



# Skin manifestations of arthropod-borne infection in Latin America

Adrián Bolívar-Mejía<sup>a</sup>, Camila Alarcón-Olave<sup>b</sup>, and Alfonso J. Rodríguez-Morales<sup>c,d</sup>

## Purpose of review

Arthropods are a significant cause of human skin lesions and infections, especially in Latin America. This review summarizes recent articles on the cutaneous manifestations of arthropod-borne diseases, with an emphasis on those diseases causing direct skin damage but also considering those systemic diseases with cutaneous manifestations.

## Recent findings

Studies have shown a variety and increase of cutaneous manifestations caused by arthropod-borne infections, including petechiae, purpura, ulcers, nodules, atrophic, miliary and hyperpigmented lesions. Although unspecific, when considering other features they become a useful tool in the diagnostic approach. Unusual cutaneous presentation of these diseases has been found to be associated with development of immunity, virulent strain, drug resistance and immunosuppressive states. Also, because of globalization, climate change and large-scale migration, these manifestations have spread to new areas.

## Summary

Cutaneous manifestations of arthropod-borne infections are varied and nonspecific. Their atypical presentations are mainly related to immune impairment and strain virulence. When considering a patient with skin lesions, other clinical and laboratory features must be taken into account in order to make an accurate diagnostic approach.

## Keywords

arthropod-borne infection, epidemiology, Latin America, skin manifestations

## INTRODUCTION

Many arthropod-borne diseases (ABDs) are considered among the currently accepted neglected tropical diseases, most of them present in Latin American countries [1]. This multifactorial and multietiological group of diseases causes enormous suffering and burden to humans and animals, being responsible for hundreds of millions of cases each year in the region [2]. Usually, these diseases are strongly related to poverty and restricted to the tropics; however, many of them are expanding their range into new areas because of global travel and large-scale emigration [2,3].

Arthropods are a significant cause of human skin lesions, as people are unavoidably exposed to biting and stinging not only in the rural, suburban environment but also in the urban environment, so physicians and other healthcare providers from endemic and nonendemic areas are frequently confronted with patients having skin lesions related to this cause [4].

The purpose of this review is to describe the cutaneous manifestations of arthropod-borne diseases, which still remain a public health problem, particularly in tropical developing regions including Latin America. The review emphasizes those diseases causing direct skin damage, such as leishmaniasis, verruga peruana (Peruvian wart and chronic *Bartonella bacilliformis* infection) and onchocerciasis, but also considers those systemic ABDs with cutaneous

<sup>a</sup>Faculty of Health, Universidad Industrial de Santander, <sup>b</sup>Faculty of Medicine, Universidad Autónoma de Bucaramanga, Bucaramanga, Santander, Colombia, <sup>c</sup>Faculty of Health Sciences, Universidad Tecnológica de Pereira, Pereira, Risaralda, Colombia and <sup>d</sup>Working Group on Zoonoses, International Society for Chemotherapy, Aberdeen, UK

Correspondence to Alfonso J. Rodríguez-Morales, Department of Community Medicine, Faculty of Health Sciences, Universidad Tecnológica de Pereira, Pereira, Risaralda 660003, Colombia. Tel: +57 300 8847448; e-mail: arodriguez@utp.edu.co

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## KEY POINTS

- ABDs can include infection that can be restricted to skin (e.g. cutaneous leishmaniasis), but can also be manifested in the skin as part of a systemic disease (e.g. yellow fever).
- Latin America is endemic for many ABDs that can be of importance for skin involvement, such as leishmaniasis, onchocercosis, Chagas disease, verruga peruana, yellow fever, dengue and malaria, among others.
- Given their reemergence and global migration, clinicians all over the world should consider the epidemiology and clinical manifestations of these ABDs that need to be suspected in patients with a travel history to Latin America.

manifestations, such as dengue, yellow fever, malaria and Chagas disease. The aim is to make physicians more aware of these presentations, helping to reduce morbidity and mortality by making a timely diagnosis and using appropriate treatment.

## LEISHMANIASIS

Leishmaniasis is well known as an ABD caused by *Leishmania* species (protozoa). It occurs in humans and animals, is transmitted by sandflies of the genera *Phlebotomus* and *Lutzomyia* [5,6]. The parasite is only transmitted by the bite of a female sandfly that is found around humans, especially in organic matter, such as rodent burrows or manure [7]. Leishmaniasis is a worldwide zoonotic distributed disease, being considered endemic in over 95 countries, with an estimated incidence of 2 million new cases per year according to the WHO [8<sup>•</sup>]. In Latin America, it can be found from Mexico up to Argentina, but higher rates are reported in Brazil and Peru [8<sup>•</sup>,9].

According to the clinical presentation and geographic distribution, disease has been classified as: Old World leishmaniasis, which includes cutaneous leishmaniasis and visceral leishmaniasis, and New World leishmaniasis, which includes mucocutaneous leishmaniasis, cutaneous leishmaniasis as well as visceral leishmaniasis [5,6].

Visceral leishmaniasis tends to be a chronic disease that involves bloodstream and inner organs and is caused by two *Leishmania* species: *L. infantum/chagasi* and *L. donovani* [5,6,10]. Cutaneous leishmaniasis is caused mainly in the Old World (Europe and Africa), by the parasite species *L. tropica*, which usually causes benign ulcers and *L. major*, which causes more severe and destructive ulcers [10], and in the New World (Latin America) *L. braziliensis*,

considered the most prevalent species in Brazil and in the region, causing both cutaneous leishmaniasis and mucocutaneous leishmaniasis [11].

According to their clinical manifestations, it is important to know that cutaneous leishmaniasis rarely will progress to death, but the cutaneous lesions may cause serious social, economic, and psychological impacts and stigma in the patient [12<sup>•</sup>]. Cutaneous leishmaniasis compromises not only the skin but also the mucosa, causing at the very beginning small papules related or not to lymphadenopathy that subsequently ends in the formation of painless skin ulcers [11]. The first sign after the inoculation of the promastigotes, which happens at from 2 weeks to 2 months after the exposure, includes the formation of a nodule that also can look like a plaque, in the position of the bite. After the incubation period there appears the initial lesion consisting of a red furuncle or papule. The papule progresses and starts to gain in size and acquire a violaceous tone, then evolves after 2 or 3 months to a skin ulcer, with indurated borders and a diameter usually ranging between 2 and 6 cm, but sometimes higher, and not necessarily round (Fig. 1). Finally, secondary nodules, known as satellite lesions, appear around the ulcer [13]. These lesions are commonly seen in the ears, nose and the perineal region, but particularly on the upper and lower limbs [5,6]. The clinical manifestations depend, however, on several factors such as involved *Leishmania* species, host factors (including immunogenicity) and parasite virulence [13,14]. Mucosal



**FIGURE 1.** Chronic cutaneous leishmaniasis lesion at the back of the lower part of the leg (above the ankle).

leishmaniasis usually is focalized; however, cutaneous leishmaniasis can be focalized (one lesion, occurring in up to 60% of cases) but also diffuse (multiple lesions) [14,15].

Localized cutaneous leishmaniasis is characterized by the typical lesion described previously, with solitary or multiple nodules around the lesion and near to the regional lymph nodes. The approximate time of healing varies depending on the *Leishmania* species. A typical scar is characterized by hyperpigmentation (Fig. 2) and atrophic and irregular borders [13]. After 3–5 months, chronic scars are seen to be clear, and their borders could be more regular (Fig. 3). Diffuse leishmaniasis is the disseminated form, characterized by multiple nodules. It starts as a primary lesion that appears on the limbs, face or buttocks [13,15].

Mucocutaneous leishmaniasis is a serious form of leishmaniasis characterized by destructive lesions. It begins with similar lesions to those seen in cutaneous leishmaniasis, but in contrast it does not show a resolution, and the infection extends to other sites such as the mucosa, cartilage and even the respiratory tract, causing disfigurement and important repercussions on the patient's quality of life [13,16<sup>■</sup>].

Because of its large spectrum of manifestations, leishmaniasis in its more complex form can be a serious disease, involving not only the skin with its destructive lesions but also affecting in a significant



**FIGURE 2.** Recent scar of a patient with cutaneous leishmaniasis.



**FIGURE 3.** Chronic scar of a patient with cutaneous leishmaniasis.

way the quality of life of the patient. Thus it is important that health professionals make an early diagnosis on the basis of the characteristic lesions [13,15,16<sup>■</sup>].

Vaccine candidates for leishmaniasis are under development [12<sup>■</sup>]; their potential efficacy would be cost-effective compared with chemotherapy, particularly in Latin America [12<sup>■</sup>].

### **VERRUGA PERUANA (PERUVIAN WART)**

Verruga peruana (or Peruvian wart), also known as the chronic phase of Carrión's disease (infection due to *Bartonella bacilliformis*), has been reported mainly in Peru, some areas of Ecuador and southern Colombia, with unconfirmed reports of cases in Asia (Thailand) and sporadic cases in Bolivia, northern Chile and possibly Guatemala [17<sup>■</sup>,18,19<sup>■</sup>]. In addition to *B. bacilliformis*, recently a new etiological species has been described causing verruga peruana, *Bartonella ancashi* [17<sup>■</sup>]. The bacteria is transmitted by the biting of sandflies of the genus *Lutzomyia* [17<sup>■</sup>,18,19<sup>■</sup>].

Classically, two phases are described: the acute hematic phase known as Oroya fever and the chronic eruptive phase known as verruga peruana [17<sup>■</sup>,18,19<sup>■</sup>,20]. The acute hematic phase is characterized by fever and hemolytic anemia, having as cutaneous manifestations pallor and jaundice. It is

followed by the chronic eruptive phase in 5% of treated individuals [20,21<sup>■</sup>].

The chronic eruptive phase is the most common clinical presentation in endemic areas, affecting mainly children and teenagers [20,21<sup>■</sup>,22,23]. Commonly the eruptive phase adopts three patterns, which can be found combined in one patient [22,23]: the miliary form, consisting of small papules less than 3 mm diameter that are globular, bright red, sometimes itchy and often numerous; the mular form, composed of nodular tumors with a diameter greater than 5 mm that are erythematous, often sessile and eroded; and the nodular or subdermal form, consisting of deep nodules, with normal skin color without altering the skin's surface [21<sup>■</sup>,24]. These lesions usually contain serosanguinous fluid, which exudes on contact, are generally multiple and are localized to the upper and lower limbs and face [19<sup>■</sup>,20,21<sup>■</sup>]; however, compromise of the mucous membranes is considered to occur in around 4% [25], with reported cases of oral mucosa, conjunctiva and eyelids involvement [26,27].

Frequently, a combination of the different patterns can be found in a single patient [22,23]. Recurrence of these lesions has also been described. These can occur for up to 4 years, presenting with a mild miliar pattern (usually with <10 active lesions), moderate miliar pattern (with up to 100 active lesions) or severe miliar pattern (>100 active lesions) [23].

Patients from northern Peru are at higher risk, given their high incidences that have been reported in the last 2 years [28]. At Ancash, the new etiological agent *B. ancashi* was described [17<sup>■</sup>], although most cases are due to *B. bacilliformis* in confirmed studies [29–31]. New emerging contexts of these ABDs that can affect the skin emphasize the need for reestablishment of prevention policies [17<sup>■</sup>]. However, studies in other countries such as Colombia and Ecuador are required to better define the importance of disease in this region [22,32].

## ONCHOCERCIASIS

Onchocerciasis (river blindness), is a disease caused by the filarial nematode *Onchocerca volvulus*, transmitted by species of the genus *Simulium* [33<sup>■</sup>]. This involves skin and eyes, being the second leading cause of infectious blindness in the world, mainly affecting Africa and some Latin American countries which traditionally has included Brazil, Ecuador, Guatemala, Venezuela, Mexico and Colombia (being declared eradicated there in 2013) [34<sup>■</sup>]. In Ecuador, Guatemala and Mexico, transmission also was interrupted [33<sup>■</sup>].

Skin manifestations can range from very mild to severe complex alterations with significant aesthetic

and functional sequelae [35,36]. The severity of these lesions will depend on the parasite inoculum, the strain, the exposure time, the time evolution of the lesion and the host immune response. Thus, the first clinical manifestations are associated with the appearance of an itchy rash, which can occur with or without edema [35,36]. The natural evolution of skin lesions has been described in four phases, which are: an acute popular onchodermatitis phase; followed by the appearance of onchocercomas, subcutaneous nodules within which are encapsulated adult worms and whose size may reach 10 cm, configuring the second phase, chronic popular onchodermatitis; followed by the third phase, lichenified onchodermatitis; and finally atrophy and depigmentation, phases in which the skin condition is severe enough to produce atrophy, wrinkling and skin depigmentation, conferring the affected individual with an older appearance [35–37].

## DENGUE

Dengue fever is another ABD, caused by a flavivirus, Dengue virus, with five types, DENV-1, DENV-2, DENV-3, DENV-4 and a recently described DENV-5 (Valisakis N, unpublished data), transmitted in humans by the bite of the *Aedes aegypti* mosquito, with reemergence and geographical expansion because of climate change and migration [38,39]. It is considered an important public health problem, being endemic in over 100 countries [39], especially in the tropical and subtropical areas of the world [40<sup>■</sup>]. In Latin America, dengue is an endemic disease in all the countries except for Uruguay. Higher number of cases are reported in Brazil (South Cone) and Colombia (Andean region) [41]. The vector is usually found in the domestic environment, near to humans, and is closely related to contaminated water storage [41,42].

Although it is frequently self-limiting, it can have a wide spectrum of clinical manifestations including some cutaneous ones [39,42,43]. Classically, there are three known stages of the disease: febrile phase, nonfebrile phase and critical phase. Depending on the phase, different cutaneous manifestations appear in the patients [43,44]. It has been reported that 80% of the patients at the febrile phase will have skin manifestations. In this phase, patients develop a centrifugal maculopapular eruption in the majority of cases, but it can also develop a scarlatini-form or petechial eruption that starts in the dorsum of the hands and spreads to arms, legs and torso. This eruption becomes confluent but preserves zones of the skin, which are usually known as 'white islands in a red sea' [44,45]. Dengue hemorrhagic fever can present with usual manifestations, such as

epistaxis, petechiae, purpura and ecchymosis [44–46].

It is important to emphasize that dengue fever has important cutaneous manifestations that could help healthcare personnel to make an early diagnosis and an appropriate approach to the patient.

## YELLOW FEVER

Yellow fever, so named because of the jaundice seen in affected patients [47], is caused by the yellow fever virus, which is transmitted by several different species of mosquitoes of the genera *Aedes* and *Haemagogus* [47,48]. It is geographically distributed in most of the north and central areas of Africa, nine South American countries and several Caribbean islands [47]. Approximately 80% of the infections are symptomatic, with a 20–70% fatality rate among patients developing severe disease [47,48].

Classically, three periods have been defined: an initial period, which is indistinguishable from other tropical diseases, characterized by fever, muscle pain, headache and vomiting; the remission period; and the intoxication period, wherein cutaneous manifestations generally take place [48,49]. Approximately 15–25% of the individuals progress to the intoxication period presenting with fever, nausea, kidney and liver impairment. Typically, the main cutaneous manifestation of yellow fever is jaundice [49,50]; it usually appears at the fourth day of evolution, being more evident on palms, forearms and chest [47]; however, hemorrhagic lesions such as petechiae, purpura, epistaxis, gingival hemorrhage have also been described [48,50,51]. Facial erythema, conjunctival congestion and dotted hemorrhages in the soft palate are also seen [47,52]. Disease progression can be fatal and it has been stated that cutaneous manifestations could serve as markers of severe disease and high risk of mortality [52].

## CHAGAS DISEASE

Chagas disease (American trypanosomiasis) is an infection caused by the protozoan *Trypanosoma cruzi* and mainly transmitted by species of the Reduviid genera *Triatoma* and *Rhodnius*, among others, but recently also has particularly emerged as a food-borne disease [53,54], being endemic in 17 countries of Latin America [53–55]. Given the increasing global travel and large-scale migration to North America, Europe, Australia and Japan, Chagas disease has become of global concern [55]. Clinical manifestations in this disease are related to their phases: acute, indeterminate or unapparent, and chronic. In immunocompromised individuals,

reactivation can also occur [53,55,56]. Cutaneous manifestations may be present both in the acute phase and during recrudescence of the infection [56,57<sup>■</sup>]. Clinically, cutaneous Chagas disease may produce indurated erythematous plaques with necrosis, erythematous papules and nodules, panniculitis or skin ulcerations [56,57<sup>■</sup>,58].

During the acute phase, several dermatological manifestations may occur, such as the chagoma (red, indurated swelling at the site of inoculation) and the Romaña's sign (the triad of conjunctivitis, periorbital edema and preauricular lymphadenopathy appearing after conjunctival inoculation). A diffuse morbilliform eruption in the weeks after acute inoculation can also occur [53,54,56,57<sup>■</sup>, 58–61].

## MALARIA

Malaria is the leading cause of morbidity among the parasitic ABDs in the world. Five species of the genus *Plasmodium* (*P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P. knowlesi*) can cause human disease [62]. Only *P. falciparum*, *P. vivax* and *P. malariae* are present in humans in Latin America. The parasite is transmitted through the bites of infected *Anopheles* mosquitoes [63]. It occurs in tropical areas and is still considered a serious global health problem, particularly in children and pregnant women [64,65]. In endemic regions, it can present with unusual features, including cutaneous manifestations, because of development of immunity, increasing resistance to antimalarial drugs and the indiscriminate use of antimalarial drugs (such as chloroquine) [66–69].

Skin lesions in malaria are rarely reported but can include urticaria, erythema, angioedema, petechiae, purpura, rash in jaundice and gangrene [66–69]. Cutaneous lesions have been described both in *P. falciparum* and in *P. vivax* malaria [66–69].

## CONCLUSION

Arthropods can be the cause of direct involvement of the skin (e.g. dermatitis) [70,71], as well being vectors of skin or localized and systemic infections [72<sup>■</sup>]. Although prevention strategies for ABDs have been implemented, it still remains an important global health problem as climate change and migration tend to increase and expand [73]. Especially in Latin America, where the geographical and social conditions are prone, ABD also becomes a reemerging disease [74<sup>■</sup>].

Cutaneous manifestations of ABD are varied and nonspecific; some of them are markers of severe disease and mortality [75]. So, when considering a

patient with skin lesions, epidemiological features [76,77,78<sup>\*\*\*</sup>] and other clinical and laboratory findings must be taken into account in order to make an appropriate approach to diagnosis, treatment and control, whereby morbidity and mortality can be reduced and mitigated [79,80<sup>\*\*\*</sup>,81<sup>\*\*\*</sup>,82].

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## Conflicts of interest

There are no conflicts of interest.

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