An unexpected turn of events: A rare case of Acquired Haemophilia A after a violin spider bite

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Abstract

We report an interesting clinical case of Acquired Haemophilia A (AHA) after a probable *Loxosceles rufescens* spider bite in a 73-year-old woman, admitted to an Emergency Department (ED) of Central Italy during April 2019. AHA is a rare disease, whose acute clinical manifestations are not widely known by most ED physicians; its prompt recognition and treatment are crucial to avoid fatal bleeding. In particular, the development of AHA after a violin spider bite (another rare and poorly characterized clinical condition) has never been described. Therefore, our case report could provide useful insight into the understanding and treatment of such unusual and possibly life-threatening conditions.

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Introduction

Loxosceles spp. spider poisoning is rare in Europe, although bites from *L. rufescens*[1] have been increasingly reported from countries around the Mediterrean basin.[2] The marked synanthropy of this species and its tendency to hide in shoes or clothes left out on the floor or stored in closets, rooftops or garages make its bite a frequent report when the spider is accidentally pressed against the skin while dressing or sleeping.[3] *L. rufescens* bites may lead to a localized reaction (cutaneous loxoscelism) and, less commonly, to systemic symptoms (systemic loxoscelism).[1]

Acquired Haemophilia A (AHA) is a rare, potentially lethal bleeding disease, characterized by the development of neutralizing autoantibodies against of factor VIII (FVIII), resulting in an isolated prolonged aPTT.[4–7] Half the cases (around 50%) are idiopathic, while the remaining 50% are associated with other systemic disorders (cancer, autoimmune diseases, pregnancy and other conditions).[5,6,8,9] The bleeding phenotype of AHA is variable, ranging from life-threatening bleeds to mild mucocutaneous/muscular bleeding or no bleeding.[5,6,8,9]

Literature for both systemic and cutaneous diseases is scarce and to our knowledge no case of AHA developed after *L. rufescens* bite has been reported.

Case Report

A 73-year-old woman was admitted to our Emergency Department (ED) in April 2019 with a 12-hour history of localized bruising and swelling on the dorsal side of the left hand. She was not taking antiplatelet or anticoagulant medicines and she denied any recent trauma, travel, new medication or recent fever. The day before admission, she took azithromycin (500 mg) as antibiotic prophylaxis before a dental intervention. The patient reported previous administration of azithromycin without significant adverse events. The month before the ED admission, she had physio-kinesitherapy for rheumatic polymyalgia. In addition, she had a history of hypertension currently treated with losartan 25 mg. She denied any known allergies to medications.

On clinical examination the patient was in good conditions, vital signs were stable and within normal limits (blood pressure

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130/80 mmHg, heart rate 80 beats/min, respiratory rate 14 breaths/min and body temperature 36°C). She presented with an extensive and mildly painful hematoma on the dorsal left hand and forearm; peripheral pulse was present, and no other signs or symptoms were revealed.

A Complete Blood Count (CBC) and Comprehensive Metabolic Panel (CMP) were prescribed. The initial White Blood Count (WBC) count was 10.59 ×10³ cells/μL (n.r. 4.0-11.0×10³ cells/μL), Hb 12.4 g/dL (n.r. 11.5-16 g/dL), platelet count 225×10³ cells/μL (n.r. 140-450×10³ cells/μL), aPTT 44.5 sec (n.r. 25.1-36.5 sec), glucose 153 mg/dL (n.r. 74-109 mg/dL); other results were normal (Table 1). Angio-Computed Tomography (Angio-CT) of her left arm and orthopaedic consult were requested; paracetamol and tramadol with metoclopramide were administered to treat pain. Angio-CT did not detect any arterial or venous active bleeding, but it revealed oedema and bleeding in the sub-cutaneous tissues her left forearm. The orthopaedic consultant recommended a 24-hour observation, the repetition of blood tests the next day and suggested to maintain elevation of the left arm. On later examination that day, the patient developed agitation and confusion; body temperature was 37.5°C and she complained of nausea, vomiting and worsening pain of the left arm. Amoxicillin/clavulanic acid, indomethacin and metoclopramide were administered, and the patient was transferred to our Emergency Medicine Unit.

The next day, the hematoma was increasing in size (Figure 1), and the pain worsened; the left radial pulse was still palpable, but she developed paraesthesia of the first three fingers of the left hand. Blood tests were repeated with the following results: WBC counts 9.8×10³ cells/μL, Hb 12.4 g/dL, platelet count 212×10³ cells/μL, aPTT 44.5 sec, other results including Creatine Kinase (CK) levels and myoglobin were within the normal limits.

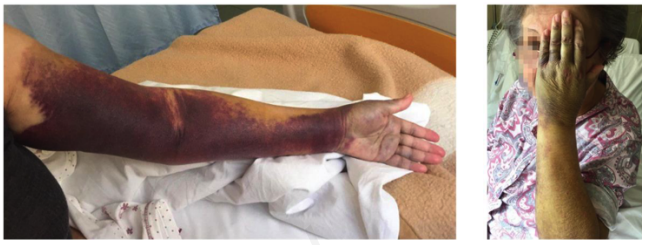

Figure 1. Hematoma of the left arm, respectively at day 3 and at discharge.

Table 1. Patient's complete blood count and comprehensive metabolic panel at admission and during the recovery.

	Reference Range	Day 1	Day 2	Day 3	Day 11
Hb (g/dL)	11.5 – 16.0	12.4	11.2	9.1	9.9
Hematocrit (%)	37.0 – 47.0	35.8	31.8	25.4	30.1
White-cell count (per mm³)	4.0 – 11.0	10.59	14.46	9.97	6.07
Neutrophils (per mm³)	1.8 – 7.0	7.67	10.5	9.68	3.37
Lymphocytes (per mm³)	0.9 – 4.5	1.99	2.88	0.2	1.72
Monocytes (per mm³)	0.1 – 1.2	0.86	1.03	0.08	0.84
Eosinophils (per mm³)	< 0.7	0.06	0.03	0.01	0.13
Basophils (per mm³)	< 0.2	0.01	0.02	0	0.01
Platelet count (per mm³)	140 - 450	225	277	138	212
Sodium (mEq/L)	135 - 145	140	141	138	144
Potassium (mEq/L)	3.5 – 5.1	3.95	3.56	2.61	4.55
Creatinine (mg/dL)	0.50 – 0.90	0.66	0.63	0.7	0.63
Lactate dehydrogenase, LDH (U/L)	135 - 214	-	210	264	257
Creatinine kinase, CK (U/L)	< 170	-	83	529	33
Myoglobin (μg/L)	25 - 58	-	44	149	< 21
C-reactive protein, CRP (mg/dL)	< 0.5	-	4.43	11.21	1.05
Procalcitonin (ng/mL)	< 0.5	-	0.09	8.68	0.27
Prothrombin (%)	80 – 130	88	87	89	97
I.N.R.	0.87 – 1.12	1.09	1.09	1.08	1.02
aPTT (sec.)	25.1 – 36.5	44.5	51	36.7	58.3
aPTT ratio	0.84 – 1.22	1.55	1.78	1.28	1.91
Ddimer (mg/L)	< 0.3	-	0.37	-	-
Fibrinogen (mg/dL)	200 – 400	-	493	-	357
Antithrombin (%)	83-128	-	83	-	-
*LAC	Absent	-	-	-	Neg
*aPTT Mix	-	-	-	-	31
aPTT Mix T+2	-				54.3
Anti-fVIII Ab (UB/mL)	Absent	-	-	-	9.0
*vWF:RiCof%	50 - 150	-	-	-	120
fVIII (%)	60 - 150	-	-	-	6.7

*(Lupus anticoagulant panel, LAC; Mixing test: aPTT incubated Mix, aPTT Mix; activity of the ristocetin cofactor – von Willebrand factor, vWF:RiCof%).

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Suspecting a compartmental syndrome, a second orthopaedic consult was requested: in the absence of indication for surgical treatment, the consultant advised for watchful observation and repeat blood testing. On later examination that day, the patient's clinical status worsened and a large hematoma of the neck appeared. CBC and CMP were repeated: WBC counts was 14.46×10³ cells/µL, Hb 11.2 g/dL, platelet count 277×10³ cells/µL, aPTT 51 sec, CRP 4.43 mg/dL (n.v.<0.50 mg/dL), procalcitonin 0.09 ng/mL (n.v.<0.50 ng/mL) and ISTH Disseminated Intravascular Coagulation (DIC) Score[10] was calculated and ruled out DIC (see Table 1). While further questioning the relatives for additional information, a new anamnestic clue was revealed: the patient's husband stated that the day before admission to our ED, the patient had removed an arachnid from her arm while doing household chores. Based on this finding, a violin spider bite was suspected. Blood cultures were drawn and resulted negative, a laryngoscopy was negative for internal bleeding; therefore, linezolid and piperacillin/tazobactam along with 1 IU of Fresh Frozen Plasma (FFP) were administered.

On the third day of admission the patient's daughter found a live spider in the patient's house and brought the specimen for proper identification. The emergency physician identified a spider of genus *Loxosceles*, with three pairs of eyes and a darker violin mark on the cephalothorax. Unfortunately, an entomologist was not available at our hospital to confirm the ED physician's suspect. On the same day blood tests were repeated: WBC counts was 9.97 ×10³ cells/µL, Hb 9.1 g/dL, platelet count 138×10³ cells/µL, aPTT 38 sec (Table 1). The next days there was an improvement of the clinical status and blood exams; a contrast-enhanced-CT and magnetic resonance imaging of the left arm were performed and revealed extended necrosis of the subcutaneous tissues of the left forearm. On day 8 the patient was discharged with the diagnosis of spontaneous hematoma of the left arm and multiple diffuse hematomas after a probable violin spider (*L. rufescens*) bite. She was in a good clinical status, vital parameters were stable, but blood exams and coagulation factors levels (FVIII, FIX, FXI) were prescribed because a persistent isolated aPTT prolongation (51.9 sec).

On day 11 from the presentation of symptoms, blood test reports confirmed aPTT prolongation (54.9 sec; n.r. 25.1-36.5 sec) and revealed a FVIII deficiency (4.1%; n.r. 60-150%). The patient was admitted again to our ED and an emergency haematologic consult was requested. Tests were performed to clarify the cause of isolated aPTT elongation (see Table 1). Based on clinical and laboratory findings, the patient was sent to our ED with the diagnosis of Acquired Haemophilia A (AHA) and methylprednisolone at a dose of 1 mg/Kg was administered. After therapy was started, the patient was transferred in our Emergency Medicine Unit for the second time. During hospitalization, the immunotherapy with steroids was continued, total-body contrast-enhanced-CT and blood exams for tumour markers were performed; no signs of neoplasia were found. Blood exams for monitoring the coagulation showed an improvement of aPTT values; the patient condition was good and vital parameters stable. On day 18, the patient was discharged with a diagnosis of AHA after probable *L. rufescens* bite, with the recommendation to continue steroid therapy *per os* (prednisone 25 mg QD) and she was referred to the haematological outpatient clinic specialized on coagulation disorders.

Two months after hospital discharge, the patient was in good clinical conditions and there was an improvement in the laboratory exams (aPTT 38 sec, fVIII 120%, fVIII Ab negative). Based on haematological consulting, steroid therapy was progressively reduced and definitively stopped after four months; to our knowledge no relapse has been reported.

Discussion

Loxosceles spp. bites are rare, but literature about this argument is growing.[2] *L. rufescens* is the most common species in the Mediterrean basin and in Italy.[1] To allow a correct diagnosis of a spider bite (defined as a documented spider bite, based on Rader's classification),[10,11] the spider must be observed biting, captured during or immediately after the bite, identified by an expert and the bite must cause symptoms typically associated with a spider of that species.[1,11] In our case, the clinical features of the wound were indicative of *Loxosceles rufescens* bite (pain absent immediately after the spider bite and increasing over the course of a day, progressive appearance of bruising and swelling);[1,2,11–13] the localization of the bite was typical (arms and legs are the most commonly affected areas),[1,2,11–13] the situation and the season were also consistent with *Loxosceles* spp. activity (spiders usually hide in dark corners inside houses, between clothes and are active between April and October).[11] Furthermore, Tuscany is an endemic area for *L. rufescens*. Unfortunately, the spider (as in many cases reported in literature)[1,14] was not captured during or immediately after biting. We classified the wound as probable spider bite as per Rader's criteria.[1,11] Symptoms of *Loxosceles* bite could produce local or systemic signs, respectively called cutaneous and systemic loxoscelism. Cutaneous loxoscelism is characterized by a local erythema and swelling, that can progress into ecchymosis and rarely can lead to necrosis and ulcer formation in a few days after the bite.[1,2,13] Concerning cutaneous loxoscelism there are three possible levels of severity: i) unremarkable: very little damage, self-healing; ii) mild reaction: redness, itching, slight lesion, self-healing; iii) dermonecrotic: necrotic skin lesion, requiring medical and sometimes surgical treatment. This last condition, although very rare, is considered the most "characteristic" lesion of *Loxosceles rufescens* bites, which contributes in developing a clinical suspect. Among patients developing necrotic lesions, about two-thirds heal without complications.[15]

Systemic loxoscelism is a rarely and serious clinical condition in which malaise, fever, myalgias, nausea and vomiting are present, with or without acute haemolytic anemia, rhabdomyolisis, DIC and acute kidney disease.[1,2,13] Systemic symptoms (malaise, low grade fever, nausea, vomiting, headache and mild leucocytosis), can also develop in patient with cutaneous loxoscelsim,[1,2] as in our case. Moreover, almost one third of patients develop laboratory evidence of cutaneous-haemolytic loxoscelism.[2] This could explain the Hb reduction in our patient (Hb level decreased from 12.4 g/dL to 9.1 g/dL with mild increase of LDH level; haptoglobin level was not dosed), although it could have been caused also by the hematoma enlargement. We excluded AHA at a first evaluation, because the patient had a good response to FFP transfusion with a reduction of aPTT: this result ruled out AHA.[4–6]

Table 2. Hematological complications after violin spider bite after references.[1,2,12,13]

Clinical/laboratory findings	Enzymes Involved
Mild leukocytosis	Immune System activation
Haemolytic anemia	Sphyngomyelinasis D
aPTT prolongation	Sphyngomyelinasis D, metalloproteases, hyaluronidases and serine proteases
DIC	-

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AHA is a rare autoimmune disease, characterized by low fVIII levels due to the presence of autoantibodies, resulting in mild to life-threatening mucocutaneous bleeding.[4,5,9] Diagnosis is based on laboratory findings: isolated aPTT prolongation, without correction in aPTT-mixing tests, low fVIII levels and the presence of fVIII inhibitors.[4–6,8,9] Trasfusions of FFP during active bleeding in these patients are ineffective: in fact, the presence of fVIII inhibitors inactivates fVIII in FFP and the patient aPTT will not be corrected (no correction in mixing test, as seen in our case).[5,6,16]

In our opinion the initial prolongation of aPTT in our patient was due to *L. rufescens* poisoning, because aPTT value reduced after FFP infusion. Venom contains different toxins: sphyngomyelinasis D (responsible for the major dermatonecrotic symptoms of loxoscelism and for the disruption of red blood cell membranes, resulting in hemolysis) and, among others, metalloproteases, hyaluronidases and serine proteases.[12] In particular, these enzymes seem to interfere with blood coagulation because of thrombin-like, fibrinogenase and fibrinogen activating activities.[12] For all these reasons, we attributed the initial aPTT prolongation and patient's symptoms to *Loxosceles*' venom and we excluded AHA at the time of the first diagnosis (Table 2 summarizes post-spider bite hematologic complications).

Due to the persistent aPTT prolongation, we started to suspect a form of AHA and we requested lab tests that confirmed our suspects. In 50% of cases AHA is idiopathic, while the remnant 50% is caused by cancer, autoimmune diseases, pregnancy, drugs, dermatologic diseases and other conditions.[5,6,8,16] Therefore, laboratory tests and imaging exams were performed to find the hidden cause of AHA: haematological or solid tumour, autoimmune diseases, infective diseases and other causes were excluded. Due to the close temporal relationship between spider bite and AHA manifestations, in our opinion the most probable cause that triggered the production of fVIII autoantibodies has been the violin spider's poisoning. To confirm our hypothesis it would have been interesting to characterize the anti fVIII antibodies: an IgM positivity could have confirmed the acute development of AHA. Unfortunately antibodies characterization was not requested at the time. Despite this, the absence of pre-existing aPTT alterations, the exclusion of secondary pathologies and the consequentiality of the two events supports our hypothesis.

The patient was treated with corticosteroids at immunosuppressive dose with complete remission of the symptoms in six months.[4,5,17] The rapid response to corticosteroid therapy could be explained by the secondary nature of the event: the spider bite may have caused the formation of anti-venom antibodies that cross-reacted with fVIII. The absence of relapses in the following months, with the tapering of the steroid therapy, seems to confirm our hypothesis.

Conclusions

Here, we described a case wherein a patient developed AHA induced by a probable violin spider's bite. Albeit rare, AHA is a potentially life-threatening condition. Emergency physicians must consider AHA in the range of bleeding differential diagnosis and be aware of the possible systemic complications following a spider bite, in order to provide prompt treatment and avoid potentially preventable life-threatening haemorrhages.

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