CASE REPORT

Plasmapheresis for Pulmonary Hemorrhage Following Viperine Snakebite: Case Report with Review of Literature

Supriya Sampley[1], Vinay Sakhuja[2], Deepak Bhasin[3], Kuldeep Singh[4], Harpal Singh[5]

Abstract

Introduction: Snakebites are one of the commonest occupational hazards in tropical countries and viperine bites are potential to cause systemic toxicity. Coagulopathies and acute kidney injury (AKI) have been documented and easily dealt with in past, but pulmonary hemorrhage has been rarely seen and plasmapheresis has shown promising result for the same. This case reports highlight the effective use of plasmapheresis for pulmonary hemorrhage post-snakebite.

Background: Viperine snakebite has been associated with high morbidity and mortality due to its toxic systemic envenomization. The important systemic manifestations are coagulopathy, neuromuscular paralysis, AKI, myotoxicity, and cardiovascular collapse. Antivenomization, renal replacement therapy, steroids, and other supportive care are considered to be the mainstay of treatment till date. Pulmonary hemorrhage has been an unusual manifestation of viper bite and rarely reported and steroids have been used in such scenario but with mixed results. Role of plasmapheresis has been documented in the management of snakebite but especially for hematological problems and in limb preservation/salvage strategies. The use of same, for pulmonary hemorrhage has not been studied yet. Here, we present a rare case of pulmonary hemorrhage along with renal failure following viper bite which was successfully treated with plasmapheresis. To the best of our knowledge, it is a rare presentation and has not been reported in the literature reviewed till date.

Case description: A previously healthy, 36-year-old man presented to our hospital 48 hours after a viper bite. He developed local as well systemic manifestations evident as hemolysis and renal failure. Gradually, he started having hemoptysis followed by respiratory failure requiring ventilatory support. CT chest done was s/o bilateral pulmonary hemorrhages correlating clinically with ongoing tracheal bleed. He had no other bleeding manifestations and had normal coagulation profile. He was initially treated with methylprednisolone therapy, but then did not show any improvement and finally plasmapheresis was done as rescue therapy. Following this, he had improvement in respiratory parameters and settling tracheal bleed with resolution of radiological changes. He was successfully weaned off from the ventilation and also his renal failure also improved with near normalization of pulmonary and renal functions.

Conclusion: This case highlights the unusual presentation of pulmonary hemorrhage in a patient with viperine bite with normal coagulation and was aggressively managed with plasmapheresis. Hence, plasmapheresis can be used as life-saving modality in patients with systemic envenomization post-viperine bit.

Keywords: Acute kidney injury, Plasmapheresis, Pulmonary hemorrhage, Viper bite.

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Introduction

Snakebites are one of the common causes of morbidity and mortality in tropical countries. The most dangerous and highly venomous species include Cobra, Russell's Viper (RV), and Krait. Bite with RV is the most challenging in medical field, in view majority of clinical manifestations. Its envenomation causes local effects as well as systemic toxic effects. Local site necrosis, cellulitis and systemic complications, such as, coagulopathy, acute renal failure (ARF), and hemolysis has been reported with viper bites. In pulmonary involvement, respiratory paralysis and pulmonary edema are seen but complications of coagulopathy are exclusively reported with viper bites. Case reports citing local and systemic bleeding manifestations are there, but severe pulmonary hemorrhage is not commonly reported. Second, management of snakebite-induced diffuse pulmonary hemorrhage with plasmapheresis along with conventional treatment has not yet been well documented.

Here, we report a case of viperine snakebite with pulmonary hemorrhage and acute kidney injury (AKI), which recovered

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effectively with plasma exchange therapy, and to the best of our knowledge, this is the first reported case of its kind.

Case Description

A 36-year-old man, police officer by profession, hailing from Jammu, presented to our hospital, with a history of snakebite over left foot when he accidently stepped over it. He was immediately taken to state medical college where he received around 20 vials of anti-snake venom and IV fluids, antibiotics, and other supportive care. On the very next day of bite, patient started having decreased urine output along with deranged renal functions. In view of AKI, patient was started on hemodialysis. He was then brought to our hospital for further care on day 3 of snakebite.

After initial evaluation and stabilization in emergency room (ER), he was immediately admitted to medical intensive care unit. He was received in dull drowsy state, but arousable and had stable hemodynamic. Chest examination revealed bilateral decreased air entry. On local examination, swelling at the site of bite with cellulitis and blister formation was noted.

His baseline investigations showed: hemoglobin (Hb) 7.6 g/dL, total leucocyte count (TLC) 15,000, and platelets ~50,000. Had normal coagulation profile with activated partial thromboplastin time (aptt) 15 seconds and International Normalized Ratio (INR) ~1.19, and his bedside clotting time was around 5 minutes and bleeding time was around 32 seconds. His kidney function tests were deranged with urea 167 mg/dL and creatinine 6.17 mg/dL, along with total creatine phosphokinase (CPK) ~52,168 indicating rhabdomyolysis.

Liver function tests showed transaminitis: serum glutamic-oxaloacetic transaminase/pyruvic transminase (SGOT/PT) ~1,985/252 and total bilirubin 4.56 with direct 0.64 and indirect ~3.92. Also, had component of sepsis with procalcitonin of 4.79. He was started on oxygen support at flow ~2 L, intravenous antibiotics, and was given another 10 vials of antivenom. He continued to have acute kidney shutdown with anuric status, for which he was supported on hemodialysis heparin free and ultrafiltration. Further had persistent fall in Hb requiring multiple blood transfusions and during workup for anemia, hemolysis came out to be positive with fragmented cells and spherocytes noted on peripheral blood film and lactate dehydrogenase (LDH) was high ~4,128.

Almost after 1 week of snakebite, he had worsening of hypoxemia and developed bilateral infiltrates on chest X-ray along with pleural effusion. He was then taken of high-flow nasal cannula (HFNC) oxygen support with flow ~50 L/minute and FiO_2 requirement was around 0.4. He then had first episode of hemoptysis. CT chest done at this time showed: multifocal peribronchial air space opacification with ground-glass opacification in bilateral upper and right middle lobe along with moderate pleural effusion with underlying lung collapse (Figs 1 and 2). On the basis of clinical and radiological suspicion: probable diagnosis of diffuse alveolar hemorrhage was kept and steroids were started. Inj. methylprednisolone 80 mg/day (~1 mg/kg/day) was started in two divided doses and that was continued for ~15 days. Thereafter, steroids were tapered off in next 5 days. His coagulation profile was monitored, which was still within normal limits/INR ~1.17 and thrombocytopenia had recovered to ~2.5 lakh. He was continued on HFNC oxygen support and bilateral pleural drain was inserted for moderate effusion which on analysis yielded transudative picture and had been sterile.

2D echocardiography showed good biventricular systolic functioning with ejection fraction (EF) ~55% and ultrasound abdomen showed bulky hypoechoic bilateral kidneys with reduced corticomedullary differentiation (CMD).

Autoimmune pathology in view of pulmonary and renal involvement was ruled out as antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (C-ANCA), and perinuclear antineutrophil cytoplasmic antibodies (P-ANCA) came out to be negative. His sputum culture grew *E. coli* and antibiotics were upgraded to meropenem. Post-steroid and other supportive care along with regular hemodialysis, patient did not show any signs of improvement clinically and hemoptysis continued with progressive fall in Hb and persistent AKI.

Hence, plasma exchange therapy was considered as a rescue therapy.

On 20th day of admission, first plasma exchange was performed using centrifugation technology via internal jugular venous access. 5% Hum albumin was used as replacement fluid and monitoring for his electrolytes/fluid balance and proteins and coagulation profile was done. Post-first session of plex, his renal parameters started improving with urine output ~25 to >50 mL/hour. After third plex, he had secondary sepsis hit with leukocytosis and procalcitonin ~21; hence, polymyxin B was added empirically. He was then electively intubated in view of worsening type I respiratory failure.

Five sessions of consecutive plasma exchange were done and intermittent hemodialysis continued for renal support. During the further course of illness, patient started showing clinical signs of recovery with improving oxygen requirement and settling leukocytosis. His renal function improved and creatinine started settling to 3.5 mg/dL. His urine output gradually improved from initially 500 mL/24 hour pre plex to around ~2,100 mL/24 hour post-third session of plex.

Pulmonary hemorrhage settled down as evident by minimal tracheal bleed and static Hb. Bronchoscopy was done, which showed clear airways.

A repeat high resolution computerised tomography (HRCT) chest showed multifocal peribronchial consolidations and bilateral effusion (Figs 3 and 4). He was continued on antibiotics and supportive care. Finally, after successful weaning trials, he was extubated, following which, he maintained well on low-flow oxygen. He remained hemodynamically stable throughout the

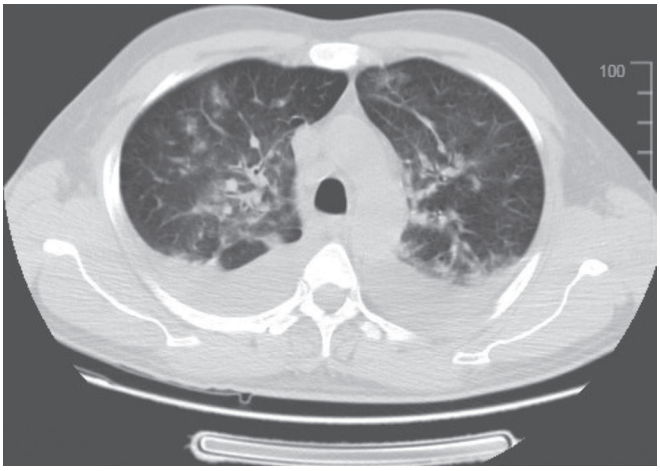


Fig. 1: HRCT chest done at 1st week of admission showing multifocal peribronchial air space opacifications with ground glass opacification in bilateral upper and right middle lobe with pleural effusion

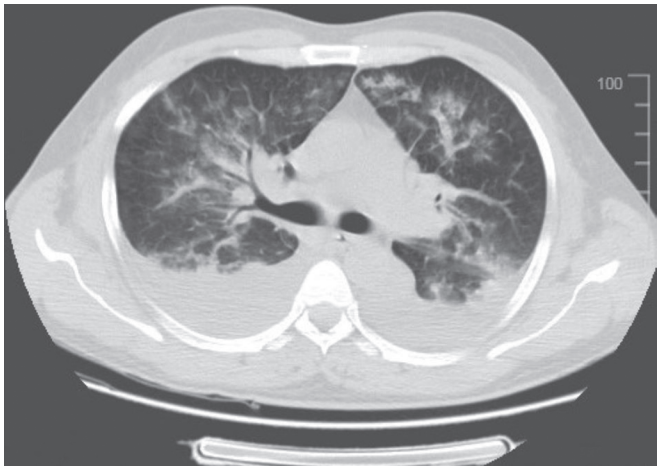


Fig. 2: HRCT chest done at 1st week of admission showing multifocal peribronchial air space opacifications with ground glass opacification in bilateral upper and right middle lobe with pleural effusion

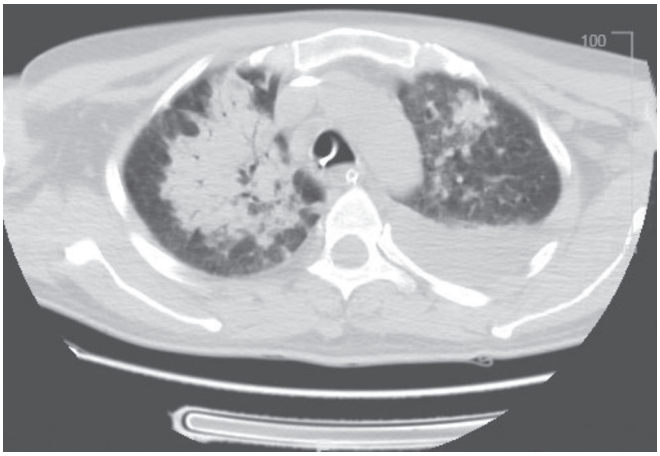


Fig. 3: A repeat HRCT chest done at 3rd week of admission, showing multifocal peribronchial consolidations and effusion suggestive of diffuse alveolar haemorrhage with clinical settings of hemoptysis

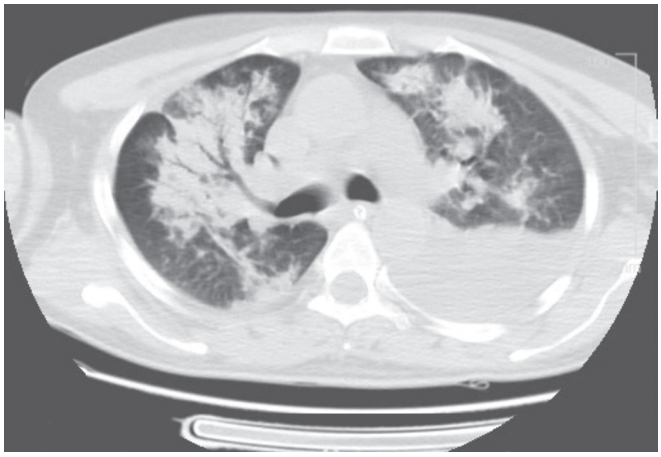


Fig. 4: A repeat HRCT chest done at 3rd week of admission, showing multifocal peribronchial consolidations and effusion suggestive of diffuse alveolar haemorrhage with clinical settings of hemoptysis

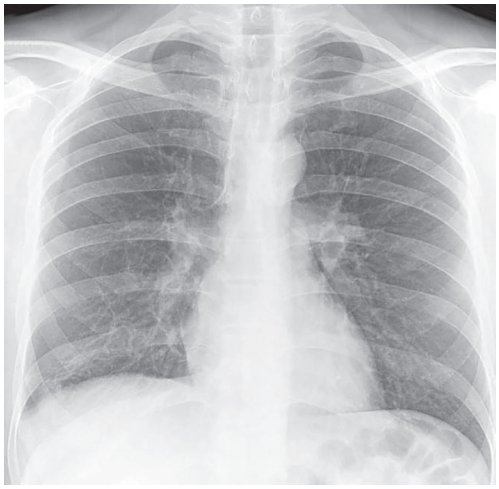


Fig. 5: HRCT chest X-ray clear from infiltrates

hospital stay. His serial X-rays showed clearing out infiltrates with residual right basal collapse consolidation. He was finally discharged in stable condition. At time of discharge, he had creatinine of ~1.2 with good urine output and cleared out chest X-ray. On follow-up in outpatient department (OPD), patient was found to be healthy with no sequelae, had fully recovered AKI, and his creatinine was 0.96 and chest X-ray was clear (Fig. 5).

Discussion

Snakebites are one of the common occupational hazards in tropical countries with high mortality and morbidity. The World Health Organization (WHO) has estimated that nearly 125,000 deaths occur among 250,000 poisonous snakebites worldwide every year, of which India accounts for 10,000 deaths.[1,2] In tropical countries, snakebite has been considered as neglected tropical disease by WHO.[3]

Mortality due to poisonous snakebites in India is the highest in the world, with around 10,000 deaths per annum due to social, cultural, and economic reasons contribute immensely to the death toll.[4]

Around 90% of snakebites are caused by the "big four crawlers": Common krait, Indian cobra, RV, and saw-scaled viper and the highest morbidity and mortality has been seen by hump-nosed viper being vasculotoxic.

The pathophysiology for high morbidity and mortality by viper bites is attributed to systemic envenomization. Russell's viper bite severity includes local manifestations like pain, swelling, and blister formation at the site of the bite. Systemic manifestations include coagulopathy, thrombotic complications, rhabdomyolysis, AKI, and neurological complications.[5] Bleeding is one of the major complications either from the bite site or from the mucosal surfaces of various organs. The postulated theory behind this is the presence of certain proteinases like hemorrhagins and hemolysins which act on the vessel wall causing endothelial destruction along with coagulopathy lead to bleeding.[6]

Mortality due to RV bite is attributed to shock, pituitary, and intracranial hemorrhage, massive gastrointestinal hemorrhage, acute tubular necrosis, and bilateral cortical necrosis.[5,7,8]

In our patient apart from the local manifestations, he developed systemic involvement sequentially. Had AKI initially requiring dialysis support. As per the literature, envenomation is considered

to be one of the common causes of community-acquired AKI in tropical countries, particularly in Southeast Asia.[9,10] The incidence of renal involvement with snakebite envenomation ranges from 1.4 to 28.0%[2,11] and is commonly seen with the family Viperidae.[12–14] The fatality rate reported due to snakebite-induced AKI is around 8.0–39.0%[15–19] and approximately 15.0–55.0% require renal replacement therapy (RRT).[15–18] A landmark study performed by Chugh et al. reports ARF in 5–30% of the victims which usually occur in few hours to as late as 96 hours. Documented pathophysiology behind AKI includes tubular necrosis, cortical necrosis, interstitial nephritis, glomerulonephritis, vasculitis, intravascular hemolysis, rhabdomyolysis, and shock, which all lead to renal ischemia, hence kidney injury.

In consideration to pulmonary involvement after snakebite, literature reports, the clinical involvement as respiratory paralysis, pulmonary edema, hemorrhage, and thrombosis involving pulmonary vasculature.[20] Pulmonary involvement with bleeding and thrombosis has been exclusively seen with viper bites, especially with Bothrops species bites, which is endemic more in Central and South America. In one of the largest case series of RV bites by Kularatne et al. showed that 77% of patients had evidence of coagulopathy; however, the numbers with actual bleeding manifestations were less, and none of them had showed frank pulmonary hemorrhage.[21] However, there are other abundant case reports of RV bites causing bleeding manifestations in other internal organs, but pulmonary hemorrhage is still rarely seen. Hemorrhagic manifestations due to viper bites have been attributed to combined effects of consumptive coagulopathy, platelet dysfunction, and direct action of hemorrhagins (metalloproteinases) in viper venom.[22] Similar etiology can be postulated for our patient as he developed hemorrhage with normal coagulation profile.

Presence of both AKI and diffuse alveolar haemorrhage (DAH) in a single patient has been rarely reported, as to the best of the literature studied. In our patient, the main pathophysiology for renal and pulmonary involvement could be attributed to thrombotic microangiopathy (TMA), as he had intravascular hemolysis evident by anemia, indirect hyperbilirubinemia, and fragmented cells in peripheral blood smear. Rhabdomyolysis further supports the development of AKI. Histological evidence could not be made as renal biopsy was not possible due to critical state and negative consent by family of the patient for the same.

Early intervention when patient develops AKI and pulmonary hemorrhage can result in effective outcome. Case reports are there, where medical management/dialysis support and steroids were used and had mixed results. Fatal outcome due to pulmonary hemorrhages after snakebite has been reported in a case report by Palangasinghe et al., where conventional treatment with antivenom and hemodialysis for ARF was performed.[23] Another report by Srirangan et al. highlights the development pulmonary hemorrhage in a patient with hump-nosed viper bite and it was managed effectively with systemic steroids.[24]

Conservative management with fluids, dialysis, early steroids, and other supportive care was attempted in our patient but then reviewing the case for pulmonary hemorrhage and AKI, role of plasma apheresis was considered. This has previously been supported by clinical studies, where successful application of plasmapheresis has been reported. The documented beneficial effect of plasma exchange is the elimination of venom toxins from blood compartment, redistribution, and elimination of venom toxin from the extravascular space. In addition, mediators of inflammatory and coagulopathic pathway invoked by snake toxins can also be removed and may be life-saving in severely ill patients. The first case of plasma exchange to treat patient with snake envenomization was reported by Kornalik and Vorlova in 1990, where plex was used to treat hemorrhagic diathesis following Bothrops bite.[25]

Similarly, Zengin et al. have shown the early use of therapeutic plasmapheresis for hematological problems and limb preservation post-snakebites.[26] In support, another study performed by Rasulov and Berdymuradov reports the use of plasmapheresis in 24 patients with poisonous snakebites, all of whom recovered and were discharged from the hospital.[27] In all the above-mentioned studies, plex was primarily used for hematological abnormalities. American Society for Apheresis has placed the role of plasmapheresis in envenomation as grade 2C, category 3 (weak recommendation, optimum apheresis therapy not established, decision should be individualized) evidence.[28] The clinical indication and efficacy of plasma exchange in snakebite envenomation is unclear. However, patient's refractory to conventional therapy with anti-snake venom, plasma exchange can be considered.

Further in support to the management of snakebite-induced AKI, apart from RRT, plasmapheresis again has a well-established role. Some published cases of snakebite-associated TMA with AKI have reported successful treatment with plasmapheresis, with normalization of renal function.[29,30]

Use of plasmapheresis for pulmonary hemorrhage due to snakebite has been so far rarely reported and we report this case to be the first of its kind where a good outcome was achieved with aggressive management with plasma exchange.

Despite early antivenomization and aggressive supportive management, our patient had developed late manifestations in the form of sepsis, renal failure, and pulmonary hemorrhage, but with use of plasma exchange, our patient had a good clinical outcome with no residual sequelae and complete renal recovery. Furthermore, in our patient, plasmapheresis was considered primarily for pulmonary hemorrhage where it proved to be effective and also helped in renal recovery. To the best of the studied literature, there has been no case report on use of plasma exchange for pulmonary hemorrhage due to snake envenomization.

Conclusion

Supporting the past evidence and reviewing literature, prompt diagnosis, early antivenomization, early dialysis, and plasmapheresis should be considered in snakebite with systemic envenomization where pulmonary–renal involvement can have high morbidity and mortality. Hence, we can save lives of younger victims, who are commonly involved, due to field work, where the incidence of snakebite is high.

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