificity and thus can yield false negatives or positives under some clinical circumstances (Isbister et al., 2013; Ratnayake et al., 2017). In Australian rural settings without laboratory instrumentation it may be the only option, but in our case the available evidence suggests that it probably yielded a false positive, as has been occasionally noted after coagulopathic envenoming from some Australian elapids (White, 2013). It should be stressed that failure of the 20WBCT may often be due to “operator error” (e.g. extent of training of personnel performing the test, assay temperature, use of incorrect test vessels, misinterpretation of results, etc.; Isbister et al., 2013; Auerbach et al., 2016; Ratnayake et al., 2017).

It is also noteworthy that although our patient had correctly applied a PBI within a few minutes after contact with the taipan, he developed signs and symptoms of systemic envenoming in less than 30 minutes. While it is possible that early provision of antivenom prevented a more rapidly progressive paralysis, respiratory support was still deemed clinically necessary for two days. In the
aforementioned series of *Oxyuranus* spp. envenoming, Johnston et al. (2017) reported 7 bites by captive *O. microlepidotus*; 6 patients were envenomed, and these all received antivenom. All developed consumption coagulopathy, 57% had neurotoxicity, and 43% had an acute kidney injury (AKI) and/or microangiopathic hemolytic anemia (MAHA); none developed myotoxicity (Johnston et al., 2017).

Studied samples of *O. microlepidotus* venom contain paradoxin, which is closely similar to taipoxin, the heteropentameric presynaptic neurotoxin described from coastal taipan (*O. scutellatus*) venom, several postsynaptic neurotoxins, procoagulants that function as Va and Xa homologues, myotoxic phospholipases A₂, natriuretic peptides, and numerous other components (Fohlman, 1979; Hamilton et al., 1980; Bell et al., 1988; Crachi et al., 1999; Fry et al., 2005; Clarke et al., 2006; Vink et al., 2010; Earl et al., 2012). Venom composition variability has been thoroughly documented in several medically important viperids and elapids (e.g. Minton and Weinstein, 1986; Chippaux et al., 1991). It is probable that the specimen that envenomed our patient secreted venom that either lacked, or contained much lower concentrations, of several medically important toxins (procoagulants) commonly found in most tested venoms of this taxon.

Johnston et al. (2017) asserted that one vial of antivenom “should be sufficient to treat most taipan envenoming because all of the detectable venom antigens were bound by antibody present in one vial of antivenom”. This view has been previously criticised (Weinstein et al., 2016) because of problems and pitfalls of the methods (ELISA assays) used to support their recommendations. Treatment must be provided per individual patient with consideration for their co-morbidities and individual risks; guidelines provide a starting reference, but,
ultimately, one “size” does not necessarily “fit all”. Coastal taipan (*O. scutellatus*) envenoming can rapidly (in several minutes) clinically progress after removal of the PBI (Southern et al., 1996; SAW, personal observations), and thus it is essential to initially provide adequate antivenom, as clinically indicated. The persistence of a unilateral ophthalmoplegia in this case is uncommon and not readily explained, as venom paralytic effects are typically bilateral because of the systemic distribution of venom, a non-systemic exception being localised effects from paralysis ticks attached close to a cranial nerve (White, 1995). Delayed resolution of bilateral ptosis and partial ophthalmoplegia does occur in some patients who develop paralytic features after Australian elapid envenoming and longer term residual hyposmia or anosmia also may occur, and not always in association with neurotoxic envenoming (Sutherland and Tibballs, 2001; White, 2010; 2013; Sethi et al., 2017). A patient seriously envenomed by a common tiger snake (*Notechis scutatus*, Elapidae) experienced a similarly persistent unilateral (left) ophthalmoplegia that lasted for at least ten months and did not fully resolve (lost to follow-up after one year; SAW personal observations). Although it is speculative to consider possible causes of these patients’ persistent unilateral ophthalmoplegia, it is noteworthy that it may present in patients with internuclear ophthalmoplegia (INO) that arises from an interruption of fibres connecting the oculomotor nuclei, and can be unilateral or bilateral (Karski et al., 2013). Unilateral INOs are most commonly associated with ischaemia (Kaski et al., 2013). Unilateral ophthalmoplegia also has been rarely reported in other disease states such as acute myeloid leukemia (Mott and Carlson, 2012), ophthalmoplegic migraine (Patel et al., 2015), and occasionally with various central nervous system infarcts.
In conclusion, we have described a serious envenoming inflicted by a wild *O. microlepidotus* that featured progressive neurotoxicity and without defibrinating coagulopathy. Management of our patient emphasized several important observations: the 20WBCT may give false positive results and must be considered together with clinical observations of the patient; prompt and correct application of PBI may delay onset of venom effects; early administration of antivenom may provide a clinically important window for successful patient retrieval from remote locations; prompt intubation and airway protection should be performed whenever possible, as clinically needed, especially during retrievals from remote locales; some populations of *O. microlepidotus* may produce venom without clinically significant levels of defibrinating procoagulants, and possibly with anticoagulant components; clinically indicated antivenom should be administered as early as possible when medically feasible, and the dose should be based on the severity of the individual patient’s envenoming, as well as the patient’s therapeutic response.

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Declaration of Interest Statement

One of the authors reports the following: Julian White does provide advice to the antivenom manufacturer (Seqirus, formerly CSL, Ltd), as part of a contract between his employing hospital and Seqirus. He is not paid by Seqirus and Seqirus has no input or influence on any of his reports, clinical practice or comments.

All of the remaining authors declare no conflicts of interest.

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Highlights

- Documentation of a serious envenoming by a wild inland taipan (*Oxyuranus microlepidotus*) in the remote Australian outback
- Defibrinating coagulopathy was absent; a 20 minute whole blood clotting test may have been a false positive, or possibly indicated a transient anticoagulant coagulopathy
- The patient developed progressive neurotoxicity; had a complicated retrieval from the outback; was ultimately treated with Polyvalent and Taipan monospecific antivenom
- An initial bilateral ophthalmoplegia was notably more pronounced on the right side, and persisted as a unilateral right sided ophthalmoplegia
  - Full recovery achieved after 1 week