Pulmonary oedema complicating snake bite due to *Bungarus caeruleus*

Agarwal R, Singh A P, Aggarwal A N

ABSTRACT

Cardiotoxicity is an unusual manifestation of severe neurotoxic snake envenoming and is previously unreported with snake bites due to kraits. We describe a 26-year-old male Indian farmer who developed cardiogenic pulmonary oedema after neurotoxic snake envenoming by *Bungarus caeruleus* (Indian krait). We also review the literature on cardiac manifestations, the possible mechanisms and treatment of patients with cardiotoxicity accompanying neurotoxic snake envenoming. Cardiac involvement can complicate the course of snakebites. Recognition of cardiac involvement can warn the emergency physician and intensivist to be cautious, and anticipate the complications, such as pulmonary oedema, so that they can be rapidly and appropriately managed.

Keywords: *Bungarus caeruleus*, cardiotoxicity, indian krait, neurotoxins, pulmonary oedema, snack antivenin, snake bite, snake envenoming

Singapore Med J 2007; 48(8):e227–e230

INTRODUCTION

Snake envenoming is a common medical emergency in the tropical countries.[1] An estimated 35,000–50,000 people die of snake bites every year in India.[1] Neurotoxic snake envenoming is the most important cause of snake bite fatality[2] and is mainly due to the Elapidae family, which includes the *Naja* and *Bungarus* species, commonly referred to as the cobras and kraits, respectively. Neuromuscular paralysis from snake bites occurs as a result of the blockade of neuromuscular transmission.[3] Toxins from cobra venom predominantly act postsynaptically, whereas those from krait venom mainly act presynaptically. However, most snake venom contain both presynaptic and postsynaptic neurotoxins.[4]

Snake antivenin (SAV) is a specific antidote to snake venom actions. However, there are no clear guidelines on the optimal dose in the management of patients with severe envenoming, and doses as high as 1,400 ml have been used empirically in the hope of an early recovery.[5] It is also not clear whether there is any use of SAV once neuroparalysis has already set in; and there are reports of patients with severe envenoming who have recovered without the use of SAV.[6,7] In our institute, we presently use a protocol of a total dose of 150 ml of SAV in patients with severe neurotoxic envenoming.[2] Cardiac involvement is an infrequently recognised manifestation of snake bites, and is seen mainly with viperine bites.[8] Cardiac involvement in elapid bites has been uncommonly reported. Moreover, it has been reported to occur only with cobra bites. In this report, we describe a patient with an elapid (*Bungarus caeruleus*) snake bite, and during the course of hospital stay, he developed cardiogenic pulmonary oedema. We also review the manifestations and treatment of cardiac involvement in elapid snake bites.

CASE REPORT

A 26-year-old male farmer was admitted with complaints of breathlessness six hours after being bitten by a snake while working in the fields (the dead snake was brought in and identified as *Bungarus caeruleus*). On examination, the patient was afebrile with normal vital signs. There were clearly-defined fang marks on the dorsum of the right foot with no local oedema or pain. The patient was administered polyvalent SAV (Bengal chemicals, Calcutta, India), which neutralises the venom of *Bungarus caeruleus, Naja naja, Viper russelli, Echis carinatus,* 150 ml over one hour. However, he developed bilateral ptosis, dysphagia, progressive limb weakness and paradoxical diaphragmatic movements, eight hours after the bite. The patient was transferred to the respiratory intensive care unit, where he was orotracheally intubated and mechanically ventilated with the assist control mode (tidal volume 420 ml, respiratory frequency 15/minute, FiO_2 0.3, positive end-expiratory pressure (PEEP) 5, peak and plateau pressures 18 cm and 12 cm of water, respectively). The patient showed evidence of autonomic instability in the form of repeated episodes of bradycardia and tachycardia, episodes of sweating despite adequate sedation and maintenance of normoxaemia.

Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Sector 12, Chandigarh 160012, India

Agarwal R, MBBS, MD, DM
Assistant Professor

Singh AP, MBBS, MD
Senior Resident

Aggarwal AN, MBBS MD, DM
Associate Professor

Correspondence to:
Dr Ritesh Agarwal
Tel: (91) 172 275 6825
Fax: (91) 172 274 5959
Email: riteshpgi@gmail.com; ritesh@indiachest.org

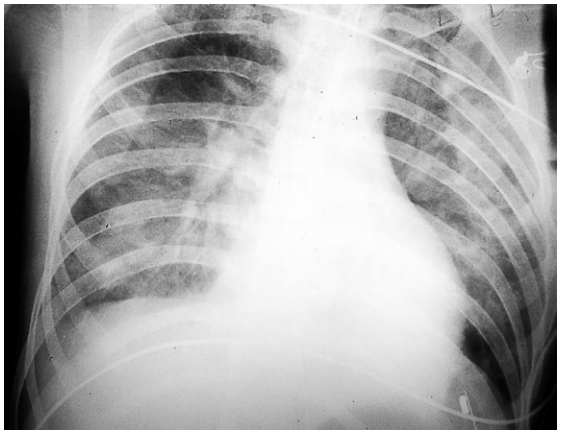

Fig. 1 Chest radiograph shows bilateral alveolar opacities suggestive of pulmonary oedema.

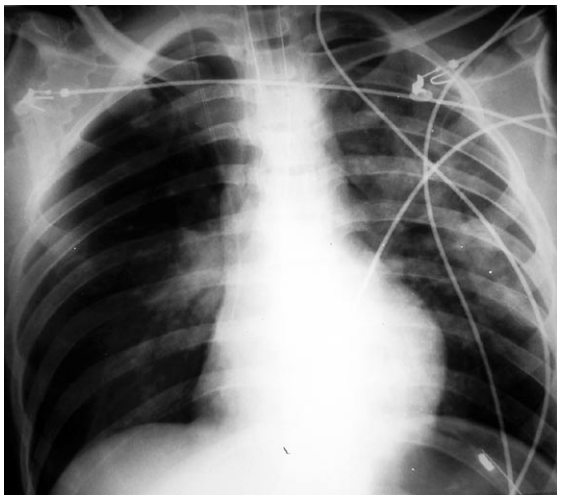

Fig. 2 Chest radiograph shows clearing alveolar opacities consistent with resolution of pulmonary oedema.

After about eight hours of mechanical ventilation (16 hours after the snake bite and ten hours following neurological symptoms), the patient started developing hypoxaemia, and oxygen requirements increased to 70%. A chest radiograph revealed results suggestive of a right lower lobe collapse. Physiotherapy and suctioning were tried. As there was no improvement, the patient was subjected to a fibreoptic bronchoscopy (approximately 20 hours post-bite, premedication with intravenous midazolam 4 mg and vecuronium 4 mg), and a mucous plug was extracted from the right lower lobe. Intra-procedure, the patient was found to have a blood pressure (BP) of 90/60 mmHg; 1,000 ml of 0.9% saline was administered, following which the BP increased to 120/80 mmHg. However, the patient's oxygen saturation did not improve and the plateau pressures started rising; suction now brought out frothy secretions in copious amounts. An arterial blood gas done showed a pH of 7.31, PaO_2 56 mmHg, $PaCO_2$ 32 mmHg and HCO_3 15 mEq/L at FiO_2 of 1. Tidal volumes were increased to 500 ml and PEEP of 14 was given at a breath rate of 20. Frusemide 40 mg and morphine 3 mg were administered intravenously. A chest radiograph revealed bilateral alveolar opacities suggestive of pulmonary oedema (Fig. 1).

Central venous catheterisation was performed through the right internal jugular vein and the opening pressure was 18 cm of saline. The procedure was complicated by the occurrence of a pneumothorax which was treated with a tube thoracostomy. Serum electrolytes, renal and liver function tests, complete blood count and coagulation profile were all normal. Creatine phosphokinase (CPK) [MB isozyme] levels were 81 U/L, troponin-T kit test was positive and electrocardiography (ECG) revealed ST depression and T-wave inversion in the anterolateral leads (aVL, Ll, V1-V6). Echocardiography revealed global hypokinesia, left ventricular ejection fraction of 40% with no evidence of valvular abnormalities, pulmonary hypertension and wall-motion abnormalities. Supportive treatment was continued and the patient gradually improved over the next 48 hours. A repeat assay for CPK-MB levels after 72 hours was normal and chest radiograph showed resolution of pulmonary oedema (Fig. 2). The patient denied any history of illicit drug abuse, including cocaine. He was discharged from the hospital after a total stay of ten days. On follow-up at six weeks, the patient was doing well, troponin-T was negative, and there was no evidence of autonomic dysfunction detected on clinical evaluation (heart rate and BP changes after Valsalva manoeuvre, handgrip and cold-water immersion tests). Urinary vanillyl mandelic acid levels and ultrasonography of the abdomen were normal. An echocardiography showed left ventricular ejection fraction was 62% and no other abnormalities were noted.

DISCUSSION

The patient had severe neurotoxic snake envenoming (patients with acute neuromuscular respiratory failure are categorised as severe envenoming).[2] The clinical profile of cardiogenic pulmonary oedema, temporal relation to snake bites, absence of other causes like illicit drug abuse and complete recovery following treatment of the snake bite, suggest myocardial involvement consequent to snake envenoming. The initial episodes of bradycardia and tachycardia, along with spontaneous sweating, also point to concomitant autonomic dysfunction consequent to snake envenoming. The presence of nonspecific T wave changes on ECG, occurrence of pulmonary oedema, raised cardiac enzymes, global hypokinesis and a depressed ejection fraction on echocardiography

(suggesting myocarditis), and improvement of all these abnormalities with treatment of snake envenoming, suggest that all these manifestations were secondary to myocarditis, rather than being consequences of autonomic dysfunction. Other possible causes include noncardiogenic pulmonary oedema secondary to the SAV used. However, this phenomenon generally occurs within six hours after antivenin administration.[9] The use of cardiodepressive drugs, e.g. benzodiazepine, for sedation while performing bronchoscopy can also trigger pulmonary oedema. Other contributory causes, e.g. ischaemic insult to the heart secondary to hypoxia from delayed intubation, aspiration/mucous plugging with poor ventilation, can contribute to the causation of pulmonary oedema in patients with snake bites, although it did not complicate the hospital course of our patient.

Cardiotoxicity has been recognised as a feature of snake envenoming. However, it is the neuromuscular paralysis and the respiratory failure with elapid bites, and the coagulation abnormalities in viperine bites, which dominate treatment efforts in patients. Nayak et al have documented the range of cardiac manifestations in snake bites.[8] In fact, 30% of their cases had evidence of cardiac toxicity in the form of disturbances in heartbeat rate (47%), rhythm abnormalities (6.7%), hypertension (6.7%) and hypotension (16.7%). Electrocardiographic abnormalities documented included sinus tachycardia and arrhythmia, bradycardia, tall T-waves and abnormalities suggestive of myocardial ischaemia and nonspecific T-wave abnormalities. Atrioventricular blocks were also seen. However, only one patient out of the 30 studied had frank pulmonary oedema. Moreover, this study was dominated by viperine bites (93%) and the profile is likely to be different if more elapid bites were studied.[8] In fact, clinically-significant cardiac abnormalities have been rarely reported in patients with elapid bites. In a retrospective series of 55 patients with severe neurotoxic snake envenoming secondary to elapid snake bites, we found no clinically significant cardiac involvement.[2] There is experimental data on cardiac involvement in elapid bites both with cobra toxins[10-12] and krait venom.[13,14] However, to the best of our knowledge, there is no report in the English literature on cardiac involvement in the form of pulmonary oedema in patients with krait bites.

On the other hand, autonomic dysfunction is common in patients with elapid snake bites. Dysautonomia after snake envenoming can be seen as mild to moderate hypertension or hypotension, cardiac rhythm disturbances, vomiting and abdominal pain, sweating, and markedly exaggerated circulatory responses to even normally innocuous stimuli (such as oral suction, posture change, etc.).[15-17] In fact, in one study, more than half of the patients with krait bites had autonomic dysfunction.[16] The mechanism of cardiac involvement in neurotoxic snake bites is not clear but is likely to be due to one of the myriad toxins seen in snake venom, which can cause morphological changes,[12,13] enzyme alterations,[11] ultrastructural disturbances[18] and genetic alterations[19] of the myocardial tissue. In a recent experimental study, analysis of gene expression profiles in mice in response to cobra venom treatment revealed 203 genes in the heart, brain, kidney, liver and lung whose expressions were altered by at least three-fold. Of these, 50% were differentially expressed in the heart, and included genes involved in inflammation, apoptosis, ion transport and energy metabolism. Moreover, ECG recordings and serum troponin T measurements indicated declining cardiac function and myocardial damage.[19]

Another point of interest is the progression of neurotoxicity, despite administration of SAV. This is commonly seen and is an artefactual observation secondary to the lag period between the snake bite and onset of symptoms, and the administration of SAV during the lag period.[20] Our patient probably had toxic myocarditis (secondary to a krait venom toxin), and rapid administration of intravenous fluids probably tilted the delicate intravascular fluid balance into resultant pulmonary oedema. No specific treatment apart from snake antivenin is required for the cardiac involvement. Other supportive measures, such as management of pulmonary oedema with diuretics and change in ventilator strategy (as was done in our patient), and treatment of dysrhythmia, may be required in specific cases.

In conclusion, our case serves to underscore the fact that cardiac involvement in the form of toxic myocarditis can complicate the treatment course of snake bites and alter management. It is a phenomenon that should be kept in mind, and routinely investigated for using an ECG. If abnormal findings ensue, monitoring the patient with serial ECGs and cardiac enzymes in anticipation of cardiac complications is necessary. Recognition of cardiac involvement can forewarn the emergency physicians and intensivists to be cautious, and anticipate the complications such as pulmonary oedema, so that they can be rapidly and appropriately managed.

REFERENCES

1. Warrell DA. WHO/SEARO Guidelines for the clinical management of snake bites in the Southeast Asian region. Southeast Asian J Trop Med Public Health 1999; 30 (Suppl 1):1-85.
2. Agarwal R, Aggarwal AN, Gupta D, Behera D, Jindal SK. Low dose of snake antivenom is as effective as high dose in patients with severe neurotoxic snake envenoming. Emerg Med J 2005; 22:397-9.

3. Lewis RL, Gutmann L. Snake venoms and the neuromuscular junction. Semin Neurol 2004; 24:175-9.
4. Harris JB. Snake venoms in science and clinical medicine. 3. Neuropharmacological aspects of the activity of snake venoms. Trans R Soc Trop Med Hyg 1989; 83:745-7.
5. Agrawal PN, Aggarwal AN, Gupta D, et al. Management of respiratory failure in severe neuroparalytic snake envenomation. Neurol India 2001; 49:25-8.
6. Sethi PK, Rastogi JK. Neurological aspects of ophitoxemia (Indian krait)- A clinico-electromyographic study. Indian J Med Res 1981; 73:269-76.
7. Bomb BS, Roy S, Kumawat DC, Bharjatya M. Do we need anti snake venom (ASV) for management of elapid ophitoxaemia. J Assoc Physicians India 1996; 44:31-3.
8. Nayak KC, Jain AK, Sharda DP, Mishra SN. Profile of cardiac complications of snake bite. Indian Heart J 1990; 42:185-8.
9. Singh A, Biswal N, Nalini P, Sethuraman, Badhe A. Acute pulmonary edema as a complication of anti-snake venom therapy. Indian J Pediatr 2001; 68:81-2.
10. Hider RC, Khader F. Biochemical and pharmacological properties of cardiotoxins isolated from cobra venom. Toxicon 1982; 20:175-9.
11. Barrington PL, Soons KR, Rosenberg P. Cardiotoxicity of Naja nigricollis phospholipase A2 is not due to alterations in prostaglandin synthesis. Toxicon 1986; 24:1107-16.
12. Sun JJ, Walker MJ. Actions of cardiotoxins from the southern Chinese cobra (Naja naja atra) on rat cardiac tissue. Toxicon 1986; 24:233-45.
13. Kiran KM, More SS, Gadag JR. Biochemical and clinicopathological changes induced by Bungarus coeruleus venom in a rat model. J Basic Clin Physiol Pharmacol 2004; 15:277-87.
14. Mirajkar KK, More S, Gadag JR. Isolation and purification of a neurotoxin from Bungarus caeruleus (common Indian krait) venom: biochemical changes induced by the toxin in rats. J Basic Clin Physiol Pharmacol 2005; 16:37-52.
15. Laothong C, Sitprija V. Decreased parasympathetic activities in Malayan krait (Bungarus candidus) envenoming. Toxicon 2001; 39:1353-7.
16. Kularatne SA. Common krait (Bungarus caereleus) bite in Anuradhapura, Sri Lanka: a prospective clinical study, 1996-98. Postgrad Med J 2002; 78:276-80.
17. Agarwal R, Aggarwal AN, Gupta D. Elapid snakebite as a cause of severe hypertension. J Emerg Med 2006; 30:319-20.
18. Wu WG. Cobra cardiotoxin and phospholipase A2 as GAG-binding toxins: on the path from structure to cardiotoxicity and inflammation. Trends Cardiovasc Med 1998; 8:270-8.
19. Cher CD, Armugam A, Zhu YZ, Jeyaseelan K. Molecular basis of cardiotoxicity upon cobra envenomation. Cell Mol Life Sci 2005; 62:105-18.
20. Agarwal R, Singh N, Gupta D. Is the patient brain-dead? Emerg Med J 2006; 23: e5.