

Single Case

Diagnostic Histopathological Findings on a Tick-Bite Lesion without the Presence of an Insect Body

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Keywords

Acquired tick resistance · Basophil · Cement substance · Cutaneous pseudolymphoma · Tick bite

Abstract

Tick bite is detected when the insect's body remains, and portions, such as the mouthparts, may be used to confirm the species and the potential for microbial infection. Moreover, a histopathological diagnostic standard for tick-borne illnesses has not yet been established. Thus, this study aimed to perform a histopathological examination of the lesion in a patient in whom a tick was not identified along with its bite. The patient was a 47-year-old man who presented with a lesion caused by a tick bite; the lesion was resected en bloc from the subcutaneous fat on the left side of the neck. Histopathological findings showed necrosis and thickening of the epidermis, ulceration, a strong periodic acid-Schiff stain-positive substance over the epidermis, extravascular exposure of erythrocytes in the dermis, thrombi, sclerosis of collagenous fibers, pseudolymphoma with a predominance of T cells, and marked infiltration of basophils extending from the epidermis to the subdermal sebaceous layer. Tick-bite lesions may be detected histopathologically, even if the presence of the insect body is not confirmed, as in this case, if the injection of tick saliva and local reaction of the salivary component are histologically evaluated.

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Introduction

Ticks are blood-sucking ectoparasites that transmit various pathogens to host animals and humans, causing severe infections such as Lyme disease. Therefore, an early and accurate diagnosis followed by appropriate treatment is necessary. The diagnosis is straightforward

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when the insect body remains attached to the skin or when there is a clear history of tick bites and can also rely on histopathological examination. In the absence of tick body parts, such as mouthparts, it may be difficult to establish a definitive diagnosis. In this study, we examined skin biopsies of a patient with a clinical history of tick bites to identify common histopathological findings that may provide useful clues for diagnosing tick-bite lesions. This study aimed to present indirect histopathological evidence of tick bites for acquired tick resistance (ATR) without the presence of organic tick components.

Case Report/Case Presentation

A 47-year-old male patient with a history of two previous tick stings (at 35-year-old and 42-year-old) arrived at our clinic having had tick bites on the left side of the anterior neck 10 days before presentation. The initial clinical examination revealed erythema with a central ulcer on the left side of the anterior neck, a slightly hard spherical mass with good mobility, and a mass with a diameter of approximately 20 mm palpable subcutaneously. The body of the tick had already been shed and was not observed. Dermoscopy showed diffuse flushing as well as white oval and reticulated structures (shown in Fig. 1a). Histopathologically, the lesion showed complete loss of part of the epidermis, with dense infiltration of lymphocytes, histiocytes, and numerous eosinophils in a nodular pattern around blood vessels and between collagen fibers in the upper and lower dermis and the subcutaneous adipose tissue (shown in Fig. 2a–c). Extravascular exposure of erythrocytes, fibrin deposition, and nuclear fragmentation were observed in the dermis at the ulcer site. In the dermis surrounding the ulcer, large histiocyte-like cells with abundant fibrinous spores were distributed among the collagen fibers. On observation with periodic acid-Schiff stain (PAS), wing-like structures were present in the stratum corneum in the upper epidermis of the ulcer's edge. Toluidine blue staining was negative, and immunohistochemical staining showed a dense infiltration of CD4-, CD8-, and CD20-positive cells in a nodular pattern from the dermis to the dermis adipose layer. CD123-positive cells densely infiltrated all the epidermis,

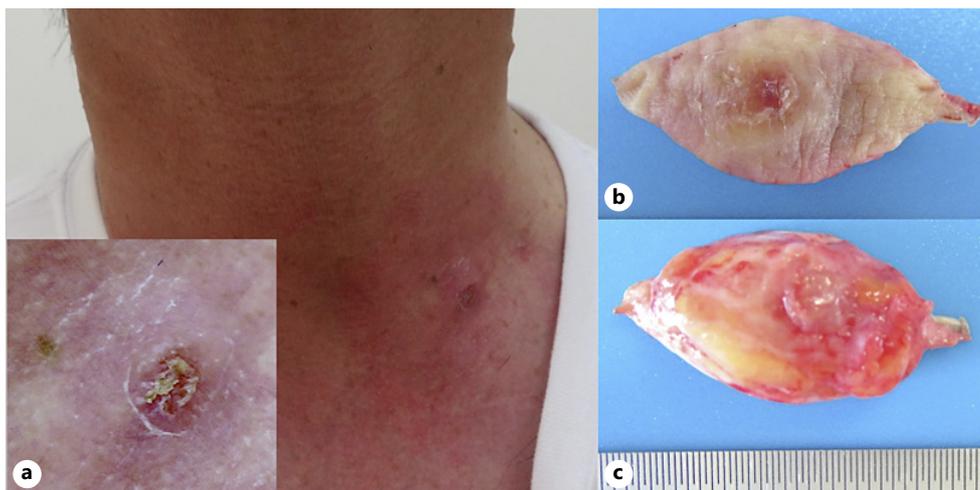


Fig. 1. Clinical presentation and surgical resection. **a** An erythema with a central ulcer on the left side of the anterior neck. Dermoscopy shows diffuse flushing and white oval and reticulated structures (inset outlined with a black box). **b, c** The ventral and dorsal views of the resected specimen, respectively.

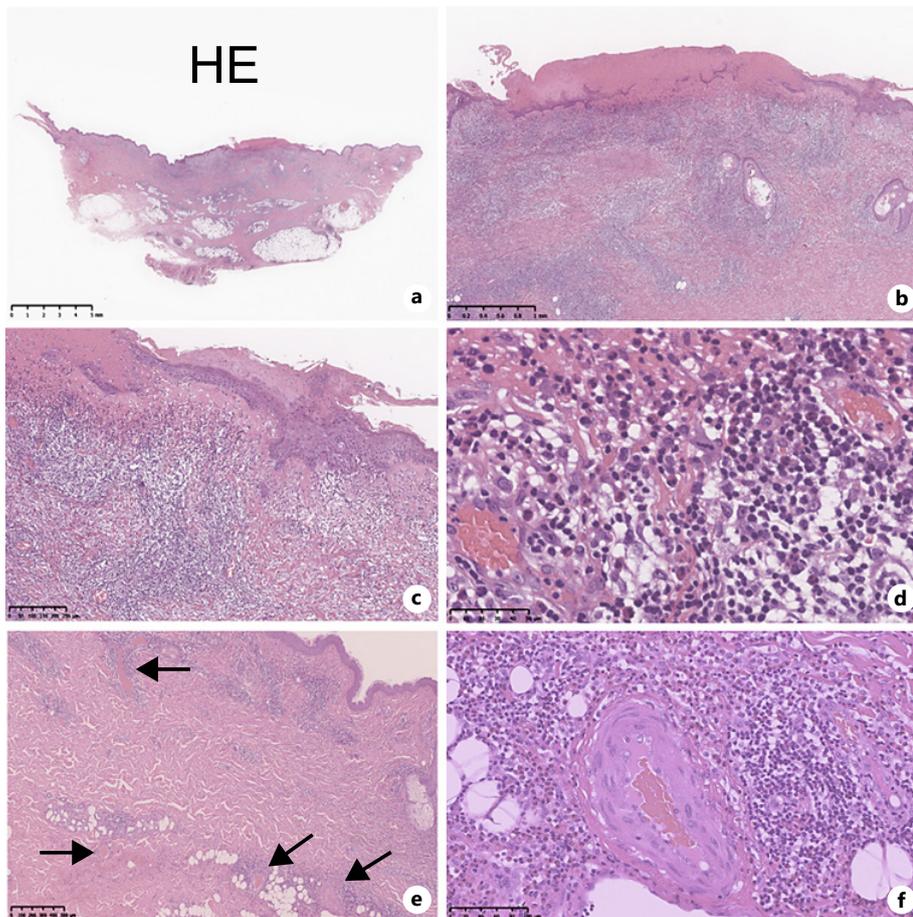


Fig. 2. Histopathological findings. Hematoxylin-eosin (H&E) stain. **a** Total image of the resected specimen. H&E stain. Original magnification, $\times 4$; scale bar, 5 mm. **b** An ulcer and eosinophilic epidermal necrosis are observed in the middle of the lesion. H&E stain. Original magnification, $\times 20$; scale bar, 1 mm. **c** Epidermal necrosis extends in a wing-like pattern, with a pale eosinophilic material between the normal epidermis and stratum corneum at the limbus, which is lighter than the necrotic epidermis. In the dermis, nodular inflammatory cell infiltration and collagen fiber sclerosis are seen. H&E stain. Original magnification, $\times 100$; scale bar, 250 μm . **d** Extravascular exposure of red blood cells in the dermis is seen. H&E stain. Original magnification, $\times 400$; scale bar, 50 μm . **e** The lumen is occluded in the dermal layer by acidophilic, unstructured material. Scattered thrombi can be seen (arrow). H&E stain. Original magnification, $\times 30$; scale bar, 500 μm . **f** Thrombus occluded by acidophilic unstructured material is seen. Degeneration of the vessel wall and infiltration of lymphocyte-dominated cells are seen. H&E stain. Original magnification, $\times 200$; scale bar, 100 μm .

dermis, and adipose septum layers. Basophils were immunostained with Mouse Monoclonal Antibody CD123 (NCL-L-CD123, Leica Biosystems Newcastle Ltd, United Kingdom. Specificity: Human CD123. Immunogen: Prokaryotic recombinant protein corresponding to 101 amino acids of the external domain of the human CD123 molecule). The differential diagnosis was pseudolymphoma (PSL) caused by a tick bite; however, simple resection of the subcutaneous tumor, including the fatty layer, was performed for diagnosis and treatment (shown in Fig. 1b, c). The final diagnosis was a tick-bite lesion with histopathological features resembling those of PSL. There was no onset of Lyme disease, and the patient was healthy with no symptoms after 6 months.

Discussion/Conclusion

The mechanism underlying the development of tick-borne illnesses [1] begins with secretions from tick salivary glands that are mostly composed of water and ions but include cement substances, anti-hemostatic factors (antiplatelet, anticoagulant, anti-vasoconstrictor, and vasodilator), immunosuppressive substances, enzymes, and other proteins. Ticks stick to and feed on their hosts for 7–15 days. Tissue fixation with a suboral piece and further with cement material that includes proteins, lipids, and glycoproteins occurs. Ticks then feed on their hosts, concentrate blood, and return 33–50% of the blood and some of the water to their hosts, during which they transmit pathogens to their hosts. When ticks adhere to their hosts, small blood vessels are destroyed, which bleed; however, the hemostatic mechanism is not compatible with the anticoagulant contained in the saliva: the insect body of the tick becomes difficult to eliminate by immunosuppressants and anti-inflammatory agents, and blood-feeding from the host becomes possible for an extended duration. In this case, extravascular exposure of the red blood cells in the dermis was observed (shown in Fig. 2d). Cement material adhering to the skin can be broadly classified into external cement that covers and exists within the epidermis and internal cement that exists within the dermis. Hematoxylin-eosin staining is generally described as diffuse or bright eosinophilic. In 2017, the cement substance was reported to be strongly PAS-positive diastase-resistant, which indicated the presence of various glycoproteins [2]. In the present case, a strong PAS and positive findings, which indicated the presence of cement in the epidermis (shown in Fig. 3a), were observed. Histopathological changes, such as type-I cryoglobulinemia in tick bites, have been reported to be a strong clue for pathological diagnosis in the absence of a history of tick bites or tick mouthparts on biopsied skin. Vascular eosinophilic hyaline thrombus is a frequent histological manifestation of tick bites. This finding may be related to the secretory products of the tick saliva. The histopathology of type-I cryoglobulinemia is characterized by eosinophilic, hyaline PAS-positive homogenous material filling the small vessels in the upper dermis with perivascular mononuclear cell infiltrate in the absence of vasculitis [3]. In this case, eosinophilic hyaline thrombi were also observed in the dermis (shown in Fig. 2e, f), and the thrombi were positive for PAS (shown in Fig. 3b, c). Cutaneous PSL refers to a group of skin diseases characterized by benign lymphoproliferative processes that clinically and/or histologically simulate cutaneous lymphomas. Various causative agents have been described; however, definitive causative factors of PSL have often not been identified, and these cases are referred to as idiopathic PSL [4]. Persistent nodular arthropod-bite reactions are characterized by either predominantly T-cell or B-cell cutaneous lymphoid hyperplasia, and the B form is considerably less represented than the T form [5]. This case indicates a T-cell-predominant PSL, and there were more CD4-positive cells than CD8-positive cells (shown in Fig. 3d–f). Basophils are circulating granulocytes that account for <1% of blood leukocytes and infiltrate skin lesions in human skin disorders such as chronic idiopathic urticaria, allergic contact dermatitis, atopic dermatitis, prurigo, lepromatous leprosy, bullous pemphigoid, eosinophilic pustular folliculitis, Schönlein-Henoch purpura, *Cimex lectularius* bites, scabies lesions, and tick bites [6, 7]. In mice, it has been demonstrated that histamine released from basophils rather than mast cells plays a crucial role in the manifestation of ATR. Histamine released from skin-infiltrating basophils rather than skin-resident mast cells plays a crucial role in the manifestation of ATR, probably through the promotion of epidermal hyperplasia, which may inhibit tick feeding. Histological examination revealed the infiltration of basophils at tick-feeding sites during the second infestation, but not the first infestation. When the mice were re-infested with ticks, skin-resident memory CD4-positive T cells secreted interleukin-3 in response to tick antigens, leading to basophil infiltration at the tick-feeding sites [8, 9]. In humans, the contributions of basophils in ATR remain unclear. The patient, in this case, had a history of repeated infestations. It has been

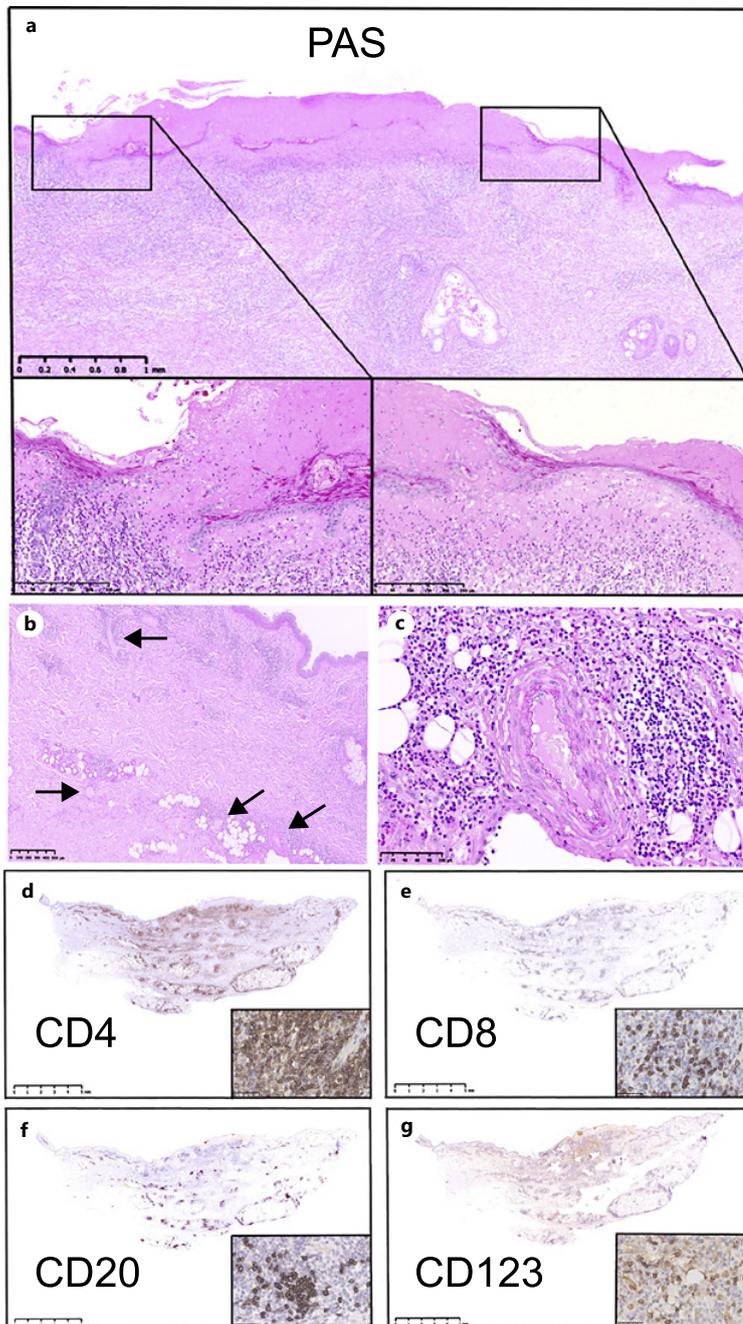


Fig. 3. PAS and immunohistochemical stain. **a** In Fig. 1b, the suburbs of the paleophilic part are strongly PAS-positive. PAS. Original magnification, $\times 20$; scale bar, 1 mm (inset outlined with two black boxes). PAS. Original magnification, $\times 100$; scale bar, 250 μm . **b, c** PAS of the area corresponding to Fig. 1 e, f, respectively. Eosinophilic substances in the thrombus show positive PAS (arrow). PAS. Original magnification, $\times 30$; scale bar, 500 μm and $\times 200$; scale bar, 100 μm , respectively. **d–f** T-cell predominant PSL. There are more CD4+ cells than CD8+ cells. **d:** CD4. **e:** CD8. **f:** CD20. Original magnification, $\times 4$; scale bar, 5 mm (inset outlined with a black box). Original magnification, $\times 400$; scale bar, 50 μm . **g** CD123+ basophils densely infiltrate all layers. CD123. Original magnification, $\times 4$; scale bar, 5 mm (inset outlined with a black box). CD123. Original magnification, $\times 400$; scale bar, 50 μm .

suggested in previous studies that cutaneous basophilia may be induced at the tick-feeding site. CD123 is an interleukin-3 receptor alpha chain and, therefore, reacts with interleukin-3. In this case, toluidine blue staining was negative, and CD123 staining was positive. Basophils densely infiltrated all layers of the epidermis, dermis, and adipose septum (shown in Fig. 3g).

In summary, it was demonstrated that the presence of histopathological evidence of extravascular exposure of red blood cells, highly-positive PAS for cement substances, PAS-positive vascular eosinophilic hyaline thrombus, CD4-positive T-cell-predominant PSL, and infiltration of basophils indicates a tick-bite, even if there were no mouthparts in the pathological sample. The patient's lesion showed extravascular exposure of erythrocytes, cement material that was strongly positive for PAS, and a thrombus with a lumen filled with PAS-positive eosinophilic vitreous-like material. Although these findings have been reported individually in the literature, their simultaneous presence in the same specimen could be interpreted as the specificity of each finding, which could contribute to the establishment of histopathological diagnostic criteria for a tick-bite illness. Furthermore, basophils have recently been found to be important for ATR and immunity to tick sucking in mice. In this patient, immunostaining showed no mast cells and marked infiltration of CD4-positive T cells and basophils in almost the same area. These findings suggest that the ATR may be involved in human ATR without evidence. Histological specimens were obtained from patients with a history of tick bites, and the histological findings from the same specimens obtained in this study may not be common among patients. The histological findings on tick-bite lesions should be considered while separately conducting histopathological examinations in patients with and without a history of tick bites.

In conclusion, the presence of PAS-positive epidermal material comprising glycoproteins from tick saliva and extravasation as well as basophilic granulocytes provides indirect evidence of tick bite. This is histochemically supported by the detection of CD20 (B cells), CD4/CD8 (T-cells), and CD123. The current study is based on a single observation. Similarly, it is interesting and most probably histologically useful if it can be reproduced.

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Statement of Ethics

Written informed consent was obtained from the patient for the publication of this case report and accompanying images. All the procedures adopted in this study were by the ethical standards of the World Medical Association Declaration of Helsinki. Ethical approval was not required for this study by the local and national guidelines.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

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Author Contributions

Tomoaki Takada collected and analyzed data and wrote the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author upon reasonable request.

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