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Superficial fibrin thrombi … and other findings: a review of the histopathology of human scabietic infections

Background: Cutaneous infection with the mite *Sarcoptes scabiei var. hominis* is associated with epidermal and dermal changes. After noting superficial fibrin thrombi in two biopsies with scabies mites, we comprehensively reviewed the histopathologic findings in scabietic infections to determine the frequency of this finding.
Methods: Twenty five biopsies of scabies infection were retrieved from the archives of our institution; only cases containing scabietic mite parts or scybala were included. The microscopic features were documented.
Results: Nearly half (40%) of the cases showed fibrin thrombi within vessels of the superficial dermis. Other frequent findings included dermal eosinophils (88% of cases), epidermal spongiosis (76% of cases), lymphocyte atypia (64%), a superficial and deep infiltrate (52% of cases), dermal neutrophils (52%) and endothelial cell swelling (52%). Half of the cases contained polarizable mite elements. Less commonly encountered features included extravasated erythrocytes (44%), dermal edema (32%), pink 'pigtails'(28%), intraepidermal pustules (24%), plasma cells (20%) and vasculitis (4%).
Conclusions: The pathologic characteristics of scabietic infection are wide-ranging. Spongiosis, superficial and deep inflammation, and dermal eosinophils and neutrophils are seen in the majority of cases. Superficial fibrin thrombi are not uncommon in scabietic infection, and may provide a helpful diagnostic clue when mites are not visible on initial sections.

Keywords: fibrin thrombi, histopathology, infectious, scabies, scabietic

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Scabies is a contagious skin infection/infestation caused by the ectoparasite mite, *Sarcoptes scabiei var. hominis*. The mite is transmitted by direct skin-to-skin contact and rarely via fomites.[1] Skin entry occurs within 30 min of contact, during which female mites deposit eggs as they burrow into the superficial epidermis, typically tunneling no further than the stratum granulosum.[2]

After the eggs hatch, the larvae migrate to the skin surface and also dig burrows called molting pouches. The development from egg to adult takes 10–13 days.[3,4]

Clinically, scabies may present in several different forms: classic acute infection, nodular scabies and crusted scabies. The most common presentation is of a symmetrically distributed papulovesicular rash, typically associated with intense pruritus, with a predilection for the interdigital web spaces, flexural areas of the wrists and axilla, waist, buttocks, thighs and ankles.[5,6] Nodular scabies is characterized by violaceous and pruritic nodules most frequently located in the axillae, genitalia and abdomen. These reddish to brown nodules may persist for weeks to years after treatment and are believed to represent persistent hypersensitivity reactions to mite parts.[5–7] Crusted scabies is most frequently identified in patients with immunosuppression or mental and physical debilitation. It is characterized by gray to white hyperkeratotic or crusted plaques that primarily involve acral sites, although a more widespread distribution may occur.[5–7] Patients with crusted scabies have a high-mite burden.

Although scabies infection is frequently diagnosed by visualizing mites on skin scrapings performed at the bedside or in the clinic, occasionally a skin biopsy may be obtained for confirmation or because the diagnosis is not suspected. At a microscopic level, cutaneous infection with the mite *Sarcoptes scabiei var. hominis* has been associated with a number of epidermal and dermal changes. A perivascular and interstitial mixed dermal inflammatory infiltrate, hyperkeratosis, acanthosis, epidermal spongiosis, acantholysis and vasculitis have all been previously described findings in scabietic infections.[8–11] We recently diagnosed two unique cases of scabies at our institution: in addition to the diagnostic mite parts, prominent fibrin thrombi were identified in superficial dermal vessels. The occurrence of superficial fibrin thrombi associated with scabietic infection has not been systematically characterized in the literature. These cases prompted us to review all cases of scabies from the last five years diagnosed at our institution to document the frequency of fibrin thrombi in scabies infestation. Other histopathologic findings in the biopsy specimens were also cataloged to augment the existing literature on the histopathologic features that characterize scabietic infection.

Methods

After obtaining approval from the Institutional Review Board (IRB), we searched the dermatopathology case files of our institution from January 2007 to June 2013 for cases containing the word 'scabies' within the diagnosis field. Of the biopsies retrieved, only those cases in which scabietic mite parts or fecal matter (scybala) were identified within the biopsy were included in the study. Data including age, gender, clinical impression, type of biopsy and location of lesion were collected from the pathology final reports.

The original hematoxylin/eosin (H&E)-stained slides were retrieved from the archive and were examined by three board-certified dermatopathologists (JG, HE and SS). The presence of scabietic mite parts or scybala was confirmed for each case and the slides were evaluated for the presence of superficial fibrin thrombi. Additional histopathologic features, including epidermal changes, type, depth, distribution and composition of any dermal inflammatory infiltrate, polarizability of mite parts, the presence of empty egg casings (pink pigtails) and evidence of vascular damage were also recorded during the slide review. Lymphocyte atypia was defined as at least focal areas of lymphocytes meeting at least two of the three criteria: (a) enlargement (b) irregular and/or convoluted nuclear contours and (c) nuclear hyperchromasia.

Results

Demographics and clinical features

A total of 25 cases were identified and retrieved from the archives for inclusion into the study. There were 10 female and 15 male patients; ages at the time of biopsy ranged from 3 months to 89 years with a mean age of 61. Of the 25 biopsies, 17 were obtained from the trunk (including abdomen, axilla, buttock, hip, back), 7 from the extremities and 1 from the scalp. There were six shave specimens and the rest were punch biopsies. Only six of the cases specifically indicated clinical concern for scabies infection; other commonly encountered clinical impressions (not exclusive as some reports listed several clinical possibilities and some reports were non-specific) included drug eruption (4), Grover's disease (3), urticaria (3), eczema (2), folliculitis (2), psoriasis (2) and granuloma annulare (2). Lesion morphology, when provided, was most frequently described as either papular or pustular (12). Only one of the biopsied patients was noted to have a pre-existing hypercoagulable state per the provided clinical information;

this patient had documented systemic lupus erythematosus.

Histopathologic findings

Results are summarized in Table 1. Mite parts were visualized in all cases. Two cases were of crusted scabies; a minority, if any, of the cases were felt to represent persistent nodular scabies as the presence of mites was an inclusion criterion. Forty percent (10/25) of the cases contained fibrin thrombi within vessels of the superficial dermis (Fig. 1A–D) and 52% (13/25) of cases showed polarizable elements: 2 contained polarizable scybala, 7 showed polarizable spines and 2 showed both (Fig. 2). Pink pigtails, believed to represent empty egg cases, were seen in 28% of cases (7/25). Dermal eosinophils were present in 88% (22/25) of cases; of these, five showed rare or few eosinophils and the rest of the cases showed a florid infiltrate (Fig. 3). A superficial and deep infiltrate was noted in 52% (13/25) of cases (Fig. 4); 8 contained a superficial to mid perivascular infiltrate and 3 other cases showed a superficial infiltrate only; the evaluation of the depth of infiltrate was limited in some of the shave biopsies. Epidermal spongiosis was noted in 76% (19/25) of cases; 16 of these cases showed minimal/mild spongiosis. Swollen endothelial cells were observed in 52% (13/25), of which six of these cases were also showing luminal thrombi. Additional histopathologic features included lymphocyte atypia (64%) (Fig. 1C), extravasated erythrocytes (44%) (Fig. 5), dermal edema (32%), dermal neutrophils (52%), intraepidermal pustule(s) (24%) (Fig. 6), leukocytoclastic vasculitis (4%) (Fig. 7) and plasma cells (20%) (Fig. 8). Of note, one case in the study showed an absence of any inflammatory reaction or histopathologic changes other than mites within the stratum corneum (Fig. 9); the pathology report stated that this patient was on methotrexate and prednisone which may account for the paucity of histopathologic findings. An example of crusted scabies is shown in Fig. 10.

Table 1. Number of scabies cases demonstrating specific diagnostic features (n = 25)

Histopathologic feature	Number (%)
Polarizable elements associated with mite	13 (52%)
Pink 'pigtails' (empty egg casings)	7 (28%)
Intraepidermal pustule	6 (24%)
Spongiosis	19 (76%)
Moderate spongiosis	3 (12%)
Minimal/mild spongiosis	16 (64%)
Superficial fibrin thrombi	10 (40%)
Dermal edema	8 (32%)
Dermal neutrophils	13 (52%)
Dermal eosinophils	22 (88%)
Numerous eosinophils	17 (68%)
Few/rare eosinophils	5 (20%)
Lymphocyte atypia	16 (64%)
Superficial to deep perivascular infiltrate	13 (52%)
Superficial to mid perivascular infiltrate	8 (32%)
Superficial perivascular infiltrate	3 (12%)
Extravasated erythrocytes	11 (44%)
Swollen endothelial cells (no vasculitis)	13 (52%)
Vasculitis	1 (4%)

Discussion

Scabies is a common infection that may present with a variety of clinical manifestations. Skin burrows and scabietic nodules are pathognomonic lesions that can aid the clinician in making the diagnosis. However, these lesions are not always present and thus the clinician must take the entire clinical picture into account to establish a diagnosis. Similarly, pathologists are easily able to make the diagnosis of scabies when mites or mite parts are identified in the superficial epithelium. However, these features are not always present on initial levels (or in the biopsy at all!). Thus, the pathologist must be cognizant of the associated epidermal and dermal changes in scabies infections to prompt evaluation of deeper levels or to raise consideration of the diagnosis even in the absence of mite parts.

Prior publications have described the many histopathologic changes seen in the epidermis and dermis in scabies infection. While there is significant histopathologic overlap between classic (papulovesicular), nodular and crusted clinical forms, there are some features that are more characteristic of each.

The papulovesicular form is typically described as exhibiting irregular acanthosis, spongiosis with variable spongiotic vesiculation and exocytosis of eosinophils and neutrophils with occasional intraepidermal microabscess formation in the epidermis. Older lesions may show mounding parakeratosis and features of excoriation such as serum crust. Mites, eggs, larvae and fecal material, when present, are seen in the stratum corneum and rarely extend deeper than the granular layer. Dermal changes include a superficial and deep perivascular and interstitial mixed inflammatory cell infiltrate of lymphocytes, histiocytes and eosinophils.

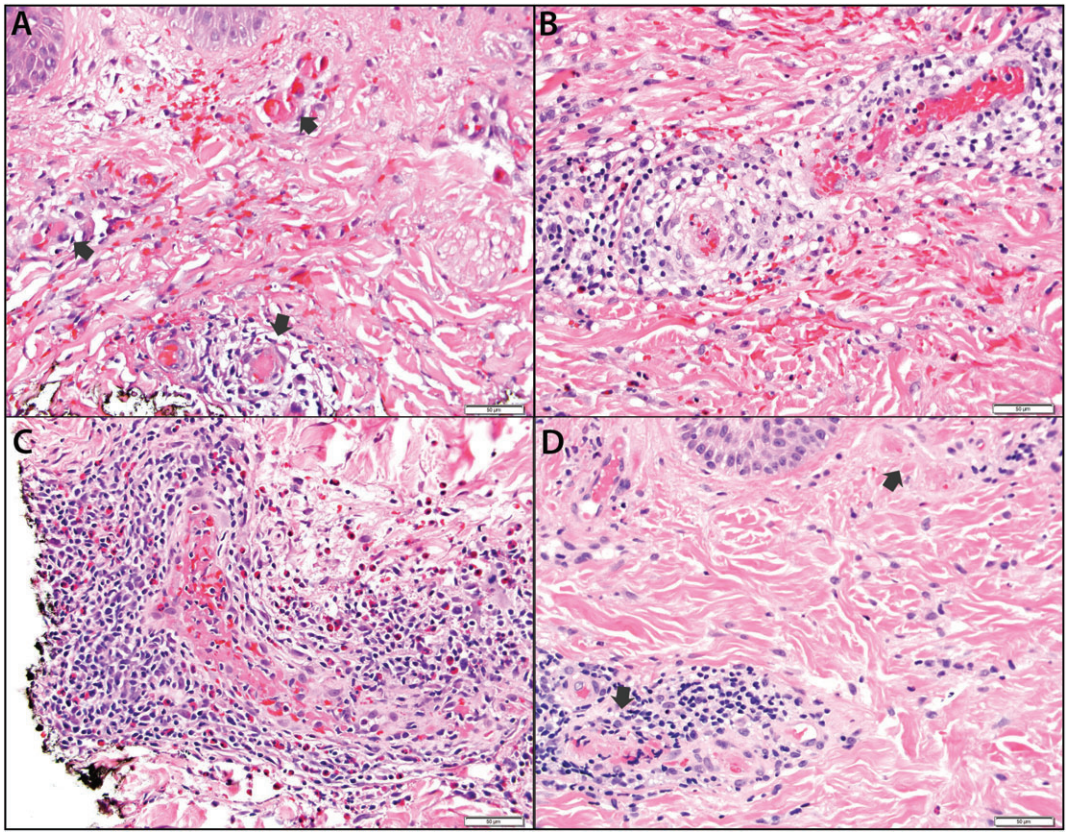

Fig. 1. Fibrin thrombi, sometimes multifocal (arrows), were identified in the superficial dermal vessels, generally in proximity to mite parts. Case 9 (A), Case 2 (B), Case 6 (C) and Case 7 (D). Note the lymphocyte atypia in (C). All images x400 (scale bar = 50 micrometers), hematoxylin/eosin.

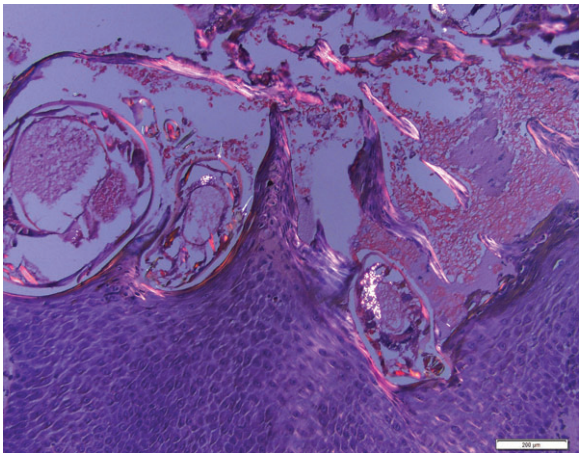

Fig. 2. Mite parts (spine and internal organs here) were often polarizable as in this example of crusted scabies. x100, hematoxylin/eosin.

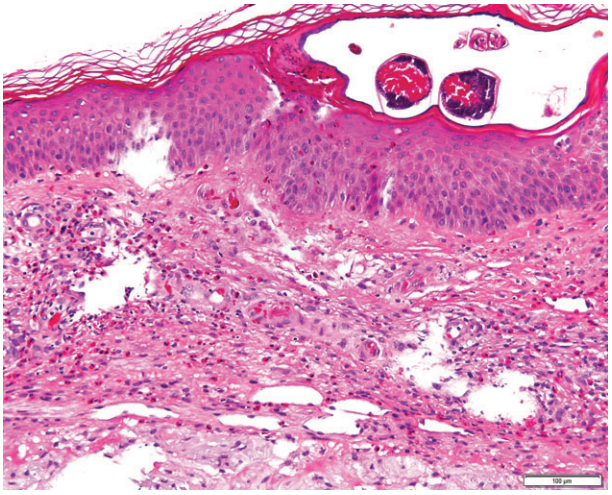

Fig. 3. Most cases showed a dense infiltrate that included many eosinophils. Case 3, x200, hematoxylin/eosin.

Vascular changes are rare but may include endothelial swelling, luminal narrowing, vasculitis and fibrinoid deposition within and around vessels.[5–7] Thrombosis of superficial dermal vessels has been rarely reported, and the few reports existing in the literature have been in association with vasculitis.[9,10]

Nodular scabies typically shows a dense perivascular inflammatory infiltrate of lymphocytes, histiocytes, eosinophils, plasma cells, and occasional atypical mononuclear cells with mitoses. Vasculitis with fibrinoid degeneration of vessel walls is reportedly a more common finding in

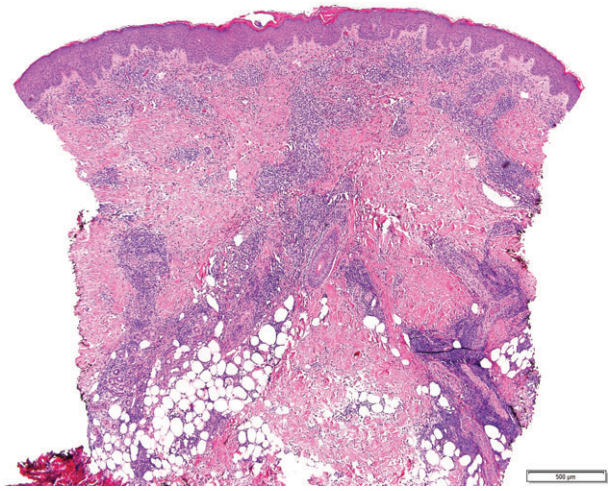

Fig. 4. The inflammatory infiltrate was superficial and deep in most of the biopsies. Case 6, x40, hematoxylin/eosin.

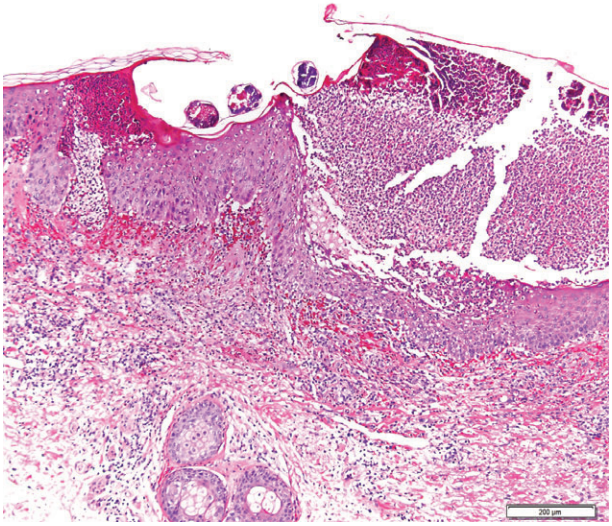

Fig. 6. Several cases showed intraepidermal pustules. Case 11, x100, hematoxylin/eosin.

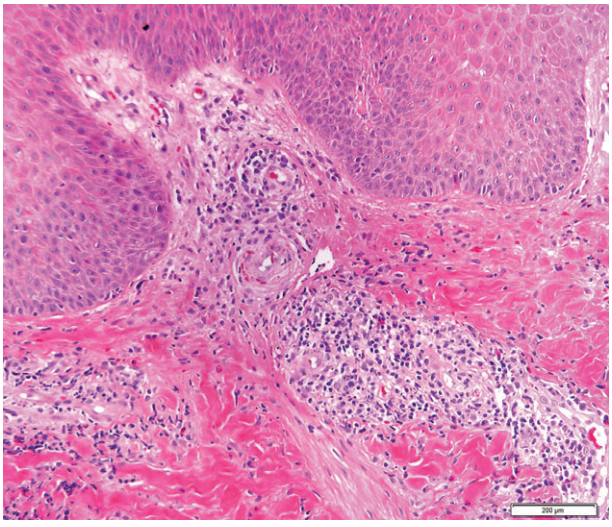

Fig. 5. Extravasated erythrocytes and endothelial swelling were commonly observed. Case 13, x100 hematoxylin/eosin.

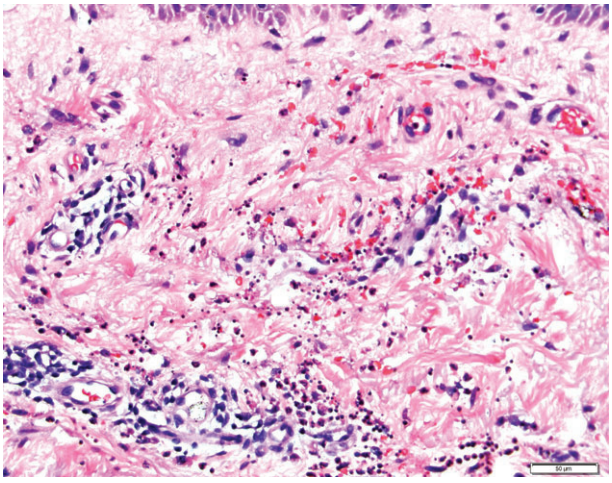

Fig. 7. Leukocytoclasis and infiltration of vessel walls by neutrophils with focal fibrin deposition, consistent with necrotizing vasculitis, were identified in one case; fibrin thrombi were not seen occluding the vessel lumens. Case 25, x400, hematoxylin/eosin.

nodular scabies,[9] although another study[7] found discrepant results. It has been suggested that the development of vasculitis may in part be because of the age of lesions, with older lesions more likely to develop vasculitis.[7] Epidermal changes are less pronounced in nodular lesions compared to the papulovesicular cases, but occasionally show focal spongiosis and microabscesses. Mites, eggs, larvae and their feces are rarely found in routine sections of nodular scabies. Liu et al. was only able to identify mites or mite parts in 22% of cases after serially sectioning through the entire specimen.[7]

Crusted scabies, as the name implies, is characterized by marked orthokeratosis and parakeratosis in which numerous mites, eggs, larvae and fecal material reside. Serum crust and extravasated erythrocytes are frequent findings. The epidermis classically shows psoriasiform hyperplasia, focal spongiosis with occasional vesiculation and neutrophilic microabscesses. The dermal infiltrate consists of a superficial and deep perivascular lymphohistiocytic infiltrate with numerous eosinophils, plasma cells and neutrophils.[9]

We conducted a comprehensive histopathologic study of scabies infections at our institution after identifying two cases that showed prominent fibrin thrombi within dermal vessels in an effort to characterize the frequency of this histopathologic feature.

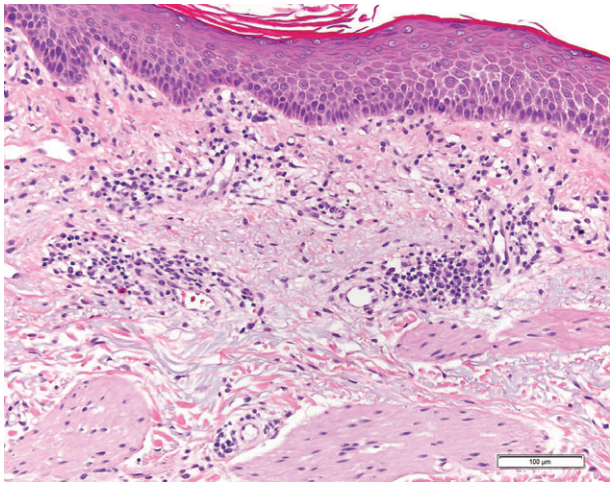

Fig. 8. Plasma cells were present within the infiltrate in a minority of cases. Case 8, x200, hematoxylin/eosin.

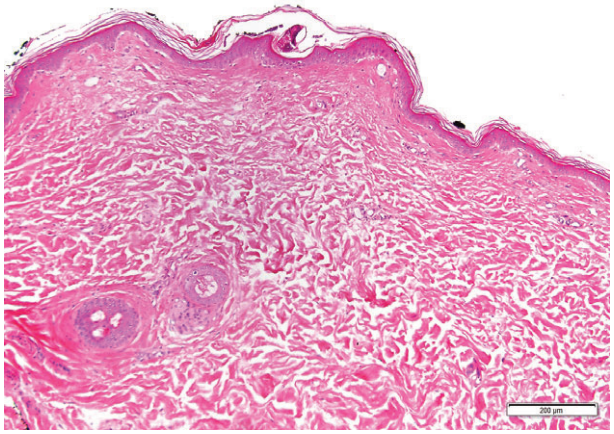

Fig. 9. Case 21 showed a complete absence of inflammatory reaction to the mite parts. x100, hematoxylin/eosin.

Our study replicates many of these previously documented findings. Similar to prior studies and classically taught dogma, our series showed the cutaneous reaction to scabies is most frequently characterized by a superficial and deep perivascular infiltrate with dermal eosinophils and epidermal spongiosis. Other more variable findings include the presence of extravasated erythrocytes, lymphocyte atypia, dermal edema, dermal neutrophils, intraepidermal pustules and plasma cells. Pink pigtails, curly eosinophilic structures firmly attached to the stratum corneum and believed to represent remnants of scabies egg casings, were seen in a minority of cases, which is a lower incidence than was cited in the first publication regarding this phenomenon.[12] Although endothelial swelling and erythrocyte extravasation was relatively common in our series, necrotizing vasculitis with leukocytoclasia was identified in only one

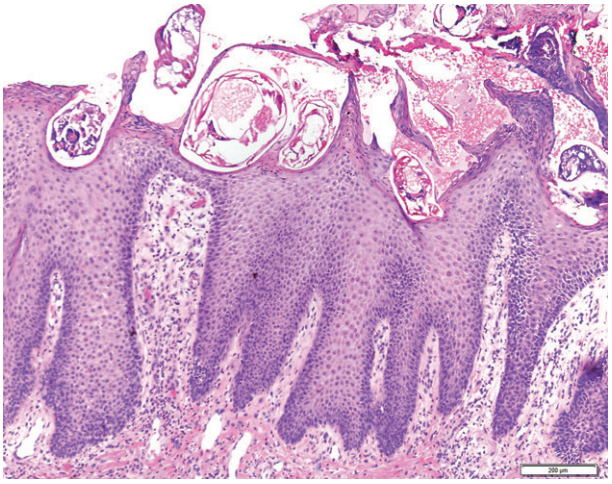

Fig. 10. An example of crusted scabies. Case 19, x100, hematoxylin/eosin.

biopsy, fitting with previous reports of it being a relatively unusual finding. Moreover, the relative infrequency of vasculitis in our series may be attributed to the requirement that mite parts be visible for study inclusion. Vasculitis in scabies infection has been previously linked to persistent nodular scabies, in which mite parts are not always readily identified.[7,9] Of note, the one case demonstrating vasculitis did not show luminal thrombi. Scabies mite spines and fecal material were polarizable in half of the cases, replicating a recent report, albeit at a lower frequency, that suggested polariscopic examination may be a useful adjunct to diagnosis.[13]

Interestingly, our review documents the relatively common occurrence of superficial fibrin thrombi in scabies infection, suggesting it may be present in nearly half of the encountered biopsies in which scabietic mite parts are visible. In all of our cases and in contrast to prior studies, thrombi were identified in the absence of vasculitis, a previously undescribed phenomenon. Although thrombosed vessels have been reported in two prior studies,[9,10] they were both associated with vasculitis and one series found these changes *only* in nodular scabietic lesions.[9] Of interest and perhaps importantly, in each of our cases, thrombi were spatially near the mite parts in the epidermis.

The exact mechanism responsible for the development of superficial thrombi is not completely understood, but may be related to a local dermal response to mite antigens. Scabies mites penetrate, burrow and reside in the stratum corneum. As a result, soluble antigens from the mite's body, saliva, body secretions and feces interact with keratinocytes and Langerhans cells in the epidermis and diffuse into the dermis to

cause an inflammatory and immune response.[14] The immune response is primarily driven by type I (immediate) and type IV (T-cell mediated) hypersensitivity reactions, resulting in the release of various cytokines that results in inflammation and can act on vessels to increase permeability.[15] Several studies have also identified deposits of C3, IgM and IgA in blood vessels, representing type III hypersensitivity reactions in scabietic lesions.[7,16,17]

Superficial vascular thrombi in the absence of vasculitis have been described in numerous entities affecting the skin, including warfarin necrosis, defects or deficiencies in protein C, protein S and prothrombin, atrophie blanche (livedoid vasculopathy), disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, antiphospholipid antibody syndrome, purpura fulminans and cryoglobulinemia.[18] In terms of arthropod-related reactions, to the author's best knowledge, this finding (thrombi in the absence of vasculitis) has only been reported in tick bites.[19,20] Ticks, in contrast to scabies mites, penetrate through the epidermis and fasten their mouthpart in the dermis where their saliva is released into the surrounding tissue. Tick saliva contains antihemostatic, anti-inflammatory and immunosuppressive agents that may contribute to thrombi formation.[20,21] We speculate that similar soluble antigens or a yet undescribed protease from scabies mites may directly exert some local pro-coagulant affect resulting in the thrombi we observe. Alternatively, the host immune response at the site of infestation may result in localized hypercoagulability.

While we cannot entirely exclude the possibility of a systemic patient hypercoagulability factor contributing to the thrombi seen in our series, the high percentage of thrombi seen in biopsies of scabietic infections makes this an unlikely scenario. Moreover, the patients from whom the initial two biopsies demonstrating thrombi were obtained (that prompted this study) were otherwise healthy and without evidence of a hypercoaguable state. The biopsy from one patient with documented history of systemic lupus erythematosus showed no evidence of dermal thrombi, further arguing against an intrinsic patient factor contributing to these histopathologic findings.

In conclusion, the histopathological characteristics observed in skin lesions of scabies infection are variable. Certain morphological features in the absence of scabies parts, such as spongiosis, superficial and deep perivascular inflammation and dermal eosinophils may suggest a scabietic infestation, although these features are certainly not specific and are seen in a range of inflammatory dermatoses. Moreover, we report that superficial fibrin thrombi are not uncommon in scabietic infection and should, when found in association with other typical findings described above, suggest this as a possible etiology. If mite parts are not seen on initial routine sections, the examination of deeper sections to look for scabies parts may prove useful.

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