CASE REPORT

Kounis Syndrome Following *Hypnale zara* (Hump-Nosed Pit Viper) Bite in Sri Lanka

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A 47-y-old man was bitten by a hump-nosed viper (*Hypnale zara*) and gradually developed retrosternal chest pain associated with ST segment elevation on electrocardiogram. He had normal troponin I levels and no evidence of coagulopathy. Initially, he was managed as having anterior ST elevation myocardial infarction with thrombolysis. Later, because troponin levels were normal, he was suggested to have the type I variant of Kounis syndrome (allergic coronary artery spasm). This was supported by high eosinophil counts in peripheral blood. He was successfully managed with supportive treatment and discharged 6 d after the snakebite. Cardiac complications are rarely reported after hump-nosed viper bites, and clinical reports of coronary vasospasm after snakebites are extremely rare in the literature. This is the first known report of Kounis syndrome after a hump-nosed viper bite.

Keywords: snakebites, coronary vasospasm, electrocardiogram, cardiotoxicity, myocardial infarction

Introduction

Kounis syndrome is hypersensitivity of coronary vessels induced by drugs, snake venom, environmental exposures, foods, and coronary stents. Vasospastic allergic angina, allergic myocardial infarction, and stent thrombosis with occluding thrombus infiltrated by eosinophils are the 3 reported variants of this syndrome.¹ The type I variant includes either coronary artery spasm without increased cardiac enzymes and troponins or coronary artery spasm progressing to acute myocardial infarction with raised cardiac enzymes and troponins. Vasospastic angina is a form of angina pectoris caused by vasospasm of coronary arteries, in which chest pain is accompanied by a transient ST segment elevation on electrocardiogram (ECG).² It is sometimes misdiagnosed as ST elevation myocardial infarction (STEMI), and it is well

known that snake venom causes allergic coronary artery vasospasm.^{3,4}

Hump-nosed vipers are the most common cause of venomous snakebites in Sri Lanka, causing 27 to 77% of all snakebites.⁵ They mostly cause local envenoming only^{6,7} and less frequently cause significant morbidities such as acute kidney injury, chronic kidney disease,⁸ venom-induced consumption coagulopathy,⁹ thrombotic microangiopathy,¹⁰ chronic wounds, and amputations of digits.⁶ The genus *Hypnale* comprises 3 species: *H hypnale*, *H zara*, and *H nepa*. The former is found in both Sri Lanka and Southwestern India, and the latter 2 are endemic to Sri Lanka. Of these 3 species, *H hypnale* is responsible for the most bites (80%) because it is frequently encountered all over the island except in the peninsula of Jaffna in the north. Cardiac complications such as myocardial infarction, atrial fibrillation, ischemic changes of myocardium, and cardiac arrest after *Hypnale* bites are rarely reported,^{11,12} although a fatal case of cardiac arrest and atrial fibrillation after *H hypnale* has been reported.¹² Such manifestations of *H zara* envenoming have not been described. An extensive literature search confirms that there is no previous report of

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Figure 1. Necrosis of left fourth finger (circled) on day 2 after snakebite.

coronary vasospasm caused by hump-nosed viper bites. Therefore, we report the first case of coronary vasospasm after *H zara* bite in Sri Lanka.

Case Report

A 47-y-old previously healthy tea estate worker was bitten by a hump-nosed viper on his left fourth finger at about 1400 while he was working in a tea estate. He lives in an estate situated Udaniella, a remote village in Ratnapura district. He is a nonsmoker and does not consume alcohol. His family history is not significant for heart disease. He was not given any native treatments and was admitted to the hospital at 1545. The snake was identified by the admitting medical officer as a hump-nosed viper.

On admission, he had severe local pain, mild swelling over the finger, and necrosis at the site of bite (**Figure 1**), but there was no local bleeding. His blood pressure was 110/80 mm Hg and his pulse rate was 80 beats·min⁻¹. Respiratory rate was 18 breaths·min⁻¹, and oxygen saturation on room air was 99% detected using pulse oximetry. Examination of the respiratory system, nervous system, and abdomen revealed no abnormality. His 20-min whole blood clotting test (WBCT20) on admission and then at 6-hour intervals for 24 h was negative (<20 min). The other laboratory findings were white blood cells (WBC) $9.8 \times 10^3 \cdot \mu\text{L}^{-1}$, neutrophils $4280 \mu\text{L}^{-1}$ (44% of whole WBC count), eosinophils $3000 \mu\text{L}^{-1}$ (31% of whole WBC count), lymphocytes $2080 \mu\text{L}^{-1}$ (21% of

Figure 2. Electrocardiogram changes 10 h after snakebite: ST segment elevation in chest leads (V₁-V₅).

Figure 3. Progressive changes on electrocardiogram 12 h after snakebite: ST segment elevation in chest leads (V_1 - V_5).

whole WBC count), platelets $280 \times 10^3 \cdot \mu\text{L}^{-1}$, Hb $13.1 \text{ g} \cdot \text{dL}^{-1}$, international normal ratio 1.12, and activated partial thromboplastin time 38/32 sec. The biochemical laboratory findings were normal.

Around 10 h after the snakebite, the patient reported central retrosternal, nonradiating chest pain, and ECG showed ST segment elevation on V_1 - V_5 (Figure 2). Repeat ECG of 1 h also had progressive changes (Figure 3). At this time, his blood pressure was 100 mmHg and pulse rate was $50 \text{ beats} \cdot \text{min}^{-1}$. The patient was transferred to the coronary care unit for further management, and thrombolysis was done using tenecteplase. Subcutaneous enoxaparin 50 mg twice daily, aspirin 75 mg, clopidogrel 75 mg, and atorvastatin 40 mg were started with cardiac monitoring. The troponin I level (6 h after the onset of chest pain) was $0.012 \text{ ng} \cdot \text{mL}^{-1}$ (normal <0.034). The 2D-echocardiogram showed anterior and apical wall hypokinesia with preserved left ventricular muscle mass with an ejection fraction of 50%. There was no apical ballooning. Because his repeat

troponin I level was $0.01 \text{ ng} \cdot \text{mL}^{-1}$ (24 h after the first), enoxaparin, aspirin, and clopidogrel were omitted, and the atorvastatin dose was reduced to 20 mg.

During the hospital stay, the patient's urine output was normal and wound debridement was done for the finger (site of bite). He was discharged on hospital day 6 on atorvastatin with arrangements for clinic follow-up. His follow-up ECG (done on day 20 after snakebite) was normal (Figure 4). His fasting blood sugar and lipid profile (done 1 mo after snakebite) were normal. Three months after the snakebite, his exercise ECG was also normal (Figure 5). According to the standard key, the hump-nosed viper was identified as *H zara* (Figure 6).

Discussion

Deficient basal release of nitric oxide due to endothelial dysfunction and enhanced vascular smooth muscle contractility with the involvement of the Rho/Rho-kinase

Figure 4. Normal electrocardiogram 20 d after snakebite.

pathway play important roles in the pathogenesis of coronary artery spasm.¹³ In Kounis syndrome, however, coronary vasospasm is caused by inflammatory mediators such as histamine, chymase, and tryptase released from mast cells as the allergic response. Although we had no facilities to test serum histamine or tryptase levels, evidence points to the coronary vasospasm of our patient as being due to an allergic reaction to snake venom because he had elevated eosinophil counts in peripheral blood ($3000 \mu\text{L}^{-1}$, normal range $20\text{--}500 \mu\text{L}^{-1}$).

In ECG, the ST segment represents the interval between depolarization and repolarization of the ventricles. ST elevation is significant when it is found on 2 contiguous leads in a 12-lead ECG. However, about 93% of healthy young men have ST elevation of 1 to 3 mm in 1 or more precordial leads, mostly in V_2 , and the ST segment is concave.¹⁴ Despite its high sensitivity, ST segment deviation has poor specificity because, in addition to myocardial infarction, there are other cardiac and noncardiac causes for ST elevation. The cardiac causes are early repolarization, left ventricular hypertrophy, hypertrophic cardiomyopathy, left bundle branch block, pericarditis, myocarditis, aortic dissection, Takotsubo cardiomyopathy, Brugada syndrome,

and vasospastic angina. The noncardiac causes are hyperkalaemia, pulmonary thromboembolism, pneumothorax, acute pancreatitis, acute cholecystitis, hemorrhagic cerebrovascular disease, and drug-induced ST elevation.¹⁵ Snake venom is a good source of vasoactive substances, and envenomation can enhance the activity of vasoactive mediators.¹⁶ This may cause coronary artery spasms resulting in ST elevation on ECG. Eosinophilic coronary periarteritis, which typically presents as vasospastic angina, is a rare localized vasculitis and is almost always associated with sudden cardiac death. Diagnosis is almost exclusively found at autopsy.¹⁷ Acute allergic myocarditis is another possibility, but it has fatal outcomes.

H zara is recorded in lowland rainforests of Sri Lanka and therefore is called the lowland hump-nosed viper. Among systemic effects, acute kidney injury, coagulopathy, microangiopathic haemolysis, and thrombocytopenia have previously been reported after *H zara* bites.^{7,18–20} Its venom is complex and causes thrombotic microangiopathy²⁰ or even death.¹⁸ In Sri Lanka, cardiotoxicity is mainly observed in Russell's viper (*Daboia russelii*) bites, which have fatal outcomes²¹; such effects with *Hypnale* bites are very rare. However, by using troponin T and ECGs, 1

Figure 5. Normal exercise electrocardiogram done 3 mo after the snakebite.

study concluded that myocardial damage does not seem to be an important feature of hump-nosed and Russell's viper bites.²²

One of the main investigations needed in the management of this patient is the coronary angiogram, but there are no facilities in our center for angiography or percutaneous

coronary interventions. In our patient, the initial working diagnosis was anterior STEMI; therefore, immediately thrombolysis was done. However, ST elevation was not corrected and continued for more than 12 h with normal troponin I levels. With actual thrombosis of coronary vessels, troponin should be elevated owing to reduced blood

Figure 6. Species of hump-nosed viper responsible for the bite: *Hypnale zara*—a male snake whose total length is 342 mm, head length 15 mm, tail length 56 mm, and snout to vent length 288 mm, ventrals 146, subcaudals 45, and mid dorsal rows 15, from Ratnapura, Sri Lanka (06°40'N 80°24'E, elevation 130 m [430 ft]). (A) Dorsolateral view. (B) Ventral view. Note that thin black arrows indicate large 5 head scales (characteristic feature of hump-nosed vipers), the thick black arrow indicates color bands on the neck of *H zara* (characteristic feature of *H zara*), the thin white arrow indicates the loreal pit (characteristic feature of pit vipers), and the thick white arrow indicates the prominent raised hump (characteristic feature of *H zara*).

supply to cardiac muscle, or ST elevation might be corrected when tenecteplase is administered. Therefore, the possibility of vasospastic angina was suggested later, and thrombolytic agents were omitted. It was difficult to differentiate vasospastic angina from STEMI until the troponin I levels were available; therefore, thrombolysis was performed immediately after reviewing the ECG and treating the patient for STEMI prior to receiving other laboratory results. Thus, thrombolysis was done unnecessarily for this patient because snake venom may cause both vasospastic angina and myocardial infarction, both of which result from transmural ischemia of the heart muscle. However, almost 11% of patients with suspected acute coronary syndrome receive unnecessary thrombolytic therapy.²³

The management of this patient was further complicated because there is no antivenom currently available in Sri Lanka for hump-nosed viper bites. However, our patient is a previously healthy nonsmoker or nonalcoholic and has no family history of heart disease. His body mass index was in the normal range (23.1 kg·m⁻²). The fasting blood sugar and lipid profile were also normal. Considering all of the available circumstantial evidence, it can be concluded that he had no risk factors for heart disease. *Hypnale* venom is procoagulant, which is hypothesized as being due to thrombin-like enzymes,²⁴ and may cause thrombosis of coronary vessels resulting in acute myocardial infarction.^{11,12} In the absence of elevation of troponin levels, however, this can be excluded, and we have to think of nonischemic cardiac causes for ST elevations for which the best explanation is snake venom causing coronary vasospasms. Normal exercise ECG conveys that the patient has no mismatch between myocardial oxygen delivery by coronary blood flow and myocardial oxygen demand.

This case highlights the complex nature of *Hypnale* envenoming that may rarely include Kounis syndrome and emphasizes the need for the production of specific antivenom for *Hypnale* spp.

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