Objective: To determine whether tissue eosinophilia is a reliable indicator of a drug-induced etiology in biopsy samples demonstrating leukocytoclastic vasculitis.

Design: Retrospective medical record review with concurrent histopathologic analysis.

Setting: University-affiliated dermatology practice.

Patients: Sixty-three patients with cutaneous small-vessel vasculitis meeting specific inclusion criteria were divided into drug-induced (n=16) and non–drug-induced (n=47) groups.

Main Outcome Measures: Corresponding histopathologic material was reviewed by a dermatopathologist masked to the etiologic associations. An eosinophil ratio was calculated for each patient, derived from the mean eosinophil score (averaging eosinophil counts from 10 high-power histologic fields), and expressed in relation to the intensity of inflammation in the histopathologic slides examined. Eosinophilia ratios were compared for both groups using the Mann-Whitney test.

Results: A significant difference was found in mean eosinophil ratios in the drug-induced vs non–drug-induced groups (5.20 vs 1.05; \( P = .01 \)). Vascular fibrin deposition was present in both groups and was not found to be significantly different \( (P = .78) \). Clinical evidence of systemic vasculitis was present in 2 patients (13%) in the drug-induced group vs 15 (32%) in the non–drug-induced group. Fourteen patients (88%) in the drug-induced group had a short-term disease course vs 27 (57%) in the non–drug-induced group.

Conclusions: Tissue eosinophilia is established as a reliable indicator of drug induction in cutaneous small-vessel vasculitis. Drug-induced small-vessel vasculitis generally follows a short-term disease course without development of systemic involvement. This information may be useful for guiding management decisions, especially when the etiology is unclear.

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VASCULITIS IS A TERM USED broadly to refer to multiple different clinicopathologic entities in which inflammation and necrosis of the blood vessels are central to the disease process.\(^1,2\) An assortment of classification schemes based on different variables, including vessel size, histopathologic features, and distinct clinical presentations, have been proposed.\(^3,4\) However, many of these schemes are difficult to use secondary to overlapping features among the diseases, making appropriate classification of the patient difficult.

Leukocytoclastic vasculitis (LCV) is a reactive process of the small blood vessels that has distinct histopathologic features characterized by the presence of vascular and interstitial polymorphonuclear leukocytes, some of which display fragmentation (leukocytoclasis). Endothelial cell swelling, fibrinoid necrosis of the vessel wall, and extravasation of red blood cells are typical.\(^5,6\) Numerous conditions, including drug reactions, infections, connective tissue and autoimmune disorders, malignancies, and ingestion of or exposure to foodstuffs and chemicals, have been implicated in the development of LCV.\(^5,6,7,9-13\) Often there is no definitive etiology, as observed by Ekenstam and Callen,\(^9\) who found that 54% of their LCV cases were idiopathic.

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Delineating a drug as the etiology of small-vessel vasculitis (SVV) is at times difficult but, when possible, often denotes a self-limiting process.\(^0,14,15\) Previous investigations have studied various histopathologic findings in an attempt to find a reliable distinguishing feature among etiologies of LCV. Mullick et al\(^16\) reported on clinical and pathologic findings in 30 patients with drug-related vasculitis. All the patients had SVV with similar features: a predomi-
Approval for the study was obtained from the institutional review board at the University of Louisville. Sixty-three patients were included in this study. Cases were obtained using the following 2 methods: (1) medical records bearing the diagnosis code for SVV between April 14, 1997, and February 16, 2004, were obtained from the files at a University of Louisville–affiliated dermatology practice (Associates in Dermatology) and (2) a computerized search for archived histopathologic slides with the diagnosis of SVV in multiple organ systems. Peripheral blood eosinophilia (defined in the study as >5% eosinophils in the peripheral blood) was a common finding in these patients.

It would be helpful if histopathologic clues could reliably help distinguish among the various etiologies of LCV. Not only would this serve as a diagnostic aid but it could also help direct disease management. Therefore, by comparing known drug-induced LCV with LCV caused by other known or unknown factors, this study attempts to determine whether tissue eosinophilia is a reliable indicator of a drug-induced etiology. Additional histopathologic and clinical observations are described.

METHODS

The corresponding slides were evaluated for the following required variables: (1) the presence of a perivascular inflammatory infiltrate composed of more than 50% neutrophils with leukocytoclasis that involves the small dermal vessels, (2) fibrinoid degeneration of vessel walls, and (3) if no evidence of fibrinoid degeneration is present, the vessels must display endothelial cell swelling with extravasation of red blood cells (Figure 2). Slides were randomized using a study number corresponding to a particular patient. Evaluation was performed by a dermatopathologist (J.C.M.) masked to the etiologic associations.

An eosinophil count was performed on each histopathologic slide by counting the number of eosinophils present in each of 10 random high-power fields (magnification ×400). The raw number of total eosinophils was divided by 10 to obtain a mean eosinophil count per high-power field (eosinophil score). To account for variability in inflammation density, 10 random high-power fields (magnification ×400) were assessed based on a scale from 1 to 4 as follows: 1 indicates 25% or less of the field involved by inflammation; 2, 26% to 50% of the field involved; 3, 51% to 75% of the field involved; and 4, 75% or more of the field involved. The sum total of the fields was divided by 10 to get the mean inflammation density score. The tissue eosinophilia ratio was calculated as the eosinophil

HISTOPATHOLOGIC ANALYSIS

The tissue eosinophilia ratio was calculated as the eosinophil
Group 1 had a male-female ratio of 2.2:1, in contrast to the ratio in group 2 of 1:1.8. The mean age in group 1 was 49.8 years (range, 2-83 years) and in group 2 was 44.8 years (range, 7-81 years). Systemic symptoms were present in 17 (27%) of all 63 patients (2 [13%] of 16 patients in group 1 and 15 [32%] of 47 patients in group 2). In group 1, the 2 patients with systemic symptoms had only 1 extracutaneous site involved (1 arthralgia and 1 hematuria). Group 2 had 9 patients with 1 extracutaneous site involved and 6 with multiple organ systems implicated. The most commonly reported symptom was arthralgia, followed by gastrointestinal symptoms and renal involvement as manifested by hematuria.

Overall, a short-term disease course was most common, with 42 (67%) of 63 patients demonstrating complete resolution of disease in 3 months or less. The remaining 21 patients (33%) had either a relapsing course or continuous disease that persisted beyond 3 months. In group 1, 14 patients (88%) had a short-term course, compared with 27 patients (57%) in group 2. The 2 cases of systemic involvement in group 1 represented disease marked by a short-term course. However, systemic symptoms were present in essentially equal proportions of group 2 patients with a short- vs long-term disease course (30% vs 35%). Table 2 summarizes systemic involvement and disease course.

Peripheral blood eosinophil values, expressed as a percentage of total leukocytes, were available in 11 of 16 group 1 patients and ranged from 0% to 7% (mean, 3.0%). In group 2, peripheral blood eosinophil values were available in 34 of 47 patients and ranged from 0% to 8% (mean, 2.2%). Peripheral blood eosinophilia was not statistically different between the 2 groups (P=.60).

The drugs most commonly implicated in drug-induced SVV were antimicrobials (in 69% [n=11] of the patients). Vancomycin was the implicated agent in 3 of these patients. In 1 case, the patient could not recall the name of the antibiotic taken. One case occurred after the administration of allergy injections and was included in group 1 because the vasculitis occurred in association with the administration of a drug and other causes were excluded. One patient had initiated treatment with 2 drugs on the same date and thus the exact medication leading to the development of SVV could not be delineated. Table 3 lists the drugs found to be associated with SVV in the present study. The development of cutaneous lesions occurred 1 day to 1 month after administration of the drug. Thirteen cases (81%) resolved in the first week after discontinuation of the medication, and 1 case resolved within 1 month of discontinuation. Two patients had a long-term course of 10 and 12 months, and each required pharmacologic therapy for resolution of their cutaneous SVV.

### Histopathologic Analysis

Tissue eosinophilia ratios in group 1 ranged from 0.14 to 23.08 (mean, 5.20) compared with group 2, which ranged from 0.00 to 8.89 (mean, 1.05) (Figure 3). This finding of increased eosinophils in group 1 was found to be significant (P=.01). Inflammation density in the group 1 and group 2 biopsy samples was not significantly different (P=.25).

Vascular fibrin deposition was present in both groups. Group 1 had 1 patient (6%) without fibrinoid degeneration of the vessels, 12 (75%) in whom up to two thirds...
of the vessels were involved, and 3 (19%) in whom greater than two thirds of the vessels were involved by fibrin deposition. Group 2 had 11 patients (23%) with no evidence of fibrin deposition, 25 (53%) with up to two thirds of the vessels displaying fibrinoid degeneration, and 11 (23%) in whom deposition of fibrin was present in greater than two thirds of the vessels. Fibrin vascular deposition was not significant between the 2 groups ($P = .78$).

Formation of thrombi was present in 31% and 21% of group 1 and 2 biopsy specimens, respectively. All the patients in whom thrombi were noted had at least one third and usually greater than two thirds of the vessels involved by fibrin deposition. There were no patients in whom thrombi were noted without evidence of vascular fibrinoid degeneration. Patients with clinical evidence of systemic symptoms in both groups ($n = 17$) had a mean fibrin deposition score of 1.6, and only 3 of these patients had evidence of thrombi. Epidermal changes were present in 6 patients (38%) and 13 patients (28%) in groups 1 and 2, respectively. The most common change noted was blister/vesicle formation. All of the patients with LCV and epidermal changes had concurrent vascular fibrin deposition.

**Table 2. Systemic Involvement and Disease Course in Drug-Induced and Non–Drug-Induced Small-Vessel Vasculitis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Drug-Induced Group, No.</th>
<th>Non–Drug-Induced Group, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short-term</td>
<td>Long-term</td>
</tr>
<tr>
<td>Cutaneous involvement only</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Cutaneous and systemic involvement</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hematuria</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia and hematuria</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia and gastrointestinal</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia, gastrointestinal, and hematuria</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>2</td>
</tr>
</tbody>
</table>

*Short-term disease is classified as having a duration of 3 months or less. Long-term disease is classified as relapsing or continuous disease of greater than 3 months’ duration.

**Table 3. Drugs Associated With 16 Cases of Drug-Induced Leukocytoclastic Vasculitis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>3</td>
</tr>
<tr>
<td>Alprazolam*</td>
<td>2</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>3</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>1</td>
</tr>
<tr>
<td>Levofoxacin*</td>
<td>1</td>
</tr>
<tr>
<td>Gatifloxacin*</td>
<td>1</td>
</tr>
<tr>
<td>Vancomycin†</td>
<td>1</td>
</tr>
<tr>
<td>Metoprolol/rofecoxib‡</td>
<td>1</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>2</td>
</tr>
<tr>
<td>Antibiotic§</td>
<td>1</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>1</td>
</tr>
<tr>
<td>Allergy injections</td>
<td>1</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1</td>
</tr>
</tbody>
</table>

*Two cases.  
†Three cases.  
‡Therapy with both medications were started on the same day.  
§Patient was unable to recall the name of the antibiotic.

The concept of eosinophilia in relation to LCV is not new. Zeek et al noted eosinophils in visceral tissue vascular-"


...ting of drug-related vasculitis, in the study by Mullick et al, which showed that eosinophilia in the peripheral blood was common in patients in whom systemic involvement was present but not in those in whom disease was limited to the skin. The authors considered the presence of 3 or more eosinophils in each high-power field to be indicative of tissue eosinophilia. However, although the study noted that eosinophils are a prominent part of the inflammatory infiltrate in the setting of drug-related vasculitis, no quantitative analysis was performed to assess this feature and its true significance.

To our knowledge, the present investigation of tissue eosinophilia is the first to systematically quantify this histologic feature in LCV, specifically in drug-induced and non–drug-induced cases. A simple method was devised to adequately sample the inflammation in the specimen, noting the number of eosinophils and the density of inflammation. These numbers were averaged, and a simple equation was applied to obtain a ratio indicative of tissue eosinophilia. To further ensure that any difference between groups was not secondary to the level of inflammation present in the tissue, statistical analysis of inflammation density in biopsy specimens was performed and was found to be statistically significant. Thus, we are confident in concluding that the presence of tissue eosinophilia is a true and statistically significant clue to aid in assessing the etiology of LCV, specifically in drug-induced cases.

However, this is not an absolute feature that can be used as 100% indicative of a drug-induced etiology. Patients who displayed prominent tissue eosinophilia were also noted in the non–drug-induced group. However, of the 47 patients in this group, only 2 had tissue eosinophilia ratios greater than 5. One patient had a history of an arthropod bite in the setting of autoimmune disease, and the increased eosinophilia may have resulted as a response to the arthropod insult. Nonetheless, tissue eosinophilia can be found in patients with non–drug-induced LCV. Furthermore, the converse may be noted where tissue eosinophils are not prominent in patients with drug-induced LCV. However, even if the eosinophil is not prominent in the biopsy sample it is pertinent. This is supported by our finding that eosinophils were present in 100% of the patients with drug-induced LCV. The same was not true for patients in the non–drug induced group, in which 10% did not display any eosinophils and an additional 15% had only 1 eosinophil.

Also important is the presence of high eosinophil ratios in the drug-induced group. One third of the patients had ratios greater than 5, and 1 had a ratio greater than 20. Therefore, we conclude that patients with an appropriate drug history and large numbers of eosinophils demonstrating LCV in their biopsy specimens likely have cutaneous SVV that occurred as a result of drug administration. Moreover, a reference tissue eosinophilia ratio of 5 or greater provides strong evidence in reaching this conclusion. Peripheral blood eosinophilia was not statistically significantly different between the 2 groups and thus is not a helpful variable for evaluating the etiology of LCV.

In the present study, specific inclusion and exclusion criteria were used in the clinical and histopathologic analyses in an attempt to limit confounding variables. For example, palpable purpura is the most common clinical presentation of SVV. Other cutaneous manifestations, including urticarial-like lesions, erythematous plaques, and nodules, have been described but in much fewer numbers than the classic lesion of palpable purpura. By limiting inclusion to a classic clinical presentation of SVV, we believe that our cases are composed of a subset of patients with more representative disease. Furthermore, different stages in the histologic evolution of LCV, specifically, an increase in mononuclear leukocytes with time, have been described. To retain consistency in biopsy specimens, only lesions with an inflammatory infiltrate composed of at least 50% neutrophils were included in this study.

Vascular fibrin deposition is typically considered an integral feature of the histopathologic spectrum in LCV. In contrast, the study by Mullick et al did not reveal fibrinoid deposition or necrosis in any of the 30 patients with drug-induced vasculitis studied. An additional study in France described cases of LCV without fibrinoid involvement of the vessel wall. Therefore, we did not include evidence of vascular fibrin deposition as a requirement in the present study. However, if fibrinoid deposition was not present in the vessels, then endothelial cell swelling and red blood cell extravasation were required for inclusion in the study. We also noted patients without fibrin deposition in the drug-induced and non–drug-induced groups, and the amount of vascular fibrin deposition was not statistically significant between the 2 groups. Phenomena secondary to this deposition, that is, thrombus formation and epidermal changes, were also present in both groups. This finding suggests that although fibrin vascular changes are frequently seen in LCV of various etiologies, they should not be considered an integral histopathologic feature of LCV. In addition, evidence of fibrin vascular deposition should not be used as a differentiating feature of drug-related and non–drug-related LCV, as was previously suggested in the study by Mullick et al.

A difficult issue in cutaneous SVV is determining which patients will develop systemic manifestations of their disease. Moreover, defining whether the disease will take a long-term course further complicates patient management. Previous studies have attempted to clarify these issues based on histopathologic findings. Hodge et al examined 54 patients with cutaneous LCV and found that the severity of histopathologic changes seen on skin biopsy samples was predictive of clinical severity but not of internal manifestations of disease. Cribier et al investigated a large group of 189 patients with respect to histopathologic features and the development of systemic manifestations. The researchers reported that the severity of histopathologic changes based on findings of fibrinoid necrosis and the depth of inflammatory infiltrate were not predictive of extracutaneous involvement. A Spanish study by Sais et al did not find an association between histologic variables and disease prognosis. In the present study, we did not observe a trend with respect to fibrin vascular deposition and the presence of systemic symptoms.

With respect to the presence of systemic symptoms, we found, as expected, that systemic symptoms were present...
ent more often in the non–drug-induced group. Of the 2 patients with drug-induced SVV and systemic symptoms, 1 reported arthralgia alone and the other reported hematuria alone. Both of these patients had acute disease that fully resolved. This is in contrast to the non–drug-induced group, in which 7 of 15 patients with systemic involvement developed a long-term disease course. Patients with systemic involvement in the drug-induced group had only 1 extracutaneous site involved, whereas multiple extracutaneous sites were often involved in the non–drug-induced group. These findings reinforce the conclusion found in many previous studies9,14,15,25 that drug-related SVV is generally a benign disease limited to cutaneous involvement and an acute disease course.

Although these findings are reassuring in a patient who has SVV in the setting of drug administration, serious systemic complications are still a possibility. Mullick et al10 reported that 19 of their 30 patients with drug-related vasculitis developed systemic manifestations and that the vasculitis was the ultimate cause of death in 84% of those patients. To our knowledge, numbers as high as these have not been replicated. A more recent prospective study20 of LCV secondary to multiple etiologies found that in patients with systemic disease, 1.9% died as a result of systemic vasculitis. As stated earlier, it is far more likely that drug-induced SVV is a limited disease. However, as previously noted by Callen,26 it is prudent for the clinician to approach every case with the possibility of systemic involvement regardless of the etiology of the vasculitis. Evaluations should be undertaken to exclude systemic involvement, which could adversely affect prognosis.

It is feasible that any drug may be responsible for the development of SVV. Furthermore, drug additives used in various formulations may be implicated. The pathogenesis of LCV is believed to be largely secondary to the development of immune complexes.5,6 Detection of soluble complexes in the blood, hypocomplementemia, and deposition of immune reactants in the vessels have all lent support to this theory.27 More recently, adhesion molecules and endothelial cell activation have been shown to play a role.28,29 Drugs may play a role via 1 or more of these complex pathogenetic mechanisms.

We found that antimicrobials, analgesics, antihypertensives, anxiolytics, diuretics, and an additive in an injectable formulation were responsible agents in the present study. As previously reported in various investigations,9,11,14,20,25 we found that antimicrobials were the most common class of drugs implicated in drug-induced LCV. The list is exhaustive, but, in addition to those reported in our study, anticonvulsives, opiates, nonsteroidal antiinflammatory drugs, aspirin, pyrazolones, propylthiouracil, allopurinol, antituberculous agents, and antifungals have been implicated in previous studies.11,16,25,30 The frequency of drug-induced LCV ranges from 10% to 45% depending on the study and the patient selection methods used.9,11,14,20,25 Although the overall incidence of LCV has not been clearly documented, it is likely that drug-induced cases make up a significant portion of patients with the disease. Thus, it is important for clinicians to be aware of the drugs commonly found to be responsible for cutaneous SVV. Moreover, novel therapies, such as biologic mediators, have been associated with vasculitis.31 Last, additives in particular medications or even different formulations of the same medication may result in LCV.

Although the terminology and classification of cutaneous SVV remains imperfect, the disease entity warrants investigation. This is especially true in clinical practice, where insight into the etiology of LCV is a powerful tool in treatment. A significant percentage of LCV cases, 25% in the present study, are drug induced. Removal of an offending drug is an easily accomplished remedy that is generally without significant cost to the patient. Further systemic sequelae of cutaneous SVV do not occur in most patients, and a short-term disease course is typical. Thus, withdrawal of medication is often the only therapy needed for disease resolution. This investigation indicates that a significant histopathologic clue, specifically, high tissue eosinophilia ratios in biopsy samples that demonstrate LCV, is a pertinent finding related to an etiology of drug administration. This useful information in a pathology report, in conjunction with an appropriate clinical history, can provide the clinician with a practical tool for delineating the etiology of cutaneous SVV.

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