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Senthilkumaran, Subramanian, Miller, Stephen W., Williams, Harry F., Savania, Ravi, Thirumalaikolundusubramanian, Ponniah, Patel, Ketan and Vaiyapuri, Sakthivel ORCID logo ORCID: <https://orcid.org/0000-0002-6006-6517> (2022) Development of Wunderlich Syndrome following a Russell's viper bite. *Toxicon*, 215. pp. 11-16. ISSN 0041-0101 doi: <https://doi.org/10.1016/j.toxicon.2022.06.004> Available at <https://centaur.reading.ac.uk/105532/>

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To link to this article DOI: <http://dx.doi.org/10.1016/j.toxicon.2022.06.004>

Publisher: Elsevier

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Development of Wunderlich Syndrome following a Russell's viper bite

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Abstract

Snakebite envenomation is a high priority neglected tropical disease that predominantly affects rural communities living in developing countries. Due to myriad of complications including coagulopathies, neurotoxicity, nephrotoxicity and local tissue destruction, treating snakebite victims is a major challenge for clinicians. Russell's viper (*Daboia russelii*) is one of the 'Big Four' venomous snakes in India, and it is responsible for the most snakebite-induced deaths and disabilities. Acute kidney injury occurs frequently following Russell's viper bites and it is a critical factor contributing to disabilities, deaths and excessive treatment costs. In addition to commonly observed envenomation effects, Russell's viper bites induce some rare complications such as priapism, sialolithiasis and splenic rupture. Here, we report a case of Wunderlich syndrome that developed in a 22-year-old male following a Russell's viper bite. The patient displayed severe coagulopathies, abdominal tenderness, and hypotension. Notably, a peri-nephric haematoma was identified through ultrasound and computerised tomographic imaging. The haemorrhage was successfully treated using angioembolisation, and the patient recovered without any difficulties. Although a clinical condition such as this is rare, it is important to create awareness among treating clinicians about its occurrence, diagnosis and clinical management.

Key words: Snakebite envenomation; Wunderlich syndrome; Russell's viper; per-nephric haematoma; acute kidney injury.

1. Introduction

Snakebite envenomation (SBE) results in as many as 150,000 deaths and around 500,000 permanent disabilities annually worldwide [1, 2]. In India alone, around 58,000 deaths occur every year due to SBE [3]. Russell's viper is one of the 'Big Four' venomous snakes in India and is responsible for the majority of SBE incidents and associated deaths, disabilities and socioeconomic ramifications in India [4-6]. The bites from Russell's viper are known to induce local inflammation, tissue damage, coagulopathies often resulting in haemorrhage, neurotoxicity and nephrotoxicity [7-9]. Notably, the development of acute kidney injury (AKI) following Russell's viper bites is common and it often necessitates expensive renal replacement therapy [10, 11]. Russell's viper bites are also known to induce several rare envenomation effects such as priapism [12], splenic rupture due to excessive haemorrhage [13] and sialolithiasis (development of calculi in salivary glands) [14] among others. Hence, it is important to promptly diagnose and treat such rare complications as they could lead to serious consequences. Wunderlich syndrome (WS) is a rare clinical complication that represents a peri-nephric or peri-renal haemorrhage that spontaneously (non-traumatic) develops in the renal subcapsular space. The typical clinical symptoms of WS include sudden onset of flank pain, palpable flank mass,

47 and hypovolemic shock [15]. Failure to diagnose and promptly treat WS may result in serious morbidities
48 or death [16]. The most common non-traumatic causes of WS include benign and malignant tumours,
49 vasculopathy and infections [17]. To the best of our knowledge only one case of spontaneous peri-
50 nephric haematoma following SBE has been reported previously [18]. We report a case of WS that
51 developed in a 22-year-old male following a Russell's viper (*Daboia russelii*) bite in South India. This
52 patient was successfully treated with angioembolisation without any further complications. This case
53 report will inform clinicians that WS after SBE (specifically Russell's viper) is a possibility and aid in
54 successful diagnosis and clinical management.

55 2. Case Report

56 A 22-year-old male was bitten by a snake on his right ankle while working on a farm. The snake
57 was immediately killed, and it was identified as a Russell's viper by a herpetologist (**Figure 1A**). The
58 patient was taken to a local hospital within 30 minutes of the bite, and he displayed severe local pain,
59 swelling and gum bleeding. His 20-minute whole blood clotting time (WBCT) was prolonged. Due to the
60 unavailability of antivenom in the hospital, he was transferred to another local hospital within two hours
61 (from the bite) where he was administered with 80 mL polyvalent antivenom produced against the 'Big
62 Four' snakes [Russell's viper, cobra (*Naja naja*), krait (*Bungarus caeruleus*) and saw-scaled viper (*Echis
63 carinatus*)] of India (Bharat Serums and Vaccines, India). His complications were managed
64 conservatively in the second hospital, however, he still displayed prolonged WBCT, developed
65 haematuria and sub-conjunctival haemorrhage (**Figure 1B**). Therefore, he received another 200 mL of
66 antivenom over the next 36 hours. On the third day of admission (72 hours following the bite), he
67 developed diffuse, severe abdominal pain, as well as nausea and vomiting. He was initially managed
68 conservatively (using anti-emetic drugs and fluids) for around four hours. However, later he became
69 hypotensive with decreased urine output. Hence, he was transferred to the Emergency Department for
70 intensive care management approximately 80 hours following the bite.

71 There was no history of any trauma or significant medical, surgical or familial factors of any
72 health conditions for the patient. Upon examination, he was conscious but in severe pain around the
73 bite site and abdominal region. He was pale with cold and sweaty extremities. His blood pressure was
74 70/40 mm Hg, and the pulse rate was 116 beats/min. Abdominal examination revealed fullness in the
75 right lumbar and iliac regions with severe tenderness and guarding. The baseline laboratory
76 investigations upon admission showed a haemoglobin level of 6.5 g/dL, total leukocyte count of
77 22,000/ μ L, platelet count of 120,000/ μ L, blood urea of 64 mg/dL, and creatinine of 1.4 mg/dL (**Table 1**).
78 His coagulation profile was significantly altered with a prolonged prothrombin time (PT), activated partial
79 thromboplastin time (aPTT) and increased international normalised ratio (INR) of clotting. Additionally,
80 the fibrin degradation products and D-dimer (14.68 mg/dL) levels were elevated while the fibrinogen
81 level was decreased (101.4 gm/dL) (**Table 1**). The levels of all the electrolytes such as sodium,
82 potassium, chloride and bicarbonate were normal. However, serum creatinine kinase level was
83 increased to 216 U/L (normal: 24 - 195). His liver function tests revealed increased bilirubin (direct,
84 indirect and total) and serum glutamic oxaloacetic transaminase (SGOT) levels although all the other
85 parameters were normal. The possibility of macroangiopathic haemolytic anaemia (MAHA) was ruled
86 out using peripheral smear of blood which appears to be normal. Similarly, thrombotic microangiopathy
87 was not found in this patient. Haemoglobinuria and myoglobinuria were also absent. His abdominal
88 ultrasound imaging revealed a hypo-echoic collection around the upper pole of the right kidney indicating
89 a haematoma (**Figure 1C**). A renal doppler analysis was conducted to rule out any arteriovenous fistulae
90 as a cause for blood collection. A non-contrast computerised tomographic (CT) scan of the abdomen
91 revealed a large peri-nephric hyper-dense collection in the right kidney extending into the
92 retroperitoneum [45-50 Hounsfield units (HU)] (**Figure 1D and 1E**). The urology experts were consulted,
93 and they advised conservative management with close observation since the patient displayed signs of
94 venom-induced consumption coagulopathy. He was resuscitated according to the standard protocols
95 and transfused with four units of packed red cells and four units of fresh frozen plasma. Twelve hours
96 later (92 hours after bite), he experienced constant, dull pain in the right flank with tachycardia,
97 hypotension and oliguria. His haemoglobin level was decreased from 9.0 g/dL after transfusion of red
98 cells to 7.5 g/dL with an international normalised ratio (INR) of clotting value of 1.6 and platelet count of

99 110,000/ μ L and creatinine level of 2.1 mg/dL (**Table 2**). Haemoglobinuria and myoglobinuria were
100 absent.

101 Despite all the above management approaches, the patient's condition continued to deteriorate,
102 and repeat CT imaging revealed that the peri-nephric haematoma had expanded, and bleeding had
103 extended into the retroperitoneal cavity. Following careful review of the patient's status and available
104 imaging, a decision was made to perform an emergency selective coil angioembolisation of a
105 haemorrhagic branch of the inferior pole renal artery (**Figure 1F**). The procedure was performed via the
106 right femoral artery with particles of 500-700 microns and fibered micro-coils to effectively control
107 haemorrhage while preserving nephrons. Upon completion of the procedure, an angiogram confirmed
108 complete occlusion of the embolised arteries. The patient's haemodynamic status and haemoglobin
109 levels were subsequently improved.

110 The unremarkable results of the anti-neutrophil cytoplasmic antibody, perinuclear anti-neutrophil
111 cytoplasmic antibody, erythrocyte sedimentation rate, C-reactive protein, anti-DNA antibody, extractable
112 nuclear antigen (ENA) panel screening, anti-phospholipid antibodies, anti-nuclear antibody and
113 rheumatoid factor tests excluded the possibility of any non-snakebite related causes of WS. He was
114 discharged 10 days after admission to our hospital. Weekly follow up ultrasound scans revealed
115 stabilisation in size of the haematoma, however, by the third week the lesion began to contract. Follow
116 up ultrasound scan three months later revealed complete resolution of the haematoma with a normal-
117 sized right kidney and no evidence of malignancies.

118 **3. Discussion**

119 WS is a life-threatening condition and most often it occurs due to benign or malignant neoplasms,
120 and vasculopathy in renal tissues. It is characterised by acute development of spontaneous renal
121 haemorrhage into the subcapsular and perirenal spaces [15]. Angiomyolipoma and renal cell carcinoma
122 are common causes as well as vascular diseases such as polyarteritis nodosa, infections and other less
123 common aetiologies [17]. In these conditions, compromised blood vessels may spontaneously rupture
124 and bleed into the peri-nephric, subcapsular space [19]. Lenk's triad, described as acute flank or
125 abdominal pain, palpable abdominal mass and hypovolemic shock is present in around a quarter of
126 patients with WS [15, 20]. The diagnosis of WS is normally based on clinical presentation and the use
127 of imaging tools to detect the presence of haematoma. Ultrasound scan may be the initial modality
128 utilised to detect the lesion, however, CT and magnetic resonance imaging (MRI) are typically very
129 sensitive in the diagnosis of haematoma [21]. The treatment of WS depends on the size and severity of
130 the lesion. Conservative management including observation may be recommended for uncomplicated,
131 small lesions. Larger haematomas and those with higher risk of haemorrhage are medical emergencies
132 and they may be treated with embolisation or surgical management with either full or partial nephrectomy
133 [22].

134 The development of AKI after SBE with corresponding elevations in creatinine and blood urea
135 nitrogen (BUN) is commonly reported in the literature, although peri-nephric haematoma following SBE
136 is a rare phenomenon [23, 24]. As stated above, WS presents with sudden spontaneous renal
137 haemorrhage into the subcapsular and perirenal space with flank pain and hypovolemic shock due to
138 non-traumatic causes [15], features that are not commonly found in SBE victims. A previous report
139 described that a 34-year-old male patient bitten by a Russell's viper developed AKI and subsequently,
140 a peri-renal haematoma [18]. This patient was bitten on the foot and developed oliguria, hypotension
141 and multiple coagulopathies. On the eighth day of hospitalisation, the patient developed abdominal
142 tenderness, hypotension and a peri-renal haematoma was discovered using ultrasound scan. Despite
143 intensive resuscitative therapy which included transfusion of platelets and fresh frozen plasma, the
144 patient died 10 days after the bite. An observational study of AKI caused by SBE conducted in Benin
145 reported that 6% of the cases developed renal capsular haematomas [25]. A study that reviewed 92
146 cases of WS in Tamil Nadu, India from 2016 through 2018 did not find SBE as a potential aetiology for
147 WS [21].

148 In the present case, none of the common aetiologies for WS were discovered. It is likely that this
149 complication was developed directly or indirectly through the toxic effects of the Russell's viper venom.
150 The venom of Russell's viper is known to contain many toxic components that can alter haemostasis
151 and cause bleeding and/or clotting complications. Snake venom metalloproteases (SVMP), the most
152 abundant toxin family in their venom, possess fibrinogenolytic as well as other coagulopathic effects
153 [26]. Factor X activator (RVV-X) from Russell's viper venom is a well-known SVMP that activates factor
154 X, in turn cleaving factor II (prothrombin) to yield the active form of thrombin in coagulation cascades
155 [27]. Some SVMPs can also activate prothrombin and inhibit platelet function. SVMPs also degrade
156 basement membrane components in blood vessels leading to endothelial dysfunction and haemorrhage
157 [28]. The cleavage and release of native proteins and fragments from the extracellular matrix may lead
158 to increased vascular permeability, stimulation of the functions of matrix metalloproteases, and serve to
159 amplify the immune response to the initial damage [28, 29]. Damage associated molecular patterns
160 (DAMPS) contribute to further inflammation in the affected areas. Snake venom serine proteases
161 (SVSP) are present in many viper venoms, and indeed, a factor V activator (RVV-V) [30] and a thrombin-
162 like serine protease (Russelobin) have been isolated from Russell's viper venom [31]. Some SVSPs
163 may activate protein C which ultimately inactivates factor Va and factor VIIIa. This promotes negative
164 feedback regulation of the coagulation cascades, which will ultimately lead to bleeding complications
165 [32]. Together with enzymatic and non-enzymatic mechanisms, venom phospholipase A₂ (PLA₂) may
166 inhibit the production of activated factor X by interfering with the tenase complex [33]. Clinically
167 significant bleeding is commonly observed in victims following Russell's viper bites [34]. We have also
168 previously reported excessive bleeding and subsequent splenic rupture in a Russell's viper bite victim
169 [13]. Due to his age and healthy conditions, the rupture of pre-existing renal artery aneurysm may not
170 be a cause for WS although we cannot completely rule out this possibility. Such rare and abnormal
171 condition was not apparent in angiogram.

172 While the exact pathophysiological mechanisms underlying the development of WS in this case
173 are unknown, there are several possibilities that may explain why this patient has developed the peri-
174 nephric haematoma. The kidneys are highly vascular organs, and they receive approximately 1L of
175 blood flow per minute which equates to 20% of resting cardiac output. The kidneys are thus exposed to
176 a high circulating volume of venom toxins as they travel throughout the vasculature. One possibility is
177 that these toxins may have caused sufficient vascular damage which resulted in haemorrhaging in this
178 region of the kidney and resulted in the development of peri-nephric haematoma. Another possibility is
179 that the area of the renal polar artery which developed the haematoma may have had a previously
180 undetected defect which predisposed the vessel to further injury upon subsequent exposure to venom
181 toxins. Although this patient did have laboratory evidence of AKI, it remains unclear if SBE-induced AKI
182 increases the risk of WS as so few cases exist. Similarly to the previous case report [18], this patient
183 also presented with signs and symptoms of systemic coagulopathy such as gingival and sub-
184 conjunctival bleeding and AKI. Although AKI with tubular necrosis and interstitial nephritis have been
185 reported following SBE in the past, peri-nephric haematoma or WS is rarely encountered [35].
186 Physicians treating SBE should be aware that any patient that presents with flank pain, even if the
187 symptoms are delayed by multiple days following SBE, may require additional diagnostic investigations
188 for this potentially life-threatening complication.

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304
 305
 306

307 **5. Tables**

308 **Table 1: Laboratory results for the patient at the time of admission in the emergency department.**

309

Specimen	Investigation	Results	Unit	Normal range
	Haemoglobin	6.5	gms%	13.0 – 16.0
	Total RBC count	4.53	Millions/ μ L	4.00 – 5.00
	HCT	38.9	%	41.00 – 50.00
	MCV	85.9	fl	81.10 – 96.00
	MCH	29.1	pg	27.20 – 33.20
	MCHC	33.9	%	32 - 36
	Total WBC count	22.0	$\times 10^3$ Cells/ μ L	4.00 – 11.00
	Neutrophils	18.89	$\times 10^3$ Cells/ μ L	2.0 to 7.0
	Lymphocytes	3.01	$\times 10^3$ Cells/ μ L	1.0 to 3.0
	Monocytes	1.56	$\times 10^3$ Cells/ μ L	0.1 to 0.8
	Eosinophils	0.32	$\times 10^3$ Cells/ μ L	0.02 to 0.5
	Basophils	0.04	$\times 10^3$ Cells/ μ L	0.02 to 0.1
	Neutrophils	64.3	%	55 – 75
	Lymphocytes	21.8	%	15 – 30
	Eosinophils	2.3	%	1 - 5
	Monocytes	11.3	%	2 - 10
	Basophils	0.3	%	Up to 1
	Platelet Count	120	$\times 10^3$ Cells/ μ L	150 - 450
	MPV	9.8	fl	6.5 - 12.0
	PDW	10.5	fl	9.0 - 13.0
	Urea	64.0	mg/dL	15 - 40
	Creatinine	1.4	mg/dL	0.6 - 1.2

	Uric Acid	7.5	mg/dL	3.4 - 7.2
Serum	Uric acid	8.9	mg/dL	3.4 - 7.2
Citrated plasma	Fibrinogen	101.4	gm/dL	150 - 400
Citrated plasma	D-Dimer	14.68	mg/dL	0 - 5
Serum	LDH	653	U/L	230 – 480
Citrated plasma	Prothrombin time	44.12	Seconds	11.6 (control)
Citrated plasma	INR	3.45	Ratio	
Citrated plasma	APTT	Prolonged	Seconds	26 - 40
Serum	Creatinine kinase	216	U/L	24 – 195
Serum	Bilirubin (total)	3.7	mg/dL	0.2 – 1.2
Serum	Bilirubin (direct)	0.85	mg/dL	0 – 0.2
Serum	Bilirubin (indirect)	2.85	mg/dL	0.2 – 0.9
Serum	SGOT	55	U/L	5 - 35

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RBC, red blood cells; HCT, haematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; WBC, white blood cells; MPV, mean platelet volume; PDW, platelet distribution width; LDH, lactate dehydrogenase; INR, International normalised ratio of clotting; APTT, activated partial thromboplastin time; SGOT, serum glutamic oxaloacetic transaminase.

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Table 2: Laboratory results for the patient after 12 hours of admission in the emergency department.

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Specimen	Investigation	Results	Unit	Normal range
	Haemoglobin	7.5	gms%	13.0 – 16.0
	Total RBC count	4.73	Millions/ μ L	4.00 – 5.00
	HCT	39.2	%	41.00 – 50.00
	MCV	82.9	fl	81.10 – 96.00
	MCH	29.8	pg	27.20 – 33.20
	MCHC	36.0	%	32 - 36
	Total WBC count	12.0	$\times 10^3$ Cells/ μ L	4.00 – 11.00
	Neutrophils	7.6	$\times 10^3$ Cells/ μ L	2.0 to 7.0
	Lymphocytes	4.01	$\times 10^3$ Cells/ μ L	1.0 to 3.0

	Monocytes	0.28	x10 ³ Cells/ μ L	0.1 to 0.8
	Eosinophils	0.02	x10 ³ Cells/ μ L	0.02 to 0.5
	Basophils	0.01	x10 ³ Cells/ μ L	0.02 to 0.1
	Neutrophils	46.8	%	55 – 75
	Lymphocytes	41.1	%	15 – 30
	Eosinophils	0.8	%	1 - 5
	Monocytes	10.9	%	2 - 10
	Basophils	0.4	%	Up to 1
	Platelet Count	110	x10 ³ Cells/ μ L	150 - 450
	MPV	10.2	fl	6.5 - 12.0
	PDW	10.2	fl	9.0 - 13.0
	Creatinine	2.1	mg/dL	0.6 - 1.2

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RBC, red blood cells; HCT, haematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; WBC, white blood cells; MPV, mean platelet volume; PDW, platelet distribution width.

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326 6. Figure legend

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Figure 1: Development of conjunctival bleeding and peri-nephric haematoma in a patient following a Russell's viper bite. **A)** the offending snake which was identified as a Russell's viper. **B)** the victim showing conjunctival bleeding on their left eye. **C)** an ultrasound scan image of the right kidney of this patient shows a haematoma. CT images reveal a large haematoma (**D** - a large CT section showing both the kidneys) including a mass of peri-nephric hyperdense collection (**E** - specific CT section to show the haematoma with a hyperdense collection around the right kidney) around the right kidney. Abbreviations shown in figures D and E: RK - right kidney; H - haematoma; HD - hyper dense area of haematoma/collection; LK - left kidney; IV - inferior vena cava; A - aorta; LI - large intestine; LS - lumbar spine; SP - spinous process; PM - psoas muscle. 'R' at the top of the CT images indicates the right orientation of the body. **F)** an angiogram showing the occlusion of arteries following selective coil angioembolisation.

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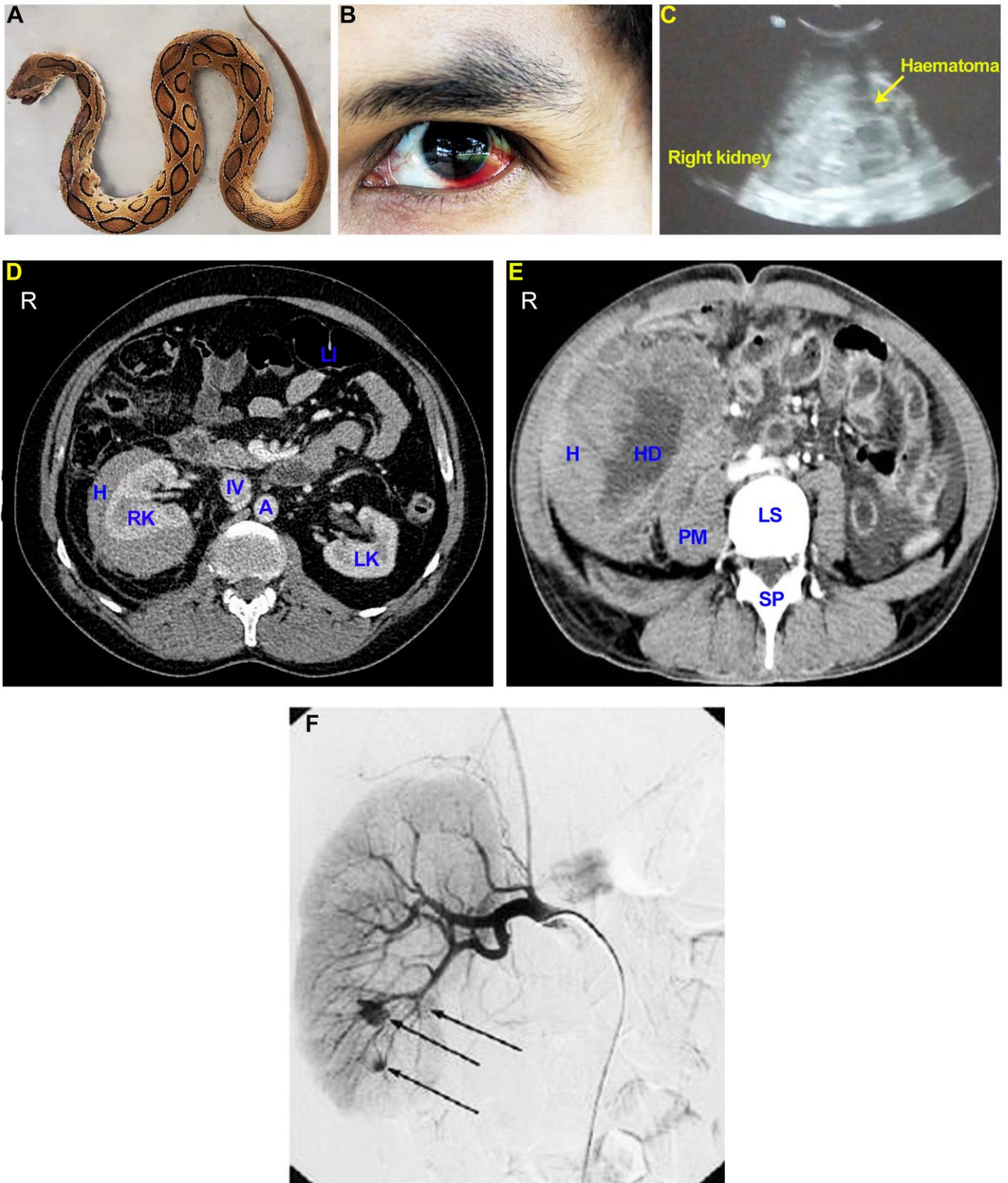
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346 7. Figure

347 Figure 1



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