Local Reactions to Tick Bites

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Abstract: A retrospective histological and immunohistochemical study has been carried out in 25 cases of tick bites recorded in our Departments. The samples that included an attached tick showed a cement cone anchoring the mouthparts to the skin and a blood-soaked, spongiform appearance of the superficial dermis, with a mild neutrophilic and eosinophilic infiltration. The vessels displayed a loose multilayered endothelial proliferation, with plump endothelia, permeated with erythrocytes. A few of them were severed, allowing copious blood extravasation. The established lesions included the following: erythema chronicum migrans–like cases, foreign body granulomas—sometimes containing remnants of the mouthparts—cutaneous lymphoid hyperplasia, either of the T-cell or the B-cell type, and tick-bite alopecia. In both the T-cell and B-cell pseudolymphomas, several vessels showed concentric endothelial and perithelial proliferation similar to that seen in the acute lesions. In the tick-bite alopecia, a lymphocytic infiltrate attacked the permanent portion of the hair follicles, whose reaction was a noticeable hyperplasia of the fibrous sheaths, although only a minority of the hairs was destroyed. The observed alterations are specific in the acute lesions and in the alopecia, where they directly arise as a result of the interactions between the host's tissues and the antihemostatic, anti-inflammatory, and immunomodulatory chemicals contained in the tick saliva. In the other lesions, the changes seem less characteristic, although the fragments of mouthparts and the special vascular changes provide a clue to their etiology.

Key Words: histology, local reactions, tick attacks

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INTRODUCTION

Local reactions to tick bites display a variety of histologic pictures, which are mostly considered nonspecific, that is, not different from those induced by other arthropod bites, or stings, or by a number of different traumatic events.[1] Therefore, the changes arising in the skin as a consequence of the feeding process of these blood-sucking mites are hardly quoted in the dermatologic literature,[2–4] although they represent an interesting example of interaction between the parasite and the host organism tissues. The acute and chronic reactions to bites from ixodid ticks (hard ticks) have been studied by us in a series of cases observed in our Departments, and have been related to the peculiar anatomy, biochemistry, and physiology of the tick-sucking apparatus.

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Figures 2–5 can be viewed in color online at http://www.amjdermatopathology.com.

MATERIALS AND METHODS

A retrospective histologic study on 27 tick-bite–induced lesions in a series of 25 patients bitten by ixodid ticks has been carried out (Table 1). All the cases selected for this purpose had a reliable anamnesis in regard to the origin of the lesions, and in some of them, the ticks had been extracted by the patients and shown to us. In 5 cases, the ticks had been still attached at the moment of the physical examination.

The lesions had all been documented through clinical and in vivo stereomicroscopic photographs and routine histologic sections. In the cases in which an attached tick had been found, its genus had been identified through reflection microscopy, based on the few details accessible without extracting the parasites, that is, the characteristics of the scutum, the presence of eyes, and the length of the pedipalps. Afterward, the tick had been included in the histologic sample, processed, and cut together with the parasitized skin, so as to achieve sagittal and parasagittal sections of its body.

New sections were cut from all the histologic specimens, and stained with hematoxylin–eosin, Pinkus' acid orcein–Giemsa for elastic fibers, periodic acid-Schiff for polysaccharides, Weigert method for fibrin, and Warthin–Starry stain for spirochetes. In addition, immunohistochemical stains were performed employing a standard avidin–streptavidin–peroxidase complex method and using the following antibodies: 4KB5 (anti-CD45RA) and CD10 for B lymphocytes, UCHL1 (anti-CD45RO) for T lymphocytes, anti-CD4 and CD8 for helper and suppressor/cytotoxic lymphocytes, anti-CD68 for macrophages, and Bcl-2 as a marker of transformed follicular center B cells.

RESULTS

Clinical Manifestations

In the cases in which the tick was still attached, the clinical changes ranged from hardly detectable inflammation to wide, brightly red erythematous and hemorrhagic patches, with irregular contours, gradually fading toward the normal skin. The ticks belonged to the genera: *Rhipicephalus*, *Hyalomma*, and *Dermacentor*, the latter parasitizing the scalp. In the other cases, the lesions had arisen either before or after the removal of the parasite, with a latent period ranging from a few days to a few months, and had progressively and chronically developed for weeks or months until the clinical observation. They comprised the following: erythematous

TABLE 1. Lesions Included in This Study

	Gender	Age	Clinical Features	Site	Histologic Features
1	♂	72	Nodule	Axilla	B-cell pseudolymphoma with foreign body granulomatous foci
2	♀	59	Erythema chronicum migrans–like patch	Thigh	Perivascular lymphocytic infiltrate
3	♂	47	Two papulonodular lesions	Perineum	Persistent arthropod-bite reaction (T-cell pseudolymphoma)
4	♂	40	Oozing erythematous plaque	Arm	Persistent arthropod-bite reaction (T-cell pseudolymphoma) with epidermal necrosis and erosion
5	♂	35	Erythema chronicum migrans–like patch	Right leg	Perivascular lymphocytic infiltrate
6	♂	71	Erythema chronicum migrans–like patch	Thigh	Perivascular lymphocytic infiltrate
7	♀	42	Nodulo-pustular lesion for 2 months	Flank	Foreign body granuloma with central abscess
8	♂	68	Nodule for 20 days	Left leg	Persistent arthropod-bite reaction (T-cell pseudolymphoma)
9	♂	71	Nodule for 3 years	Penis	Dense perivascular lymphocyte infiltrate
10	♂	50	Nodule for 4 months	Flank	Dense perivascular lymphocytic infiltrate with eosinophils
11	♀	76	Nodule	Labium majus	Persistent arthropod-bite reaction (T-cell pseudolymphoma)
12	♂	17	Two nodules	Iliac region, groin	Persistent arthropod-bite reaction (T-cell pseudolymphoma)
13	♀	8	Attached tick (*Dermacentor*) for 24 h, erythematous area	Scalp	Tick body, cement cone with embedded mouthparts, spongiform and blood-flooded dermis, and cribriform vessels, mainly neutrophilic infiltrate around the vessels, the cone, and the hair follicles
14	♂	10	Alopecic nodule	Scalp	B-cell pseudolymphoma
15	♂	6	Alopecic deep nodule	Scalp	Foreign body granuloma
16	♀	32	Attached tick (*Hyalomma*) for a few hours, slight erythema	Thigh	Tick body, cement cone with embedded mouthparts, small fluid-filled spaces, mild edema, and slight perivascular lymphocytic infiltrate
17	♂	58	Two ulcerated nodules	Lumbar region	Foreign body granuloma with epidermal necrosis and ulceration
18	♀	59	Nodule	Thigh	Persistent arthropod-bite reaction (T-cell pseudolymphoma)
19	♂	82a	Nodule for 4 months	Areola	B-cell pseudolymphoma
20	♀	40	Attached tick (*Rhipicephalus*) for 2 days, erythematous hemorrhagic plaque	Arm	Tick body, cement cone with embedded mouthparts, spongiform and blood-flooded dermis, and cribriform vessels, mainly neutrophilic infiltrate around the cone and the vessels
21	♀	38	Nodule	Lateral aspect of the neck	Persistent arthropod-bite reaction (T-cell pseudolymphoma)
22	♂	12	Tick-bite alopecia	Scalp	Perifollicular lymphocytic infiltrate; gradual thinning of the hairs, up to complete loss, toward the center of the lesion; lymphocytic infiltrate around the isthmus
23	♂	61	Nodule	Right groin	Persistent arthropod-bite reaction (T-cell pseudolymphoma)
24	♂	75	Attached tick (*Rhipicephalus*) for a few hours, small slightly erythematous patch	Left axilla	Tick body, cement cone with embedded mouthparts and lymphocytic and neutrophilic infiltrate around the vessels and the cone
25	♂	36	Attached tick (*Hyalomma*) for 2 h, no obvious clinical changes	Navel	Tick body, cement cone with embedded mouthparts, mild perivascular lymphocytic infiltrate

nodular and nodulo-pustular lesions, erythematous erosive and oozing plaques, and erythema chronicum migrans–like patches in otherwise healthy subjects. The localization at the scalp included 2 nodules associated with inflammatory alopecia and a case of alopecia areata–like reaction (Fig. 1). The latter had occurred in a child a week after the extraction of the tick and had lasted one month before the lesion was excised. It was characterized by a roundish patch of non-scarring alopecia with slight central erythema and scaling and exclamation mark hairs on the periphery. Two photographically documented cases with an attached tick belonging to the genus *Ixodes* and a case overlapping the tick-borne lymphadenopathy syndrome (an ulcerated crusted nodule at the occipital region with retroauricular lymphadenopathy, and fever in an 8-year-old child) lacked histology and were excluded from this study.

Histologic Study

Acute Lesions

In the samples that included an attached tick (Fig. 2), the parasite mouthparts were entrenched in a hollow cone of cement, located inside the epidermis and firmly adhering to it. In the center, the cone expanded vertically, crossing the epidermis and encroaching on the dermis, where it diffused with an irregular subepidermal spray of cement. On the periphery, it spread superficially, dissecting the epidermis between the prickle and the horny layer, and progressively thinning out.

The sectioned mouthparts visible in the slides comprised one of the chelicerae and the hypostome, which, embedded in the cone, lined the dorsal and the ventral aspect of the oral canal, respectively. They hardly exceeded the thickness of the epidermis in the case of *Rhipicephalus* and *Dermacentor*, whereas, still invested by the cement, they fully reached the dermis in the *Hyalomma* genus. The partly embedded basis capituli contained the pharynx with its antireflux valves and the hypopharynx with its muscles and, dorsally, the muscle bundles serving the chelicerae.

Below the mouthparts, the cone canal widened into a funnel-shaped cavity, which opened into the underlying dermis. Here, in the biopsies taken after only few hours of parasitic activity, the changes consisted only of slight dilatation of the superficial vessels, some of which were invested by a mild perivascular lymphocytic or lymphocytic and neutrophilic infiltrate. In one case, a few, small, and barely visible, fluid-filled spaces, identifiable as collections of tick saliva, were detected.

In contrast, in the later biopsies (Figs. 2, 3), the changes were remarkably more apparent, the superficial dermis beneath the cone being permeated by a rough network of cement and occupied by a dense crowding of neutrophils, which also streamed along the cone's inner canal. More deeply, the infiltrate fragmented into a number of perivascular foci, whose cells, neutrophils, and lymphocytes heavily colonized the walls and the lumina of small arteries and veins, to such an extent that they were sometimes obliterated.

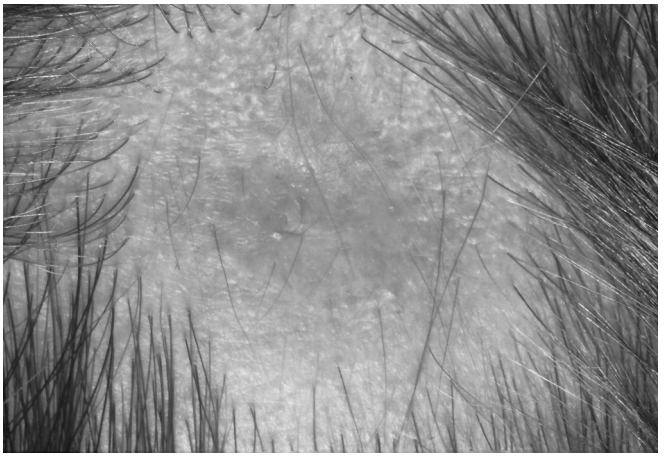

FIGURE 1. Tick-bite alopecia (case 22) with slight central erythema and scaling and exclamation mark hairs.

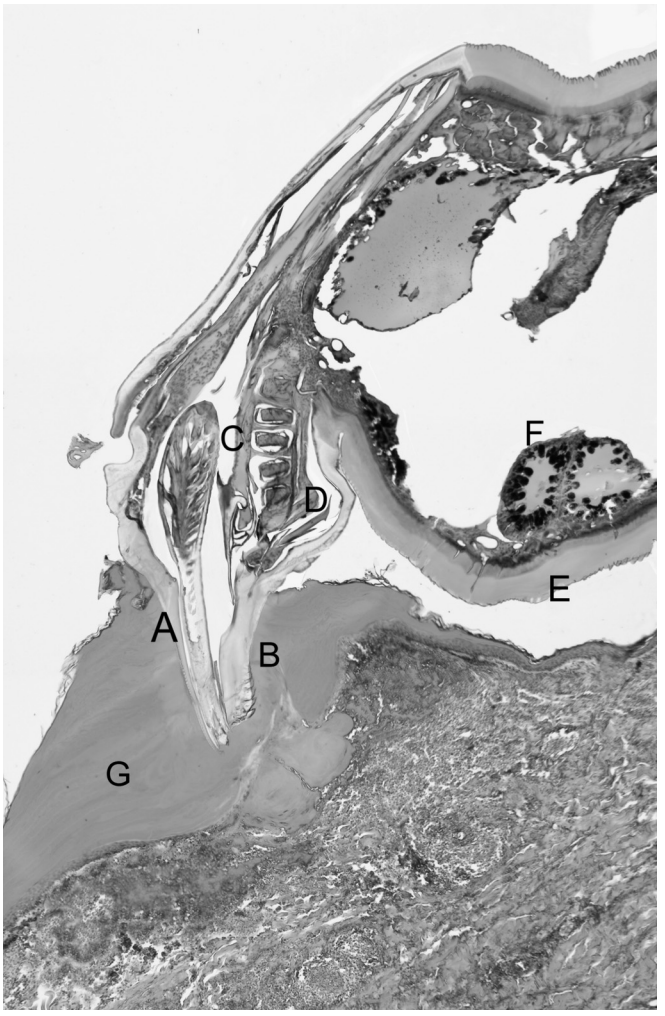

FIGURE 2. Histologic preparation of a tick bite (*Rhipicephalus*, case 20), including the lesion and the attached parasite. A, Chelicera. B, Hypostome. C, Pharynx with antireflux valve. D, Hypopharynx muscles. E, Finely folded cuticle F, Midgut. G, Cement cone expanding both vertically, across the epidermis, and horizontally, between the prickle and the horny layer of the epidermis.

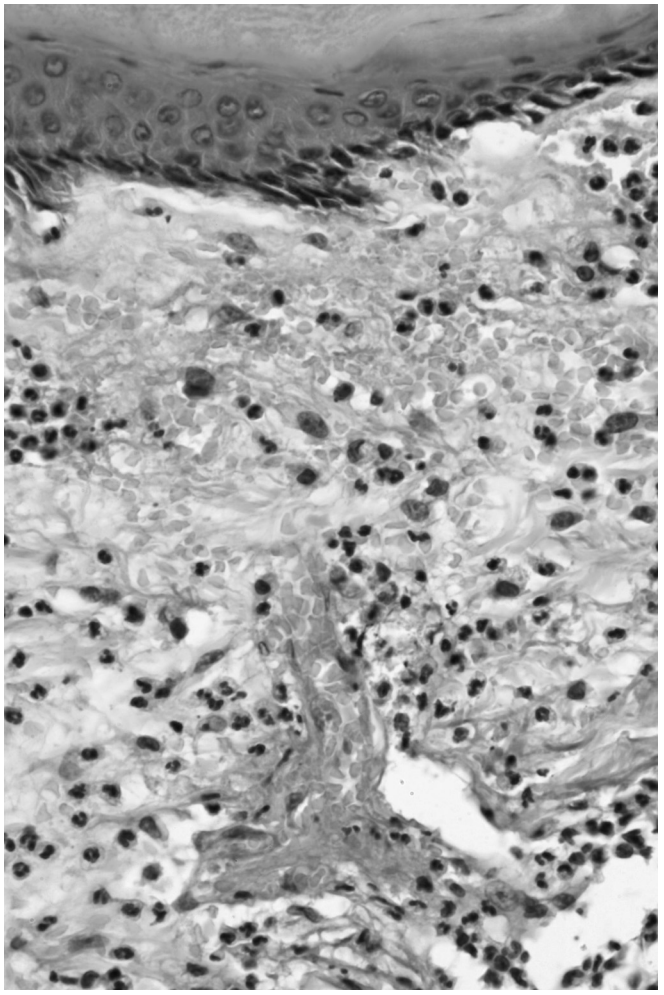

FIGURE 3. Spongiform network of fibrin filaments, collagen fibers, and endothelia replacing the normal weave of the collagen bundles. The tissue is soaked with blood and obscured by erythrocytes. A severed capillary vessel allows erythrocyte extravasation in the tissue. a+

Beneath the most peripheral portion of the cone (Fig. 3), where this was reduced to a thin subcorneal layer of cement, the infiltrate was sparse, revealing the noticeable alterations present in the superficial and mid dermis. Here, the normal architecture of the tissue was replaced by a disorganized network of slightly basophilic fibrin filaments, endothelial linings, and residual collagen bundles, soaked with blood and obscured by the erythrocytes. The small vessels were dilated and their walls were discontinued, with blood seeping through into the connective tissue. A few vessels were truncated, allowing profuse blood extravasation (Fig. 3). Moreover, several capillaries and postcapillary venules showed endothelial plumping and proliferation, giving shape to a vaguely spiral pattern with cribriform appearance of their lumina. In other vessels, the endothelial proliferation was associated to acute vasculitis and formed multiple concentric and interconnected layers with a sieve-like structure, smudged with fibrin and laden with erythrocytes, neutrophils, and eosinophils. The inflammation cells were also visible in the lumina and in the surrounding tissue.

Subacute Lesions

The alopecia areata–like patch, observed in vertical sections, showed a wide stretch of skin virtually devoid of adnexa, outlined at its lateral extremities by 2 symmetrical bands with altered hair follicles and inflammation. Considering the specimen on a 3-dimensional perspective, it consisted of a central, almost deserted area encircled by an outer ring, where the hair follicles were present, although altered and attacked by an inflammatory infiltrate (Fig. 4). In the central area, diffuse edema widened the interfascicular spaces of the connective tissue, extensive stretches of the dermis being changed into a loose, delicate network of weakly eosinophilic fibers, scattered with numerous newly formed capillaries. The tissue was sprinkled with a lymphocytic infiltrate interspersed among the thin and pale collagen fibers and was dotted with a few catagen hairs with hyperplasic perifollicular sheaths and follicular streamers, around which the infiltrate huddled, forming thick collections.

Rare remnants of hair follicles and naked hairs, surrounded by foreign body multinucleated giant cells, were visible in the mid dermis, along with a few isolated arrector pili muscles and vertical fibrous streaks. Around these residual structures, limited and focal areas of fibrosis were seen. In this central area, the elastic fibers were sparse, fragmented, and focally tangled, being totally absent only in the foci of concentric perifollicular fibroplasia (Fig. 5) and in the few and small areas of granulomatous inflammation and postinflammatory scarring.

In the two peripheral bands, the hair follicles were remarkably thinned and miniaturized, and there were an increased number of catagen and telogen figures. A few of the miniaturized hairs were ostensible in a mature anagen phase, thus fashioning "nanogen" figures, similar to those typical of alopecia areata (Fig. 6). The follicles were surrounded by a dense lymphocytic infiltrate, gathered at the height of their isthmus. However, their outer epithelial sheaths were not affected by the infiltrate, from which they were separated by noticeably thickened, multilayered, and richly cellular fibrous sheaths. The lymphocytes were mostly of the T-helper type, with a moderate admixture of B lymphocytes and some plasma cells.

More peripherally, at the boundary with the unaffected skin, the dense foci of lymphocytic infiltrate surrounded the isthmus of dimensionally unaltered hairs, which, nevertheless, showed the above-described hyperplasia of their perifollicular sheaths.

Chronic Lesions

Three specimens showed a granulomatous infiltrate, composed of epithelioid and multinucleated giant cells, with lymphocytes, monocytes, and a few plasma cells. Some giant cells contained birefractive amorphous debris, likely identifiable as residual cement, and in one case, they were phagocytizing a pair of structured shafts (Fig. 7), recognizable as fragments of the tick mouthparts. The adnexa were destroyed by the infiltrate accounting for the scarring alopecia

FIGURE 4. Panoramic view of tick-bite alopecia observed in a vertical section: Centrally, a large area virtually devoid of adnexa, with edema and a scattered lymphocytic infiltrate that thickens around the adnexal remnants; on one side, 1 of the 2 bands of skin with lymphocytic inflammation and thinned hair follicles. a+

of the scalp observed in case 15. In one case, a dense collection of neutrophils and eosinophils was present, the context of a foreign body granulomatous infiltrate.

In the remaining nodules, a massive, top-heavy infiltrate involved the whole dermis, reaching sometimes the subcutaneous fat, so as to fashion the picture of pseudolymphoma from persistent arthropod-bite reaction. In most cases, the infiltrate was composed of lymphocytes, predominantly of the T-type, histiocytes, and varying admixtures of plasma cells and eosinophils. Similarly to the less mature lesions, in several capillaries and venules, there was loss of cohesion of the endothelial walls, endothelial plumping, and proliferation with multilocular appearance of the lumina and fibrin thrombi.

In 3 cases, the infiltrate gave shape to pseudolymphoid follicles, with germinative centers and well-developed mantles, typical of B-cell cutaneous lymphoid hyperplasia (Fig. 8). The germinative centers comprised of CD10+, CD45RA+, Bcl-2 centrocytes and centroblasts, with cells in different phases of modulation, and a complement of CD68-positive tingible body macrophages. There were several mitotic figures and a great number of eosinophils were present among the lymphocytes of the mantle and between the follicles. In one case, the pseudolymphoma was adjoined by a thriving granulomatous component, with huge multinucleated giant cells and numerous eosinophils. In the older lesions, there was conspicuous fibroplasia with thickening and homogenization of

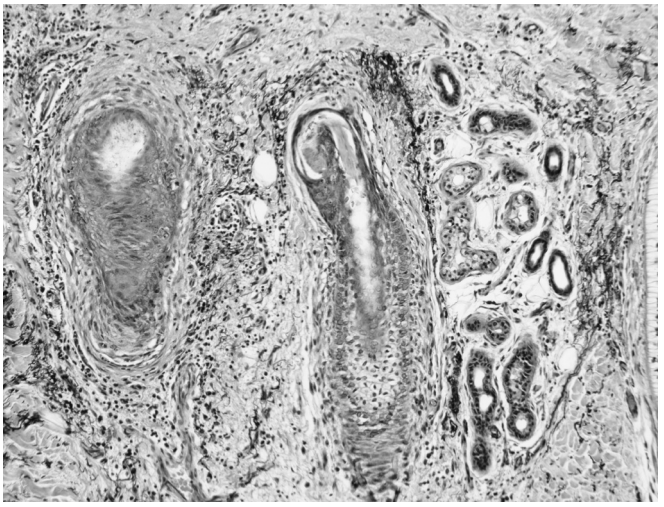

FIGURE 5. Remarkable hyperplasia of the fibrous sheaths of the hairs. Fragmentation and homogenization of the elastic fibers in the edematous tissue surrounding the hair follicles. (Pinkus' orcein–giemsa for elastic fibers). a+

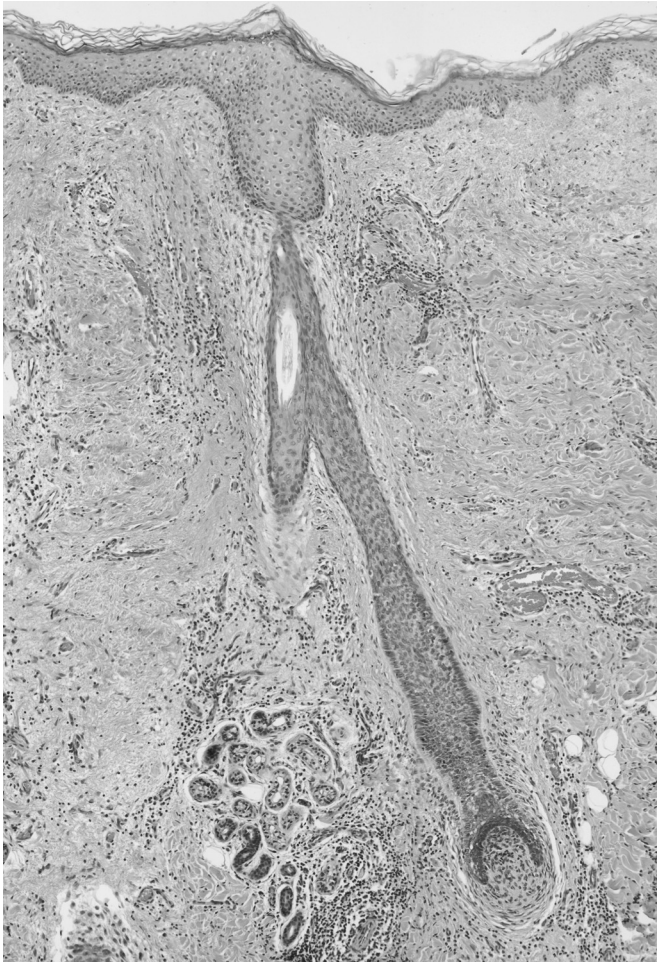

FIGURE 6. Tick-bite alopecia, detail of Figure 8: Simultaneous presence of a telogen and a nanogen figure in the same hair follicle, which also shows a multilayered perifollicular sheath.

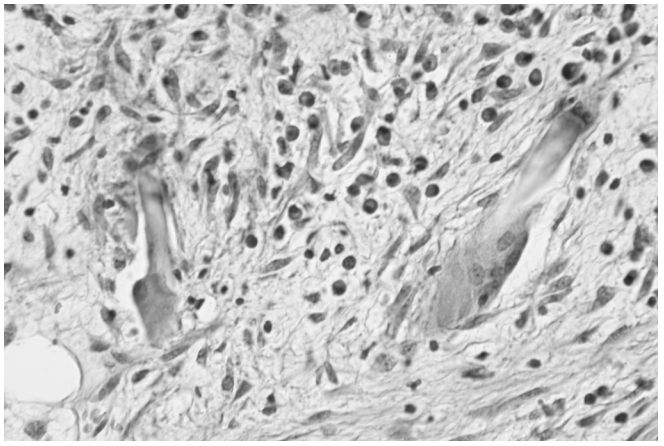

FIGURE 7. Tick-bite–induced foreign body granuloma of the scalp (case 15). Detail of an edematous area, showing 2 shafts in pair, recognizable as fragments of the chelicerae, phagocytized by 2 multinucleated giant cells.

the collagen bundles and concentric perivascular arrangement of fibrocytes and collagen layers.

In the erythema chronicum migrans–like patches, slight edema and a mild, T-and B-lymphocytic or lymphoplasmocytic, perivascular infiltrate were observed in the superficial and mid dermis. Neither in the erythema chronicum migrans–like lesions nor in the B-cell pseudolymphomas did the Warthin–Starry method reveal spirochetes, nor were serum antibodies against *Borrelia burgdorferi* detectable in the serum, through enzyme-linked immunosorbent assay.

DISCUSSION

Ticks are hematophagous Acari forming the suborder Ixodidae, which comprises 2 families of dermatologic interest: Argasidae or soft ticks, occasionally responsible for nodulo-hemorrhagic local lesions and anaphylactic shock in humans, and Ixodidae (ixodids or hard ticks), whose bites and bite-induced local reactions in the human skin are the topic of the present article.

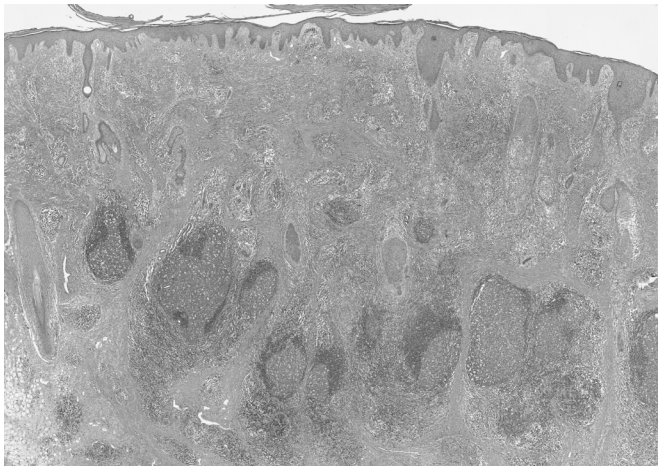

FIGURE 8. B-cell cutaneous lymphoid hyperplasia: a number of pseudolymphoid follicles with germinative centers and well-developed mantles.

The unique mode of biting and sucking blood of these mites is accomplished by the gnathosoma (capitulum), which forms the anterior section of their body.[5,6] This consists of a mobile basis capituli, articulated with the body and bearing the other components: a pair of segmented pedipalps, representing chemical and tactile sensory appendages, and the mouthparts, which are sheltered between the pedipalps and comprise a dorsal pair of slender chelicerae and the hypostome, located ventrally. The chelicerae are coated by spinous sheaths and end with laterally mobile, 2-digit pincers (chelae) with sharp denticles; the hypostome is grooved by a narrow food canal on its mid dorsal surface and has rows of recurved teeth on its ventral surface.

After assisting the tick in the selection of a suitable cutaneous district, the palps are stretched apart, whereas the chelicerae cut the skin and stick into the wound along with the hypostome. The breach is then sealed with abundant cement secretion, which—molded into the typical cone—secures the parasite at the wound site and allows its sucking apparatus to work as a vacuum pump.[7,8] The cone shields the mouthparts from the host's immune response, and completing the channel formed by the mouthparts, directs the saliva into the underlying dermis protecting the tissues lateral to them from digestion, which would weaken the attachment.[8]

A feature that clearly stands out in our study and in the parasitologists' observations[7–13] is that the tick stocky cutting/sucking device is not designed to fit into the tiny vessels of the skin. Instead, supported by the cone, it remains confined to the superficial dermis or just to the epidermis, whose thickness is properly enhanced by the cement infiltration. It is from here that it operates, drawing fluids and blood cells spilled from the ruptured vessels or seeping through their walls. The necessary vacuum is achieved through the combined action of pharynx dilator muscles and antireflux valves, whose functions can be inferred from our histologic images, in which these structures are caught in full operation. The depth of penetration of the mouthparts, the amount of the cement, and the shape and completeness of the cone depend on the species of the involved tick. The species with an incomplete cone (such as—for example—*Ixodes ricinus* and *Ixodes holocyclus*) supply inadequate lateral protection to the site of attachment, thus inducing more severely exudative lesions.[8,10,11,13] (*I. ricinus* is a European tick, which in Sicily is found in winter and over the height of 500 m above sea level.[14,15])

This mechanical activity is supported by the biological action of several chemicals contained in the regurgitated saliva,[16–28] including vaso dilators, anticoagulants, immunosuppressants and anti-inflammatory molecules, and hyaluronidases and metalloproteinases which account for the disappearance of the normal dermal framework and the cavity formation.

The skin changes, as seen in the experimental animal, develop in different phases.[7,9–13] In the first few hours, they comprise superficial capillary ectasia with perivascular hemorrhage and clear spaces filled with regurgitate immediately below the mouthparts. Later on, the alterations extend

toward the depth, whereas the vessels are obliterated by massive leukocytic and erythrocytic infiltration. At this time, a large diamond-shaped cavity, replete with blood cells streaming from the damaged vessels, forms in the dermis. This also contains secondarily secreted cement and is surrounded by a wide band of infiltrate composed of leukocytes and eosinophils. In the rapid final phase, followed by the detachment, the content of the cavity is rapidly sucked up leaving a fluid-filled space with few leukocytes and erythrocytes.

The alterations observed in our random samples of human skin overlap the initial and the intermediate phases of the parasitologists' experimental observations, although the pools of regurgitate, a quite specific and early feature in cattle, are barely detectable in only one of our cases. Instead, the true remarkable features of our study become visible later, at the time of the well-established attachment and cavity formation. They consist in the replacement of the normal fabric of the dermis with a blood-flooded spongiform tissue, in the severed or leaky-walled vessels, in the multistratification of the endothelial, and in the cribriform pattern of the capillaries and postcapillary venules, sometimes associated to severe hemorrhagic neutrophilic vasculitis. The latter looks quite different from the tick-bite–induced local leukocytoclastic vasculitis; marked by nuclear dust, necrosis, and fibrin deposits; which has been reported by other authors and is ascribed to Arthus reaction.[3,7,29]

Finally, it is only in this phase that the appearance of the eosinophilic component of the infiltrate—a common clue to parasitic attacks—is noticed, both in the human and in the animal hosts, thus representing a relatively late finding of the acute lesions.[7,12] The whole picture, to our knowledge, does not appear in other types of arthropod-bite reactions and can therefore be considered characteristic.

A recently reported trait, which does not figure in our specimens, consists in the presence of local cryoglobulin-like thrombi in the capillary and postcapillary venules of the dermis, whether or not associated with signs of leukocytoclastic vasculitis, so as to mimic the monoclonal and the mixed type of cryoglobulinemia, respectively.[29,30]

These homogeneously textured thrombi can be observed together with typical fibrin thrombi, of which they have been hypothesized to represent the final stage of a progressive conversion,[29] thus suggesting a mere local coagulative overreaction to the injury.[29]

The alopecia that sometimes accompanies or follows a tick bite of the scalp is a self-healing hair loss considered analogous to alopecia areata, to which it is clinically similar.[4,31–33] It is believed to be caused by some epilating anticoagulants injected with the saliva,[31] and it is not the only example in nature of arthropod-bite alopecia because a comparable event may be induced by the attack of some species of ants or by bee stings.[34]

As in alopecia areata, it shows a centrifugal spread, histologically evidenced by the presence of a central zone of fully established changes, and an active peripheral advancing edge. Here, the earliest alterations of the process are visible, and the behavior of the infiltrate clearly reveals the differences between this form and alopecia areata. In fact, in tick-bite alopecia, the target of the inflammation is the isthmus of the hair follicles rather than the bulb, and the main reaction of the tissue is represented by remarkable hyperplasia of the fibrous sheaths of the hairs. However, the number of the catagen and telogen follicles is increased as in alopecia areata, and a few nanogen hairs, which are typical of this form and are considered the result of multiple accelerated and interrupted cycles of hair regeneration,[35,36] are present. It results from our study that only few of the hair follicles are definitively destroyed, whereas most of them seem to undergo transient, nonscarring alterations, similar, although not identical to alopecia areata. This accounts for the regrowth of the hair observed by other authors,[31,32] a feature which could not be observed by us because of the total excision of the lesion.

The granulomatous infiltrates from tick bites do not bear per se specific traits. However, the finding of residual fragments in pairs, indicative of symmetrical structures, such as the chelicerae or their 2-digit terminal chelae, represents a clue to the identity of the parasite. These granulomas are of a mixed foreign body and immune type, being directed to both the inert and the strongly immunogenic, collagen-like proteins of the cement and/or to the viable core and the sclerotized cuticle of the mouthparts.[19–21]

In accordance with the general experience, the persistent nodular arthropod-bite reactions observed by us take on the form of either the predominantly T-cell or the B-cell cutaneous lymphoid hyperplasia,[37] the B form being considerably less represented than the T one. Although these reactions do not show distinguishing features in comparison to pseudolymphomas of other origin, they display vascular alterations significantly similar to those seen in the presence of an attached tick, whereas in the older lesions, the mentioned multistratification of the endothelial linings is replaced by multiple concentric layers of fibrosis. Moreover, the presence of copious eosinophils points to the parasitic grounds of the alterations. A frequent finding in this form is the association with a borrelial infection, which, however, was neither detected in our patients with pseudolymphoma nor was in our cases of erythema chronicum migrans–like patches.

A major challenge in the differential diagnosis of B-cell cutaneous lymphoid hyperplasia is to distinguish it from the cutaneous follicle center lymphoma with a follicular pattern and from the marginal zone lymphoma.[37–39] In our cases, the top-heavy pattern, the discreteness of the infiltrative foci, the well-developed mantles, the presence of centrocytes and centroblasts in different phases of modulation, the numerous tingible body macrophages, and the number of mitotic figures confined to the germinative centers are all signs that point to simple phlogistic activation.[39] Furthermore, the absence of a "reverse pattern" with centrocytic-like neoplastic cells peripheral to reactive foci of small lymphocytes allows the differentiation from the marginal zone lymphoma. The negativity to Bcl-2 found in our cases is of little significance for ruling out the malignancy because the t(14–18) translocation-associated overexpression of this protein is not usually present in the follicle center lymphoma of the skin, as it is, instead, in the nodal form.[37]

It should be stressed that a precise separation between B-cell pseudolymphoma and lymphoma may sometimes be impossible, either on morphologic grounds or based on genetic molecular studies, cutaneous lymphoid hyperplasia, clonal hyperplasia, and B-cell lymphoma, being currently considered

as points or phases of a continuum of malignant progression.[37–39] Correspondingly, an atypical form of T-cell cutaneous lymphoid hyperplasia from tick bite has been described.[37,40]

The unusual association of eosinophil-rich foreign body granulomatous infiltrate and B-cell pseudolymphoma, observed in one of our cases, is a rare but well-defined finding in arthropod-bite reactions, which has been attributed to a combination of immunocomplex and cell-mediated immunity following the antigen persistence, with an immunoglobalin E (IgE)-mediated reaction as part of the immunological process.[41]

In conclusion, the acute tick-bite reactions show special histologic features, which are unquestionably related to the particular morphology and physiology of the mouthparts of these arthropods. As far as the subacute and chronic lesions are concerned, the hair loss seems to be a definite arthropod-bite–induced form, which does not fit the characteristics of any other form of alopecia and does not represent the aspecific, scarring outcome of florid inflammation. In the granulomatous reactions and the pseudolymphomas observed by us, the finding of recognizable remnants of the mouthparts and the presence of special vascular changes may provide a clue to the etiologic diagnosis.

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