Histopathologic vasculitis from the periulcer edge: A retrospective cohort study

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Background: Histopathologic vasculitis is often reported in periulcer specimens, but the frequency and clinical significance of this finding have not been evaluated.

Objective: We evaluated the sensitivity, specificity, negative predictive value, and positive predictive value of histopathologic vasculitis from the periulcer edge for detecting ulcers due to cutaneous vasculitis.

Methods: We performed a retrospective chart review of patients with leg ulcers at a tertiary hospital between 2009 and 2016. Histopathologic slides were evaluated by 2 dermatopathologists who were blinded to the etiology of ulcer. Focal vasculitis was defined as involvement of fewer than 3 vessels.

Results: Vasculitis at the periulcer edge was seen in 51.6% of the specimens (32 of 62). Of the specimens with histopathologic vasculitis, focal vasculitis was seen in the majority of specimens (71.9% [23 of 32]), whereas diffuse vasculitis was observed in 28.1% (9 of 32). Periulcer vasculitis yielded a high sensitivity (100% [95% confidence interval, 29%-100%]). Furthermore, the specificity was low (50.9% [95% confidence interval, 38.1%-63.6%]) for detecting vasculitis-induced ulcers.

Limitations: Small number of vasculitis-induced ulcers.

Conclusion: Focal vasculitis from the periulcer edge is a nonspecific finding and provides little diagnostic value in determining the etiology of lower leg ulcers. Emphasis should be placed on the combination of clinical history and examination, histology, and laboratory findings when diagnosing ulcers. (J Am Acad Dermatol 2019;81:1353-7.)

Key words: clinicopathologic correlation; cutaneous vasculitis; histopathologic vasculitis; leg ulcers; leukocytoclastic vasculitis; pseudovasculitis.

Leg ulcers are a common and costly problem in the United States.[1] The majority of lower extremity ulcers are caused by chronic venous stasis, peripheral arterial occlusive disease, or combined vascular disease.[2,3] Uncommon causes of leg ulcers include pyoderma gangrenosum, infections, vasculitis, neoplasia, radiation, and other inflammatory conditions.[4] Biopsy specimen of the periulcer edge can reveal uncommon etiologies of leg ulcers.[5,6] It is not uncommon that the etiology of an ulcer cannot be determined despite a thorough history and physical examination, laboratory testing, and histology.

Cutaneous vasculitis is a rare cause of lower leg ulcers. Only 10% of patients (8 of 82) with cutaneous vasculitis present with ulcerations.[7] A biopsy specimen from the periulcer edge can detect vasculitis. Vasculitis can be primary, secondary (ie, due to drugs, toxins, infection, or cancer), or reactive/incidental. Incidental/reactive vasculitis is a

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histologic finding of vasculitis secondary to another pathologic process such as an ulceration.[8,9] When a biopsy specimen is assessed from the periulcer edge, incidental vasculitis may be confused as a primary or secondary vasculitis.

Histopathologic vasculitis from the periulcer edge is often reported as a "nonspecific" finding at our institution. The frequency of histopathologic vasculitis from the periulcer edge of leg ulcers has not been studied or reported. In this study, we examined the sensitivity, specificity, negative predictive value, and positive predictive value of histopathologic vasculitis from the periulcer edge in detecting ulcers caused by a primary or secondary vasculitis. We hypothesized that histopathologic vasculitis will be a common finding among all etiologies of leg ulcers.

CAPSULE SUMMARY

- Histopathologic vasculitis can be detected from the periulcer edge.
- Focal histopathologic vasculitis (involvement of fewer than 3 vessels) from the periulcer edge is a nonspecific finding and provides little diagnostic value in determining the etiology of ulcers.

METHODS

We evaluated histologic specimens of all patients with a diagnosis of a leg ulcer who were referred to the University of Utah Department of Dermatology from August 2009 to August 2016. We reviewed the clinical charts of each patient for demographic information, concomitant illness(es), and location and etiology of the ulcer. Biopsy specimens were obtained via punch or excision biopsy from the periulcer edge. Specimens acquired via shave biopsy or specimens from the bed of the ulcer were excluded. Indications for biopsy included chronic, nonhealing ulcers (present for more than 3 months) and/or atypical features (irregular borders, undermined edges, rolled up border, "punched-out" appearance, surrounding violaceous discoloration, reticulate purpura, surrounding palpable purpura, and/or significant necrotic eschar). If an atypical wound infection was suspected, a biopsy specimen for tissue culture was also obtained. Slides were reviewed by 2 dermatopathologists who were blinded to the ulcer's etiology. In each case, the presence of vasculitis and the number of vessels involved were recorded.

Histologic vasculitis was defined on the basis of previously utilized criteria and included red blood cell extravasation, vascular and/or perivascular infiltrates of leukocytes with or without leukocytoclasis, and fibrinoid degeneration of the blood vessel wall.[9] Focal vasculitis was defined by involvement of 1 or 2 vessels. Diffuse vasculitis was defined by involvement of 3 or more vessel. The definitions of diffuse and focal vasculitis were specified by the authors and are not based on other published criteria. We further classified histopathologic vasculitis by the size of the predominant blood vessel involved and principal inflammatory cell infiltrate. A clinical diagnosis for a primary or secondary vasculitis was based on categories in the Chapel Hill consensus criteria for vasculitis.[10] The criterion standard for diagnosing an ulcer secondary to cutaneous vasculitis was determined by a combination of clinical history and examination, histology, immunohistochemistry, and laboratory findings.[11]

Direct immunofluorescence (DIF) was performed when there was a high clinical suspicion for cutaneous vasculitis. Patients were deemed to have a high clinical suspicion for ulcerations secondary to cutaneous vasculitis if they had (1) a history of systemic vasculitis or connective tissue disorder, (2) presence of violaceous skin nodules on physical examination, or (3) acute worsening of ulceration with surrounding purpura. The age of the lesion also played a role in whether DIF was performed. Ulcerations that have been present for less than 24 hours are more likely to show immunoreactants, although some data have showed that IgM can remain active for up to 7 days.[12] DIF was not performed in the majority of cases because of a low clinical likelihood of cutaneous vasculitis.

Statistical analyses

Descriptive statistics were used to summarize patient demographics and comorbidities. Count (percentage) was used for categoric variables; and mean, standard deviation, and range (minimum/maximum) were used to summarize continuous variables. Skewed continuous variables were summarized by median and interquartile range. We calculated the sensitivity, specificity, positive and negative predicted values, and overall accuracy for histopathologic vasculitis in detecting cutaneous vasculitis. These estimates included 95% confidence intervals (CIs).

RESULTS

A total of 62 specimens from 56 patients met the inclusion criteria (Table I). Of these patients, 36 (64.3%) were female and 20 (35.7%) were male. The

Abbreviations used:

CI: confidence interval
DIF: direct immunofluorescence

lower leg (area from knee to ankle) was the most commonly affected area, followed by the proximal aspect of the leg (9.7%) and foot (4.8%). The vast majority of specimens were from chronic leg ulcers (50 of 62 [80.6%]) (mean duration, 688 days; standard deviation, 1412.9 days). Almost half of the cohort had a comorbid autoimmune condition, with rheumatoid arthritis being the most common (23.2%). In all, 79% of ulcers had at least 1 atypical feature.

The majority of biopsies (75.8% [47 of 62]) were performed by the senior author (M.J.P.). In all, 60 specimens were obtained via a 4- or 5-mm punch biopsy, whereas 1 specimen was obtained via a wedge and the other was obtained via an excisional biopsy. Depth of the biopsies ranged from 3 mm to 8 mm (median, 4 mm). Adipose tissue was seen in 87.1 % of the specimens (54 of 62).

Histopathologic vasculitis was seen in 32 of the periulcer specimens (51.6%) (Table II). Diffuse vasculitis was seen in 9 specimens, whereas focal vasculitis was seen in 23 specimens. In all, 29 specimens had small vessel vasculitis and 1 specimen had medium-sized vessel vasculitis only. Two specimens had mixed (overlapping) vasculitis; 1 with large- and medium-sized vessel involvement and the other with involvement of medium- and small-sized vessels. The predominant inflammatory cell infiltrates in most specimens with vasculitis were neutrophils (21 of 32), followed by lymphocytes (5 of 32) and mixed lymphocytes and neutrophils (5 of 32). There was 1 case of granulomatous vasculitis.

Histopathologic vasculitis was seen in a wide range of ulcer etiologies. A total of 10 biopsy specimens had a superimposed bacterial infection. Of these 10 specimens, 7 (70%) that were secondarily infected had histopathologic vasculitis (6 focal and 1 diffuse). We identified 5 patients with systemic vasculitis. Of these 5 patients, 3 (patients 1-3) with a history of systemic vasculitis had cutaneous ulcerations secondary to vasculitis. Patients 4 and 5 had cutaneous ulcerations due to pyoderma gangrenosum.

Biopsy specimens for DIF were obtained in a subset of patients (n = 13) when clinically indicated (underlying connective tissue disease and/or purpura). Of these 13 patients, 8 demonstrated vasculitis on hematoxylin and eosin staining. DIF immunofluorescence was positive for immune-mediated vasculitis in 3 of these 8 patients, all of whom had underlying rheumatoid arthritis or systemic lupus erythematosus.

Table I. Demographics and clinical presentation of patients with leg ulcer (N = 56)

Variable	Value
Sex, n (%)	
Male	20 (35.7)
Female	36 (64.3)
Age at evaluation, y	
Mean (SD)	62 (15.8)
Min/max	20/88
Duration of ulcer, d	
Mean (SD)	688 (1412.9)
Median (IQR)	240 (640)
Min/max	1/3650
Comorbid conditions, n (%)	
Autoimmune/rheumatologic	26 (46.4)
Rheumatoid arthritis	13 (23.2)
Hypercoaguable state, excluding cancer	9 (16.1)
Cancer	8 (14.3)
Cardiovascular disease	25 (44.6)
Diabetes mellitus, type 2	9 (16.1)

IQR, Interquartile range; *Min/max*, minimum/maximum; *SD*, standard deviation.

The presence of any histopathologic vasculitis had a high sensitivity (100% [95% CI, 29%-100%]), but the 95% CI was notably wide, with a lower bound of 29% due to only 3 vasculitis-induced ulcers. Furthermore, the specificity was low (50.9% [95% CI, 38.1%-63.6%]) for detecting ulcers secondary to cutaneous vasculitis (Table III). The presence of diffuse histopathologic vasculitis demonstrated better predictive performance with the same sensitivity (100% [95% CI, 29%-100%]) and improved specificity for detecting true cutaneous vasculitis (89.8% [95% CI, 79.2%-96.2%]) (Table IV). However, the positive predictive value was low. Among patients with diffuse vasculitis on histology, the probability of having true vasculitis was 33.3% (95% CI, 7.5%-70.1%).

DISCUSSION

Histopathologic vasculitis is a common finding among all etiologies of leg ulcers. In our study, half of periulcer specimens from the lower leg showed evidence of histopathologic vasculitis. The majority of vasculitis that was seen on biopsy was focal and represented reactive/incidental vasculitis. Diffuse histopathologic vasculitis is a more specific marker for detecting ulcers caused by cutaneous vasculitis. However, diffuse histopathologic vasculitis had a

Table II. Ulcer etiology and presence of vasculitis on histology

Variable	Specimens examined, n	Specimens with presence of vasculitis on histology, n (%)
All specimens examined*	62	32 (51.6)
Biopsy site (by specimen)		
Proximal leg	6	3 (50)
Distal leg, including ankle	53	27 (50.9)
Foot	3	2 (66.6)
Ulcer etiology		
Pyoderma gangernosum	14	7 (50)
Arterial insufficiency	1	1 (100)
Venous stasis ulcer	8	4 (50)
Vasculopathy	8	6 (75)
Mixed (arterial/venous/ vasculopathy)	8	5 (62.5)
Vasculitis†	3	3 (100)
Medication-induced	3	2 (66.7)
Postradiation	1	1 (100)
Neuropathic/trauma	3	1 (33.3)
Infectious etiology	1	0 (0)
Immunodeficiency (Felty syndrome)	1	0 (0)
Secondary to edema	1	1 (100)
Chronic erosive dermatitis	1	0 (0)
Unknown	9	1 (11.1)

*Includes biopsies of ulcers at different sites or period of time.
†Vasculitis with diagnostic direct immunofluorescence.

Table III. Sensitivity and specificity of histologic findings (by specimen)

	Criterion standard based on clinical evaluation, histology, and laboratory findings	
Biopsy specimen type	Vasculitis	Other
Biopsy with vasculitis	3	29 (6 diffuse)
Biopsy with no vasculitis	0	30

Accuracy, 33/62 = 53.2% (40.1%-66%); sensitivity, 3/3 = 100 % (29%-100%); specificity, 30/59 = 50.9 % (38.1%-63.6%); positive predictive value, 3/32 = 9.4 % (2%-25%); and negative predictive value, 30/30 = 100 % (88.4%-100%).

Table IV. Sensitivity and specificity of diffuse vasculitis (by specimen)

	Criterion standard based on clinical evaluation, histology, and laboratory findings	
Biopsy specimen	Vasculitis	Other
Biopsy with vasculitis	3	6
Biopsy with no vasculitis	0	53

Accuracy, 56/62 = 90.3 % (80.1%-96.4%); sensitivity, 3/3 = 100 % (29%-100%); specificity, 53/59 = 89.8 % (79.2%-96.2%); positive predictive value, 3/9 = 33.3 % (7.5%-70.1%); negative predictive value, 53/53 = 100 % (93.3%-100%).

low positive predictive value. The discrepancy between the high specificity and low positive predictive value is due to the rarity of the condition.

The comorbid conditions and common etiologies of ulcers in our patient population differed from those in previous reports. The University of Utah serves as the primary referral center in the Mountain West (Utah, Idaho, Wyoming, Montana, and Nevada) for chronic, nonhealing ulcers that are resistant to standard therapy. A multidisciplinary approach with vascular surgery, rheumatology, dermatology, and the wound care team was often needed to manage these complex cases of treatment-resistant leg ulcers. Biopsies were performed in only the most recalcitrant cases of leg ulcers, which explains why pyoderma gangrenosum and vasculopathy were some of the most common etiologies of leg ulcers in our patient population.

When histopathologic vasculitis was detected from the periulcer edge by community providers, patients were referred to our institution for additional evaluation. The majority of these patients were not determined to have ulceration secondary to cutaneous vasculitis. It is important to note that the etiology of an ulcer due to a cutaneous vasculitis cannot be determined solely by a skin biopsy. Cutaneous vasculitis is diagnosed through a combination of thorough clinical examination, histology, and laboratory findings. Infectious causes of vasculitis should be ruled out via tissue swab and/or cultures. Clinical management should include biopsy with tissue culture in an ulcer with atypical features.

There are limitations to our study. One limitation is that we had relatively few patients with vasculitis. Although sensitivity and specificity do not depend on a condition's prevalence, we would have more confidence in our sensitivity results if more patients with vasculitis had been available. Sampling errors can occur and lead to false-negative results. Additionally, adipose tissue was not captured in all specimens, thus limiting the assessment of deeper vessels. Variablity of specimen size was present because of multiple dermatologists performing the biopsy. However, the majority of biopsies were performed by the senior author of the article. Another limitation is the tertiary nature of the institution. In the majority of ulcers in our study biopsies were performed late in their disease state. This study includes only histopathologic evaluation of recalcitrant or atypical leg ulcers.

CONCLUSION

Incidental/focal vasculitis from the periulcer edge is a nonspecific finding with no diagnostic value. Biopsy specimens from the periulcer edge often show limited neutrophilic vasculitis affecting small dermal vessels. Diffuse histopathologic vasculitis warrants further laboratory testing and DIF. Clinical history and examination, histology, and laboratory findings should all be used in determining the etiology of leg ulcers.

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