Key to medically relevant Italian spider bites: a practical quick recognition tool for clinicians

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Abstract

Introduction. Spider bites are often overestimated because there are no specific clinical or histopathological aspects that characterize them, and skin lesions that resemble a spider bite are often wrongly considered to be a "true spider bite". However, even in case of a true spider bite, it is almost impossible to confirm the biting species, since very often neither physicians nor patients are trained in spider identification.

Objective. The aim of this report is to provide clinicians with a rapid and simple recognition of the few Italian medically relevant spiders, in order to take relative medical measures in case of spider bites.

Materials and methods. We defined spiders of considerable medical relevance the ones that cause local symptoms with possible systemic involvement, while we defined spiders with mild medical relevance the ones whose bite is not a medical emergency but is particularly painful or can cause lasting symptoms. We focused on the identification of the four spider taxa of major clinical interest through a brief descriptive, photographic and graphic guide, in association to dermatological manifestations.

Results. Spiders of considerable medical relevance are Loxosceles rufescens and Latrodectus tredecimguttatus, while spiders of less severe medical relevance are Steatoda paykulliana, S. nobilis, S. grossa, Cheiracanthium punctorium, Amblyocarenum spp. and Macrothele calpeiana (the presence of the latter in Italy is only accidental and very sporadic). The only species capable of causing necrosis is Loxosceles rufescens, while Latrodectus tredecimguttatus can cause more systemic symptoms.

Discussion and Conclusion. With the aim of promoting a first and rapid recognition of the species, we performed a morphological usable aspect for an initial and quick recognition according to an identification key. *Clin Ter 2021; 172 (4):336-346. doi: 10.7417/CT.2021.2338*

Key words: spiders, spider bite, wound, dermatology

Introduction

Spider bites are usually and frequently reported from the United States and subtropical and tropical areas (1-4); however, excluding Switzerland (4), no recent or comprehensive reports are available for the rest of Europe or for Italy (4).

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If suspecting a spider bite, the verification process involves three steps in which: the bite has to be observed; the spider must be caught (or photographed) during, or immediately after the bite; the spider (or the photo) must be sent to an expert arachnologist for identification (4). However, if it is true that many spider bites often go unreported, since their report is not mandatory, at the same time spider bite cases are often overestimated; indeed, since there are no specific clinical or histopathological aspects that characterize a spider bite, any skin lesion that resembles a spider bite is wrongly considered to be a "true spider bite". Even in case of a true spider bite, it is almost impossible to confirm the biting species, since very often neither physicians nor patients are trained in spider identification (5).

Considering that Italy has a relatively high number of spider species, with many favorable habitats and adequate mean annual temperatures, the relationship between overestimation and underestimation of spider bites can be confusing for both victims and physicians. Specifically, about 1.678 spider species are currently reported in Italy, among them, most are completely harmless as they are too small in size, with very small chelicerae (fangs), to bite humans (6). There are just a few dozen medium to large size species with chelicerae of adequate size that may perforate human skin. Among them, only a few have medical relevance or can cause effects more relevant than a mild localized skin irritation.

To our knowledge, there are no scientific papers that allow a rapid identification of the Italian medically relevant species, but only single case reports or reviews on spider bites. The aim of this report is to provide physicians with a rapid and simple recognition of Italian medically relevant spiders, in order to take relative medical measures and follow-up in case of spider bite.

Materials and methods

We defined spiders of considerable medical relevance those that cause local symptoms with possible systemic involvement; while we defined spiders with mild medical relevance, the ones whose bite is not a medical emergency but is particularly painful or can cause lasting symptoms.

Although scientific literature offers some tools for the recognition of the spider species present in Italy, the high number of taxa and the specificity of the subject limit their use to expert arachnologists only. It is important for clinicians to be able to identify quickly, but with certainty, the few national spider taxa of medical importance, in order to be able to exclude them or to rapidly provide adequate clinical treatment in the event of a bite.

Therefore, the key provided in this work is focused on recognizing only the four taxa of major clinical interest (two of considerable medical relevance and two of less severe medical relevance) through a brief descriptive and photographic guide.

Taxa of mild medical importance are then mentioned, without however being included in the key, avoiding complexity in the use of the guide by physicians, as these spiders usually do not go beyond temporary local symptoms (or their presence in Italy is just accidental and very sporadic, as for *Macrothele calpeiana*). However, it is important to point out that it cannot be excluded that other species of Italian spiders may also cause relevant clinical signs (e.g. accidental alien species or species for which there was insufficient evidence of the bite) and in this case, if you own the animal or a photo of the same, it is necessary to contact an expert arachnologist for the determination.

Results

Key to the four taxa of major medical relevance

Six (n=6) eyes arranged in pairs as shown in Fig. 1A-D. Chelicerae with projections that make them similar to pincers (Fig. 1D). Legs with a laterigrade posture and uniform color, without spots or rings of any type. Flattened prosoma (anterior region of the body), often with a violin-shaped cephalic spot. Abdomen is uniform in color, sometimes with a slightly evident darker cardial mark → Loxosceles rufescens

ephalothorax

Abdomen



(b)



Fig. 2 Close up of a *Latrodectus tredecimguttatus* individual in dorsal view (a); *Latrodectus tredecimguttatus*, eye arrangement in dorsal view (b); close up of a *Latrodectus tredecimguttatus* individual in frontal view (c); *Latrodectus tredecimguttatus*, eye arrangement in frontal view (d). Photos and drawings credits: Matteo R. Di Nicola.

- Eight (n=8) eyes arranged as in Fig. 2D. Glossy black legs. Black abdomen with a raised profile and 13 spots (sometimes fused together) in 3 longitudinal series (Fig. 2A): these blotches are of an intense dark red color in adult females, and of a bright red color with white edges in juvenile and adult males. Blotches can be absent or very dark and are difficult to distinguish in mature females → Latrodectus tredecimguttatus
- Eight (n=8) eyes arranged similar to those of *Latrodectus*, but with less lateral spacing (Fig. 3D). Body is of a glossy brown color in the majority of the species: depending on the species and sex it can vary from a light reddish brown to a very dark brown (females of *Steatoda grossa* and *S. nobilis*, Fig. 4A-B-C-D); an ocher or amber yellow band on the anterior edge of the abdomen (Fig. 4A-B-C). *Steatoda paykulliana* with glossy black color and red anterior band in adult females (Fig. 3A-C); this band is yellow in adult males and juveniles which also have a yellow herringbone pattern on the abdomen → *Steatoda* spp.
- Eight (n=8) eyes arranged as in Fig. 5D. Legs of the first pair clearly longer than the others. Anterior surface of

the abdomen crossed by an evident darker cardiac mark (Fig. 5A). In most species, chelicerae of adult males are longer and more curved than those of females (Fig. 5C-D) \rightarrow *Cheiracanthium* spp.

We divided medically relevant spiders in two categories, according to the medical and arachnological literature and for a rapid recognition to physicians: taxa with considerable medical relevance and taxa with less medical relevance.

Spiders of considerable medical relevance

In this chapter we included Italian spiders that, according to the literature, may lead to local damage or systemic involvement which can even lead to, in some sensitive patients, a medical emergency or death.

- Latrodectus tredecimguttatus (Fam.: Theridiidae)
- ♀ 7-15 mm. ♂ 4-7 mm.

Distinguishable from the ocular arrangement and from the peculiar coloring with intense red spots in the adult females; in young specimens and in adult males the coloration is different and the spots are bordered with a white line (7). This species can be confused with the *Steatoda* species that are usually smaller in size, consist of different patterns and



Fig. 3 Close up of a *Steatoda paykulliana* individual in dorsal view (a); *Steatoda paykulliana*, eye arrangement in dorsal view (b); close up of a *Steatoda paykulliana* individual in frontal view (c); *Steatoda paykulliana*, eye arrangement in frontal view (d). Photos credits: Stefano Lazzaretti; drawings credits: Matteo R. Di Nicola.



Fig. 4 Close up of a *Steatoda nobilis* individual in dorsal view (a); close up of a *Steatoda nobilis* individual in frontal view (b); close up of a *Steatoda grossa* individual in dorsal view (c); close up of a *Steatoda grossa* individual in frontal view (d). Photos credits Matteo R. Di Nicola.



Fig. 5 Close up of a *Cheiracanthium punctorium* individual in dorsal view (a); *Cheiracanthium punctorium*, eye arrangement in dorsal view (b); close up of a *Cheiracanthium punctorium* individual in frontal view (c); *Cheiracanthium punctorium*, eye arrangement in frontal view (d). Photos and drawings credits: Matteo R. Di Nicola.

colored spots (usually yellow, ocher, amber orange). Very old females of *L. tredecimguttatus* can be entirely black.

Widespread in sunny areas with a Mediterranean climate, where it builds a large three-dimensional spiderweb mainly under rocks and near shrubs and sparse vegetation. Non-synanthropic species. With rare exceptions (farmhouses, homes in rural areas), it is not present inside buildings. Present in regions of Italy such as Liguria, Tuscany, Lazio, Campania, Basilicata, Apulia, Sardinia, Calabria and reported but apparently rare in Sicily; reports in other regions seem to be sporadic and poorly supported by scientific literature (6). This species is not very aggressive and does not easily bite: bites usually occur by clumsily handling the spider or by accidentally compressing or crushing it against the skin. This can happen by lifting stones, bundles of grass or if a wandering specimen ends up in clothes or in a sleeping bag and is accidentally pressed against the skin.

• *Loxosceles rufescens* (Fam.: Sicariidae) ♀ 7-9 mm. ♂ 7-8 mm.

Easily distinguishable from other Italian spider species by the ocular arrangement with 6 eyes in 3 pairs and by the flattened shape of the cephalothorax; the only other genus with this ocular arrangement is *Scytodes* which has a convex prosoma (5-9). Species present only outdoors in a few Regions of the Peninsula (coastal area of Liguria, Lazio, Campania, Apulia, Calabria) and in Sardinia and Sicily, linked to barren areas with a Mediterranean climate where it builds a little web under stones and tree bark (1,7); in the rest of Italy, it is found almost only inside houses and buildings. This species is not usually a biting species and often the bite occurs by compressing the spider against the skin. This is unfortunately a common event because, due to its synanthropic habits, it is also possible to find it on beds, sofas, sheets and clothes, whereby compression against the skin occurs.

Spiders of mild medical relevance

In this chapter we included spiders whose bite is not a medical emergency but can be particularly painful or can cause lasting symptoms. In addition, a brief description of *Amblyocarenum* spp. and *Macrothele calpeiana* is provided: although there are no clear sources in the literature, these species seem to elicit very painful bites with effects lasting many hours (pers. comm.).

• *Cheiracanthium punctorium* (Fam.: Cheiracanthiidae)

♀ 10-15 mm. ♂ 7.5-14 mm.

Distinguishable from the ocular arrangement, from the legs of the first pair longer than the others and from the large dimensions of the chelicerae, which in adult males are slightly curved and of impressive length (6).

Species present in meadows, pastures and gardens; sporadic specimens can be found even in homes and buildings near typical habitats. Species mostly nocturnal wandering at night, while spending the day stay in silk sacs built among the grass, the branches of the shrubs or on walls and trunks (6,8,9). Defensive and biting species, the bite can typically occur by inadvertently touching / handling a wandering specimen or in its silk sac (10,11).

In Italy there are other similar but smaller species, with less aggressive chelicerae whose bite causes coherent but less relevant symptoms: *Cheiracanthium mildei* is the most frequent species inside buildings and in urban contexts (6).

Steatoda spp. (Fam.: Theridiidae) Steatoda grossa
♀ 6.5-10 mm. ♂ 5-10 mm.
Steatoda nobilis
♀ 9-14 mm. ♂ 7.5-11 mm.
Steatoda paykulliana
♀ 8-13 mm. ♂ 4.5-8.5 mm.

Distinguishable from ocular disposition and abdominal coloration and patterns. They build cobwebs on walls, anthropic structures, rocky areas, tree trunks (8,12). Although some species (*Steatoda grossa*, *Steatoda nobilis*) are very common near or inside homes, these are spiders that are not very aggressive and that tend to bite only if crushed against the skin or clumsily handled.

• Amblyocarenum spp. (Fam.: Nemesiidae)

♀ 20-30 mm. ♂ 13.5-20 mm

Distinguishable from the Orthognata morphology of the chelicerae, the foveal shape, the ocular arrangement and the large dimensions; this genus can be confused with other trapdoor spiders like some species of *Cteniza* (Ctenizidae). These spiders burrow tunnels in the ground and therefore have cryptic habits which do not put them into close contact with humans, except in the case of wandering adult males that abound from late summer to early winter in some Italian regions with Mediterranean climate (Sardinia, Sicily, Campania, Calabria, Basilicata) (7,13). The specimens are often defensive and bite if inadvertently touched or carelessly touched or handled.

• *Macrothele calpeiana* (Fam.: Macrothelidae)

♀ 28-35 mm. ♂ 20-27 mm.

Easily distinguishable from any other Italian species by the very long posterior spinnerets. Accidentally introduced in Italy with the transport of trees from Spain - especially olive trees - for ornamental purposes (6,7). Usually weaves a funnel web in underground tunnels close to the trunks of trees or uses cavities of stumps and walls (14). Considering the ethology of this species, contacts with humans, are minimal and the situations at risk concern in particular the transfer of trees, handling roots or clods of earth. Wandering specimens have also been found, but the risk of being bitten is low considering the shy habits of this species and given its large size which discourages touching / handling of the specimens.

Spiders mistakenly considered of medical significance

Some spider species now considered of no medical relevance, were in the past believed to have caused necrosis or other serious dermal lesions. The European taxa involved in this kind of misunderstanding are mainly Eratigena agrestis (previously named Tegenaria agrestis), Cheiracanthium spp. and Dysdera spp.. These species have been mentioned in reports that lacked in number of analyzed cases and with too many inaccuracies about the cause of the necrotic injury, often attributed to the spider bite because a spider was later found in the patient's home: it is not surprising that these species are synanthropic and commonly present inside buildings (15). These reports have been heavily questioned or completely denied by subsequent medical-scientific literature (11,16): the reported episodes believed to be incorrect diagnoses or complications not due to the direct action of the venom of the spiders mentioned. In some cases - Eratigena agrestis, Cheiracanthium mildei - the possibility of necrosis in humans has been confirmed following tests on laboratory animals such as guinea pigs and rabbits, in which a necrotic process actually took place: these conclusions, however, are not factual. In later verified reports of bites to humans, necrosis was not present (11,16-18). In this regard, the Sicariidae family (e.g. Loxosceles rufescens) appears to be the only one that includes species with a venom containing proteolytic enzymes that can cause severe necrosis in humans (19).

Traces of the bite: why the "two marks" are not a useful diagnostic feature

It is often mentioned, starting from more anecdotal elements rather than evidence from the scientific literature, that the bite of the spiders, being inflicted by two fangs, would leave two distinct marks on the skin of the patient: although this is true for some species with large and long-fanged chelicerae, it should be noted that in Italy the spiders capable of causing those two marks are only a few; furthermore, the two Italian species of considerable medical relevance (Latrodectus tredecimguttatus and Loxosceles rufescens) have small chelicerae and do not leave two marks so distant to be clearly visible and, if they are, they remain visible for a very short time before being possibly eclipsed by the skin irritation (4,20). It should also be noted that a few hematophagous insects, in searching for capillaries to suck blood, can sting two or more times and often resemble two close marks. The presence of two marks is therefore not an exhaustive and reliable element for the diagnosis of a spider bite and is not typical or sufficient to exclude bites or punctures from other arthropods.

Local and systemic symptoms in Italian spider bites

The bite of the medically relevant species included in this work usually produces mild symptoms, mostly characterized by a local reaction. Generally, after a spider bite, the bitten area is mainly characterized by the presence of one (more rarely two) visible fang marks, with blood secretion, and can be associated with pain (1-5) (Fig. 6). Few minutes after a true bite, the surrounding area becomes swollen and painful, with onset of local oedema. Subsequently, the local symptomatology and the possible systemic symptomatology depend on the venom of the species that caused the bite.

In Cheiracanthium punctorium, transient paresthesia is usually present and it is associated with the neurotoxic effect of the venom (21-26). The pain in C. punctorium is usually very strong and acute, even for the large size of the fangs. Severe systemic symptoms have rarely been described: those include shivers, sweating, vomiting, fever, tachycardia, neutrophilia, increase of total bilirubinemia, respiratory difficulty and circulatory breakdown (21-26). However, no fatal incidents due to C. punctorium have ever been recorded (7). Usually Cheiracanthium bites do not induce vesiculation, neither necrosis and become asymptomatic within two days (22). Pepe et al. described the onset of necrosis and subsequent scarring in a case of *C. mildei* (26); however, the necrotic action of the bite of Cheiracanthium has not been confirmed by Vetter et al. (27). Most likely the necrosis observed by Pepe et al. may have been caused by other pathogens (such as bacteria) rather than a spider bite. Most of *Cheiracanthium* bites take place in the evening, during outdoor activities, between the months of June and September. Yellow sac spiders are prone to bite defensively and the sac is aggressively defended (21).

A more systemic symptomatology is usually present in Latrodectus tredecimguttatus spider bites. The symptomatological set caused by the bite of this species determines the so-called latrodectism. After the bite and in association with local symptoms (such as pain, erythema, ecchymosis and oedema), abdominal stiffness, thoracic pain, muscular spasms, fasciculation, priapism, sweating, paresthesia, hypertensive crisis, and psychomotor alterations are usually present (28). Regional diaphoresis, is present in 55% of case and is a peculiar clinical feature induced by the bite of this species (29). Patients may present the so called "facies latrodectismica", induced by the contraction of facial muscles associated with peri-orbital oedema (29). Laboratory investigations sometimes may show leukocytosis, neutrophilia, increase in creatine phosphokinase, increase of myoglobin, troponin and proteinuria (30-32). Usually the bite of L. tredecimguttatus does not cause ulceration, nor necrosis and does not leave scars. The cause of all these symptoms is mainly due to the neurotoxin α -latrotoxin, that causes acetylcholine depletion at motor nerve endings and catecholamine release at adrenergic nerve endings (30).



Fig. 6 Erythematous annular lesion, characterized by the presence of a central scaly-crust in a 48 year-old Caucasian female patient, bitten by an adult male *Steatoda grossa* in Sardinia. The personal medical history of the patient was negative for other diseases. Note the "targetoid lesion" that resembles the targetoid lesion that usually occur also in case of the bite of the relative *Latrodectus tredecinguttatus* (a). Complete non-scarring healing of the lesion (b).

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Compared to L. tredecimguttatus, Steatoda grossa is usually not associated with bites of important medical significance (Fig.6); however, nausea, vomiting, headache, and severe local and regional pain may arise, inducing a cluster of manifestations called "steatodism" (33,34). Graudins et al. found that S. grossa venom has its site of action in the pre-synaptic nerve terminal to cause acetylcholine release in a manner similar to α -latrotoxin (33). Contrariwise to Latrodectus, diaphoresis is usually absent in spider bites of the genus Steatoda, allowing a differential diagnosis (34). The Western European species S. nobilis is known to be of greater medical relevance than S. grossa, most likely for the greater number of bites reported in the literature rather than for a greater action of the venom (34). For the most common symptoms resulting from S. nobilis envenomations see Dunbar et al. [35]. Among the clinical signs, the authors also cited necrosis, although there are no clinical or patological evidences in their report. Among spider bites, the symptomatology related to Loxosceles spp. is an exception, since they are nocturnal species and thus most bites happen at night, and the bite itself is consistently described as painless (1). Therefore, most Loxosceles bites will not get noticed until several hours later pain appears or the patient notices some skin alteration the next morning (1). Accordingly, the rate of verified *Loxosceles* bites will be much lower than for all other spider bites (1). After a few hours, pain develops as a very common initial symptom together with erythema (1). Pain is often accompanied by a burning sensation and/or itching and increases in intensity during the first 24 hours (1). After a mean of 3 days from the bite, the cutaneous lesion increases in size, often having an irregular shape with a central hemorrhagic blister, surrounded by a large erythema with oedema that causes a typical blue, white and red color pattern (1,5). The extension is centrifugal and gravitational



Fig. 7 Erythema and oedema, associated a local itching arose few hours after the bites in a 53 year-old Caucasian woman, bitten by a *Loxosceles rufescens* in Northern Italy (Lombardy). The personal medical history of the patient was negative for other diseases (a). A tense blister, surrounded by a mild erythema arose after 24 hours from the bite (b.

After 3 days, the vesicle collapsed leaving a necrotic area, with the formation of fibrin and a typical erythematous and bluish border, slightly raised, with a centrifugal direction. Here the necrotic area is visible after 15 days from the bite (c). After 4 months the lesions resulted in a permanent scar (d). (1). On the fourth day, the bitten area becomes ischemic and necrotic in the central part of the blister (which does not always develop) (Fig.7). The intensity of the reaction and of the following necrosis depends on the quantity of venom injected and on the kind of tissue affected (1). The wound usually heals within 3 months; if the wound requires more than 3 months for healing, then diagnoses other than loxoscelism should be considered (1). Healing of the wounds almost always leads to scarring. In absence of necrosis, the erythema and oedema completely disappear within 2-3 weeks, occasionally with the formation of a black eschar (1). Systemic symptoms may include hemolysis, coagulopathy, and a measles-like toxic erythema rash. Fever, nausea and chills may be also present.

Regarding *Amblyocarenum* spp. and *Macrothele calpeiana*, due to the size of the chelicerae, the bite can induce intense and persistent pain for several hours. However, to date there are no known cases in the literature characterized by extensive local tissue damage and / or associated systemic symptoms. Finally, regarding other italian taxa such as *Eresus* spp. (Eresidae) and *Argyroneta aquatica* (Dictynidae), their elusiveness and particular ecology make a bite almost unlikely and there are no findings of medically relevant bites in literature, except for sporadic reports (4).

Local and systemic treatments

Pain treatment and treatment of bite complications (such as necrosis, super-infection, anaphylactoid reaction) are the main aspects for the management of any spider bite. Regardless the species that caused the bite, variety of analgesics can be used to treat the pain. At the same time, it is important to avoid acetyl salicylic acid, due to the greater risk of developing bleeding. The affected area can be treated with hydrogen peroxid or plain water. The bitten extremity should be elevated, and cool compresses should be applied on the affected limb (25). Although the fangs can be carriers of pathogens, by now, there is a lack of evidence that a spider bite may vehiculate bacteria. Indeed, according to Isbister et al., a secondary infection following a spider bite is present only in 0.9% of cases (36). Therefore, generally, a systemic antibiotic treatment can be performed, only in case of ascertained infection or in patients with a high risk of secondary bacterial infections (such as diabetic and immunosuppressed patients). In this regard, broad spectrum antibiotics (e.g. amoxicillin, cephalosporin, azithromycin, metronidazole, trimethoprim + sulfamethoxazole) as well as culture-direct antibiotic treatments may be prescribed. Otherwise, tetanus immunization status should always be evaluated, and immunization provided as needed. Systemic corticosteroids can be given to reduce local oedema and pain, as well as systemic antihistamines (e.g. cetirizine) can be prescribed in case of intense itching. Topical antihistamines should be always avoided, due to an increased risk of side effects and drug reactions (37).

Regarding local treatment, it changes based on the species, eventual local superinfection and onset of necrosis and/ or eschar. Accordingly, chlortetracycline cream is effective in case of spider bites and can be prescribed for all spider bites, as a local and preventive treatment. Together with local debridement, collagenase ointment is mainly prescribed for *Loxosceles* spp., that is the genus that causes necrosis with eschar formation. Collagenase induces an enzymatic cleansing of the wound and the related necrotic material; besides, in addition to reducing the risk of potential infections, it also induces an increase in cellular and protein turnover, thus improving the histological and functional recovery of the lesion itself. However, when case collagenase ointment is prescribed, aluminum acetate, Burow's solution, povidone iodine, silver nitrate and silver sulfadiazine should be avoided, for possible increased risk of local interactions. In some cases, such as a non-healing wound, medical maggots (*Lucilia sericata*), negative pressure therapy or hyperbaric oxygen therapy may be applied to the necrotic ulcers, as valid alternative topical treatments (38).

Regarding *Latrodectus tredecimguttatus*, in case of severe symptoms and together with systemic and local support therapies, antivenom (1-2 vials diluted in 100-250 ml of 0.4% NaCl infused intravenously in 1-2 hours) may be prescribed, as demonstrated by recent publications (29-31); in addition, together with the antivenin, opioids and benzodiazepines are frequently used as muscle relaxants, although recent high quality evidence has cast doubt on the clinical effectiveness of this combination (29,31). While, regarding *Loxosceles*, small molecule inhibitors of sphingomyelinase-D have been recently identified with promising therapeutic implications (39).

In any case, as for snake bites, it is important to highlight that for all aforementioned reported spider species, the treatment of any and eventual internal complication (e.g. cardiotoxicity, nephrotoxicity, hemotoxicity) does not differ from same complications of different etiologies (40).

Discussion

Except for *Loxosceles* spp., it is usually assumed that a spider must have a body length of at least 10 mm to be able to perforate the human skin (4). Consequently, a number of Italian spider taxa may be able to bite humans, despite very few genus / species can give symptoms of medical relevance.

At the same time, it is known that many suspected spider bites can be caused by other cutaneous conditions, while only in rare cases the spider is really the cause of a cutaneous lesion (1-5). Consequently, before making the diagnosis of a spider bite, it is important to exclude other pathologies, such as: methicillin-resistant Staphylococcus aureus infections, cutaneous anthrax, dermatomycosis, hemosiderotic targetoid hemangioma, erysipelas, furuncles, rupture of a sebaceous cyst, streptococcal ecthyma, herpes virus, impetigo, Lyme disease, pyoderma gangrenosum, sporotrichosis, autoimmune vasculitis, chemical burns, diabetic ulcers, lymphomatoid papulosis, venous stasis ulcers and other arthropod bites and stings (5). The main feature to reach a true diagnosis of a spider bite remains to immediately collect the spider during or after the bite.⁴ In this regard, mnemonic devices were created to better assist clinicians in the correct diagnosis of a spider bite (1,3). The spider must be observed biting, captured during or immediately after the bite and identified by an expert (3). Specifically for Loxosceles spp., in addition to the spider morphological determination, an ELISA test on a swab from the area of the suspected bite has shown promising results in the American species *L. reclusa*, although it is not yet commercially available (5).

A cutaneous biopsy can not specify the species of the spider, although it can be used to rule out other pathological conditions: large zones of necrosis, mixed inflammatory cell infiltrate, coagulative tissue necrosis surrounded by neutrophils and signs of vasculitis are usually the main histopathological changes observed (18). The main histological differential diagnosis of spider bites are: allergic contact dermatitis (infiltrate is usually mostly in superficial and not in the deep dermis, while necrosis and vasculitis are uncommon), lymphomatoid papulosis (mixed wedgeshaped lymphocytic infiltrate containing CD30+ atypical lymphocytes), cutaneous pseudo-lymphoma (dense nodular or band-like lymphocytic infiltrate often with eosinophils), urticarial vasculitis (superficial infiltrate with neutrophils and eosinophils and leucocytoclastic vasculitis) and eosinophilic cellulitis (diffuse dermal infiltrates of eosinophils with flame figures).

The tables reported in this work, in the event of an ascertained Italian spider bite, allow clinicians to immediately identify the species and set the appropriate therapeutic and instrumental protocol, before waiting for a response of an expert arachnologist. This not only makes it possible to optimize time, but also provides greater certainty to both the clinician and the patient.

Conclusion

Although very rare, cases of spider bite in Italy do occur. In this regard, with the aim of promoting a first and rapid recognition of the species, before sending the spider to an expert arachnologist and in addition to using more complex mnemonic devices (1,3), a morphological usable aspect for a quick recognition can be the dichotomous key highlighted in this report. This model could subsequently be extended to the medically relevant spider species from other European countries.

Acknowledgements

The authors would like to thank Miriam D'Ovidio for the photos of *Loxosceles rufescens* bite; Emanuela Zedda for the photos of *Steatoda grossa* bite; Stefano Lazzaretti for the photos of *Steatoda paykulliana* individual; Marco Colombo for his advice; for the English revision. The views expressed in this paper belong to the authors only and do not reflect the views of the European Food Safety Authority.

References

 Nentwig W, Pantini P, Vetter RS. Distribution and medical aspects of Loxosceles rufescens, one of the most invasive spiders of the world (Araneae: Sicariidae). Toxicon 2017;132:19-28

- Juckett G. Arthropod bites. Am Fam Physician 2013; 88:841-7
- Stoecker WV, Vetter RS, Dyer JA. NOT RECLUSE-A Mnemonic Device to Avoid False Diagnoses of Brown Recluse Spider Bites. JAMA Dermatol 2017;153:377-378
- Nentwig W, Gnädinger M, Fuchs J, et al. A two year study of verified spider bites in Switzerland and a review of the European spider bite literature. Toxicon 2013;73:104-10
- Paolino G, Vaira F, Mercuri SR, et al. Fast recognition of Loxosceles rufescens in Italian spider bites to avoid misdiagnosis, alarmism and start a prompt treatment. J Eur Acad Dermatol Venereol 2020 doi.org/10.1111/jdv.16395
- Pantini P, Isaia M. Araneae.it: the online Catalog of Italian spiders with addenda on other Arachnid Orders occurring in Italy (Arachnida: Araneae, Opiliones, Palpigradi, Pseudoscorpionida, Scorpiones, Solifugae). Fragmenta Entomologica 2019;51:127-152. Online at www.araneae.it, accessed on October 28th 2020
- Nentwig W, Blick T, Bosmans R, et al. Spiders of Europe. Version 10.2020. Online at https://www.araneae.nmbe.ch, accessed on October 28th 2020. https://doi.org/10.24436/1
- Roberts MJ. Spiders of Britain & northern Europe, 1995, Harper Collins Publishers, ISBN 000 219981 5
- Bellmann H, Spinnentiere Europas, 1997, Kosmos, Stuttgart, Germany, ISBN 3-440-07025-5
- Stingeni L, Giorgi M, Principato M. Aracnidismo da Cheiracanthium punctorium (Aranea: Clubionidae): descrizione di un caso. Ann Ital Dermatol Clin Speriment 1998; 52:79-81
- Pepe R, Trentini M. Un caso di aracnidismo necrotico da Cheiracanthium mildei L. Koch, 1864 (Araneae, Clubionidae) nel Salento. Thalassia Salent 2002; 26:45-51
- Kulczycki A, Legittimo CM, Simeon E, et al. New records of Steatoda nobilis (Thorell, 1875) (Araneae, Theridiidae), an introduced species on the Italian mainland and in Sardinia. Bull Br Arachnol Soc 2012;15:269-272
- Decae A, Colombo M, Manunza B. Species diversity in the supposedly monotypic genus Amblyocarenum Simon, 1892, with the description of a new species from Sardinia (Araneae, Mygalomorphae, Cyrtaucheniidae). Arachnology 2014;16: 228-240
- Pantini P, Isaia M, Mazzoleni F, et al. Nuovi dati sui ragni di Lombardia (Arachnida, Araneae). Rivista del Museo Civico di Scienze Naturali "E. Caffi", Bergamo 29:21-44
- PCT Field Guide for the Management of Urban Spiders, 2012, 2nd Ed. By Stoy A. Hedges and Richard S. Vetter
- McKeown N, Vetter RS, Hendrickson RG. Verified spider bites in Oregon (USA) with the intent to assess hobo spider venom toxicity. Toxicon 2014;84:51-55
- 17. Vest DK. Envenomation by Tegenaria agrestis (Walckenaer) spiders in rabbits. Toxicon 1987;25:221-224
- Gaver-Wainwright MM, Zack RS, Foradori MJ, et al. Misdiagnosis of spider bites: bacterial associates, mechanical pathogen transfer, and hemolytic potential of venom from the hobo spider, Tegenaria agrestis (Araneae: Agelenidae). J Med Entomol 2011;48:382-388
- Magalhaes ILF, Brescovit AD, Santos AJ. Phylogeny of Sicariidae spiders (Araneae: Haplogynae), with a monograph on Neotropical Sicarius. Zool J Linnean Soc 2017;179:767-864
- Ashurst, John & Sexton, Joe & Cook, Matt. Approach and management of spider bites for the primary care physician. Osteopath Fam Physician 2011; 3:149-153

- 21. Papini R. Documented bites by a yellow sac spider (Cheiracanthium punctorium) in Italy: a case report. J Venom Anim Toxins incl Trop Dis 2012;18:349-354
- 22. Varl T, Grenc D, Kostanjšek R et al. Yellow sac spider (Cheiracanthium punctorium) bites in Slovenia: case series and review. Wien Klin Wochenschr 2017;129:630–633
- 23. Trentini M, Canestri Trotti G. Un caso di aracnidismo da Cheiracanthium punctorium (Villers 1798) (Araneae, Clubionidae). Biol Ogg 1990; 4:55-7
- 24. Principato M, Polidori GA, Ubertini S. Cheiracanthium punctorium Villers (Araneae: Clubionidae): first note in Umbria on four cases of human envenomation. Parassitologia 1994;36:120
- Stingeni L, Giorgi M, Principato M. Aracnidismo da Cheiracanthium punctorium (Aranea: Clubionidae): descrizione di un caso. Ann Ital Dermatol Clin Speriment 1998; 52:79-81
- Pepe R, Trentini M. Un caso di aracnidismo necrotico da Cheiracanthium mildei L. Koch, 1864 (Araneae, Clubionidae) nel Salento. Thalassia Salent 2002; 26:45-51
- Vetter RS, Isbister GK, Bush SP, et al. Verified bites by yellow sac spiders (genus Cheiracanthium) in the United States and Australia: where is the necrosis? Am J Trop Med Hyg 2006; 74:1043-8
- Di Paola G, Cirronis M, Scaravaggi G, et al. Latrodectism in Italy: First report of successful treatment of L. tredecimguttatus envenomation using L. mactans antivenom from North America. Toxicon. 2020;179:107-110
- Fusto G, Bennardo L, Del Duca E. Spider bites of medical significance in the Mediterranean area: misdiagnosis, clinical features and management. J Venom Anim Toxins incl Trop Dis 2020; 26:e20190100
- Díez García F, Laynez Bretones F, Gálvez Contreras MC, et al. Black widow spider (Latrodectus tredecimguttatus) bite. Presentation of 12 cases. Med Clin (Barc) 1996;9;106:344-6
- Di Paola G, Cirronis M, Scaravaggi G, et al. Latrodectism in Italy: First report of successful treatment of L. tredecimguttatus envenomation using L. mactans antivenom from North America. Toxicon 2020;179:107-110

- 32. Juckett G. Arthropod bites. Am Fam Physician 2013; 88:841-7
- 33. Graudins A, Gunja N, Broady KW, et al. Clinical and in vitro evidence for the efficacy of Australian red-back spider (Latrodectus hasselti) antivenom in the treatment of envenomation by a Cupboard spider (Steatoda grossa). Toxicon 2002;40:767-775
- Dunbar JP, Afoullouss S, Sulpice R, et al. Envenomation by the noble false widow spider Steatoda nobilis (Thorell, 1875) - five new cases of steatodism from Ireland and Great Britain. Clin Toxicol 2018;56:433-435
- 35. Dunbar JP, Vitkauskaite A, O'Keeffe DT, et al. Bites by the noble false widow spider Steatoda nobilis can induce Latrodectus-like symptoms and vector-borne bacterial infections with implications for public health: a case series. Clin Toxicol 2021;1-12
- Isbister GK, Gray MR. A prospective study of 750 definite spider bites, with expert spider identification. QJM 2002; 95:723-31
- Cantisani C, Ricci S, Grieco T, et al. Topical promethazine side effects: our experience and review of the literature. Biomed Res Int 2013; 2013:151509
- Zink A, Zink A, Gebhardt M, et al. Necrotic Arachnidism in Germany due to Bite of a Dysderidae Spider Probably Imported from South Tyrol, Italy. Acta Derm Venereol 2020;100:adv00067
- Lopes PH, Murakami MT, Portaro FCV, et al. Targeting Loxosceles spider Sphingomyelinase D with small-molecule inhibitors as a potential therapeutic approach for loxoscelism. J Enzyme Inhib Med Chem 2019; 34:310-321
- 40. Paolino G, Di Nicola MR, Pontara A, et al. Vipera snakebite in Europe: a systematic review of a neglected disease. J Eur Acad Dermatol Venereol 2020;34:2247-2260