

Bullous Reactions to Bedbug Bites Reflect Cutaneous Vasculitis

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ABSTRACT

BACKGROUND: There has been a worldwide resurgence of bedbug infestations. Bites by these insects may cause mild or severe cutaneous reactions, and anaphylaxis has been reported. Little is known about the most severe cutaneous reactions, termed bullous or complex reactions.

OBJECTIVE: To study the time course and histopathologic findings of complex (bullous) cutaneous reactions to bedbugs in order to determine the optional treatment for them.

DESIGN, SETTING, AND PARTICIPANTS: We prospectively photographed bullous reactions to observed bedbug bites at 30 minutes; 6, 12, 24, 36, 48, and 72 hours; 1, 2, 3, and 4 weeks, and biopsied reactions at 30 minutes, and 6, 12, and 24 hours. We also reviewed Internet postings and the available medical literature on bullous reactions after bedbug bites.

MAIN OUTCOMES AND MEASURES: Correlations between clinical and histologic findings using both routine and immunofluorescent techniques.

RESULTS: Bullous reactions to bedbugs are not rare. Of 357 photographs of bedbug bites posted on the Internet, 6% were bullous. In an individual with previous bullous reactions, experimental bedbug bites were associated with a progression of cutaneous responses at bite sites from immediate, pruritic, edematous lesions to a late-in-time macule, which evolved into bullous reactions by 24 hours. Bullous lesions eventually lysed but took weeks to heal. Histopathologic evaluation of bullous reactions showed a polymorphous picture with histologic evidence of an urticarial-like reaction early on that rapidly developed into a hybrid leukocytoclastic vasculitis. This vasculitis was initially neutrophilic but developed into a destructive, necrotizing, eosinophil-rich vasculitis with prominent infiltration of CD 68+ histiocytes and collagen necrobiosis. This histologic picture is similar to the dermal vasculitis in patients with Churg-Strauss vasculitis.

CONCLUSION: Historically, bedbug bite reactions have been considered to be of minor medical significance. However, the findings presented here demonstrate that the not-uncommon bullous reactions to bedbug bites reflect the presence of a local, highly destructive, cutaneous vasculitis. The histologic features of these reactions resemble those occurring in the Churg-Strauss syndrome. Therefore, efforts to prevent further bites and monitor for evidence of systemic vasculitis should be made in patients with bullous reactions to bedbug bites. Topical treatment with high potency corticosteroids may be useful in the treatment of bullous reactions.

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The resurgence of the common bedbug *Cimex lectularius* in this decade is well documented.¹ Despite a diet limited to blood, there remains no convincing evidence that the common or the tropical bedbug, *C. hemipterus*, are biological vectors of disease.² Apart from concerns about disease transmission, bedbugs are annoying, difficult to control, anxiety producing, and cause symptoms ranging from localized cutaneous responses to anaphylaxis.³ The latter reactions have been attributed to the production of immuno-

globulin E (IgE) specific for bedbug-specific salivary proteins.^{4,5}

On the basis of our observations and the limited data in the medical literature, we recently proposed that cutaneous reactions to bedbug bites are classified as usual, common, or complex.² The usual reactions occur within an hour and consist of pruritis and a punctum at the site of the bite. Common reactions occur hours later and are pruritic macules or papules at bite sites that are often erythematous and pruritic. They resemble papular urticaria seen with other arthropod bites and have eosinophil predominant perivascular infiltrates on histopathology.⁶ The third and more clinically impressive complex reactions are bullous, may have immediate, late, and delayed components, persist for days, are pruritic, painful, and frequently leave residual scarring or hyperpigmentation.^{4,7-13} When new bites occur in individuals with previous bullous reactions, inflammation may occur at sites of previous reactions.¹⁴ Although descriptions and photographs of bullous reactions have been published both in the medical literature¹² and on websites where bedbugs are the topic of discussion, their histopathology and pathophysiology is unclear.

We have had the unique opportunity prospectively to evaluate bullous cutaneous reactions to bedbug bites and to perform sequential histopathologic studies to better understand their mechanism and guide therapy. To our surprise, bullous reactions indicate the presence of a highly inflammatory, acute cutaneous vasculitis.

MATERIALS AND METHODS

Subject

A 61-year-old entomologist (MFF) who currently maintains bedbugs for research purposes presented for evaluation of severe cutaneous reactions to bedbug bites. He provided a photograph of one such reaction taken 24 hours after a bite (**Figure 1**). His only prior bedbug bites occurred 32 years previously, when he fed about 40 bedbugs on his forearm weekly. After several weeks, he developed pruritic, papular cutaneous (common) reactions at bite sites and stopped feeding the bugs on himself. In late 2008, he established a laboratory colony of bedbugs and, on several occasions over the next year, was accidentally bitten. The reactions recurred, worsened, became bullous, and he sought medical attention. As a scientist, he also desired to participate in research on the pathophysiology of these reactions. Therefore, institutional review board approval was obtained for this

evaluation (MedStar Research Institute Protocol 2009-220; Hyattsville, Md).

Bedbugs

Unfed nymphs of *C. lectularius* used in this study were obtained from a laboratory colony originally established by Harold Harlan, PhD (Crownsville, Md). The colony was kept at $27^{\circ} \pm 2^{\circ}$ and $40\% \pm 5\%$ relative humidity and fed weekly using an artificial feeding system containing outdated packed red blood cells and plasma (1.25:1; v:v;) obtained from the blood bank at the Walter Reed Army Medical Center, Washington, DC.¹⁵

Natural History of Cutaneous Reactions

In an effort to document the time-course of his cutaneous reactions, the same entomologist allowed 5 bedbug nymphs to feed to repletion on his forearm. One bite site was photographed sequentially and the remaining 4 were biopsied sequentially at intervals of 30 minutes, 6 hours, 12 hours, and 24 hours after bedbug bites. Clinical symptoms also were recorded at these intervals.

CLINICAL SIGNIFICANCE

- The complex or bullous reaction to bedbug bites is the more serious cutaneous reaction and is associated with symptoms that last for weeks.
- The bullous reaction represents an area of intense, local "hybrid" cutaneous vasculitis and is probably best treated by high potency topical corticosteroids or a short course of oral steroids.

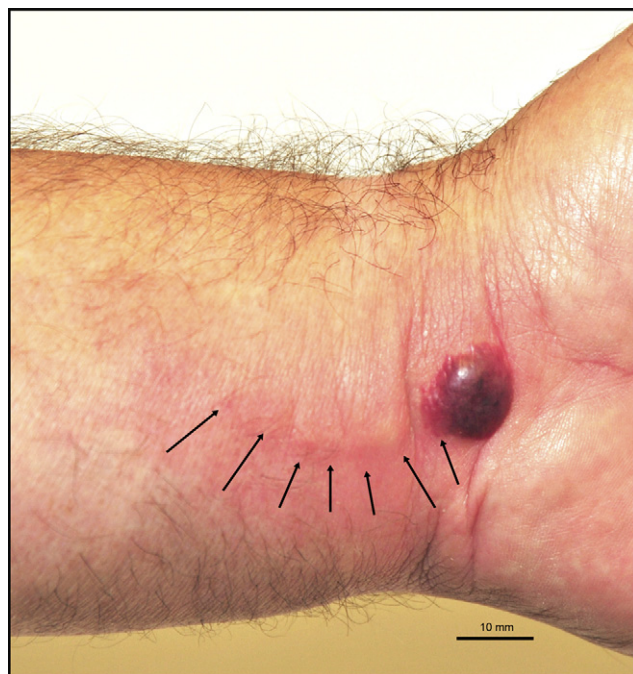


Figure 1 Bullous reaction from an accidental bite of a *C. lectularius* nymph 24 hours after the bite. There is a visible path where the nymph appears to have probed before feeding at the main site (arrow). Line equals 10 mm.

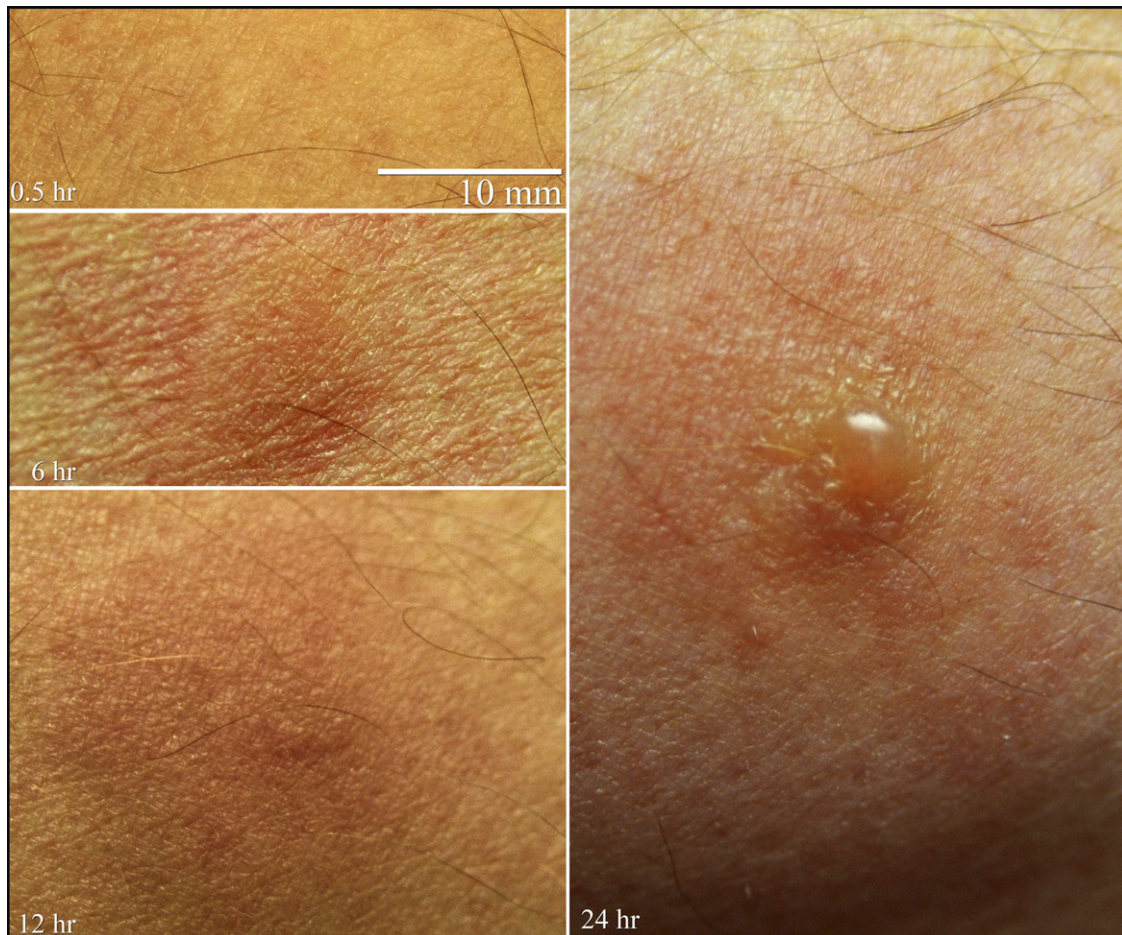


Figure 2 Sequential photographs of a bedbug feeding site in our study subject between 30 minutes and 24 hours.

Biopsies

Four-millimeter punch biopsies were placed in formalin, fixed, and provided to a dermatopathologist (MCM) for staining. Giemsa staining was used to detect mast cell degranulation while other sections were stained with monoclonal antibodies to assess the presence of mononuclear cell subpopulations CD 68+, CD4+, and CD8+. Staining was performed and scored as previously published methods.¹⁶

Review of Internet Bedbug Bite Postings

How often bullous reactions occur to bedbug bites is unknown. We sought a better understanding of their prevalence by reviewing available photographs of bedbug bites on medical websites and on postings on bedbug interest sites on the Internet. Photographs of bedbug bites on the websites www.dermatlas.com, www.flicker.com, www.webmd.com, www.sternenvironmental.com, www.badbedbugs.com, www.bedbuginfo.com, and www.bug.com were reviewed to determine the percentage of bedbug bites posted that were bullous.

RESULTS

Internet Bedbug Sites

We found 357 photographs of bedbug bites on the Internet sites visited, of which 21 (6%) were bullous. The timing, where reported, and appearance of the bullous reactions were similar to those in our patient.

Clinical Features of Cutaneous Reactions in Our Patient

The patient reported no sensation at sites of attachment while the bedbugs were feeding. Thirty minutes after feeding, mild erythema and edema developed around the bite site. A classical wheal and flare, urticarial response was not visible. Erythema, itching, and burning at and surrounding the feeding sites developed during the first hour after bites and continued during the observation period. Moreover, bite sites were subsumed by an erythematous, indurated, painful macule, which grew in size (**Figure 2**). By 24 hours, a fluid-filled blister was present at the unbiopsied site, arising from the underlying macule.



Figure 3 Sequential photographs of a bedbug feeding site in our study subject between 24 hours and 4 weeks. There was progression from blister to bulla, lysis of bulla, and gradual healing at the bulla base with scarring and hyperpigmentation.

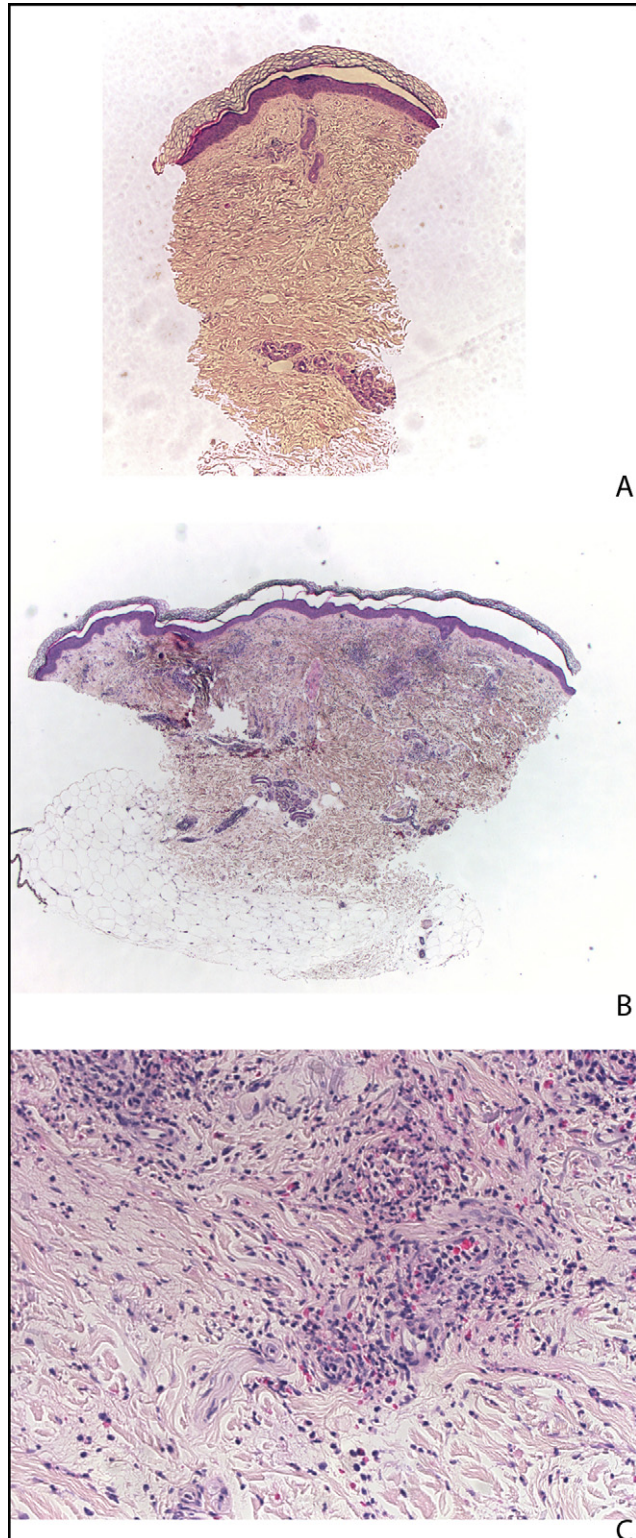
To gather further information about the natural history of these reactions, the patient subsequently photographed another bedbug feeding site at 24, 36, 48, and 72 hours, and 1, 2, 3, and 4 weeks after a bite (**Figure 3**). Bullous reactions eventually lysed and the underlying bases healed slowly over 4 weeks. Fever, chills, malaise, and other symptoms of a systemic reaction did not develop, with the first or second experimental bites, although reaction sites remained painful to touch.

Biopsy Results

There was a progression of the inflammatory response across time in biopsies. At 30 minutes, the histopatho-

logical findings associated with urticarial-type reactions were present with edema, mast cell degranulation, and a mixed cellular infiltrate (**Figure 4 A**). By 6 hours, an inflammatory vasculopathy was present with a mixed cellular infiltrate (**Figure 4, B, C**) that went on to a neutrophil-predominant leukocytoclastic vasculitis by 12 hours (**Figure 5**). By 24 hours, there was a destructive, necrotizing, eosinophil-rich vasculitis similar to that previously reported in Churg-Strauss vasculitis (**Figure 6**). That pattern has been described as “stellate necrobiosis with encrustation of degenerating collagen fibers by eosinophil granules.”^{17,18} The mast cells were focally de-

granulated in several of the specimens, where they correlated with the edema present. An unusual component of these reactions was the prominent infiltration of CD68+ histiocytes that favored, at least in part, a delayed hypersensitivity mechanism.



DISCUSSION

The pathophysiology of adverse cutaneous reactions to bedbug bites is poorly understood, and thus, treatment of these reactions remains empiric. The findings of a “hybrid pattern of vascular injury” similar to that seen in syndromes of systemic vasculitis and our review of the literature suggests that bullous reactions may reflect simultaneous immunologic reactions to multiple arthropod antigens at one site.¹⁸ At least 3 antigens have been identified in bedbug saliva and provide a robust immunogenic substrate for hypersensitivity reactions.^{5,15,19}

The reaction present at 30 minutes after bite appears to reflect mast cell-mediated immediate hypersensitivity, while the 6- and 12-hour reactions showed severe leukocytoclastic vasculitis. The blistering reactions present at 24 hours were visually similar to accelerated late-type hypersensitivity reactions seen in tuberculin skin testing in some hyperimmune individuals. However, from a histopathologic perspective, that reaction had elements of a severe delayed hypersensitivity reaction, with histiocytes and an immune complex reaction with leukocytoclastic vasculitis. The striking changes in the 24-hour biopsy were similar to the distinctive histopathologic findings in the skin noted in Churg-Strauss vasculitis.

One report of a patient with bullous reactions demonstrated specific IgE to the bedbug nitrous oxide transporting salivary hemeprotein, nitrophorin. The authors assumed that bullous reactions to bedbug bites were likely the same IgE-mediated, biphasic, late cutaneous allergic reactions we have previously described to insect stings, and intradermally injected protein allergens to include insect venoms, ragweed, and insulin in allergic individuals.^{5,20-22} The importance of a histopathologic approach to the origin of cutaneous reactions like that used in this study was demonstrated in a previous study of cutaneous reactions to another arthropod, the common flea.²³ In that study, both IgE- and IgG-specific antibody responses were present in serum to flea antigens. However, biopsy findings of cutaneous reaction sites were more compatible with a delayed hypersensitivity response.

Figure 4 (30 minute and 6 hour reactions) (A) 30 minutes. A striking urticarial-type reaction was present with very prominent edema and paucicellular infiltrate (40X). Immunofluorescence studies for mononuclear cell subtypes showed trace CD4 positivity and 1+ CD68 positivity and negative CD8 staining (not shown). Giemsa stains showed a slight increase in mast cells with 2+ degranulation (not shown). (B) 6-hour reaction. There is a striking vasculopathy with neutrophils, histiocytes, and lymphocytes in a perivenular array (25X). The cells stained 3+ for CD68 and 1+ for CD4. There was focal CD8 positivity in infiltrating lymphocytes (not shown). (C) 6-hour reaction. There also was focal extravasation of red blood cells (200X). Giemsa stains showed normal mast cells without degranulation (not shown).

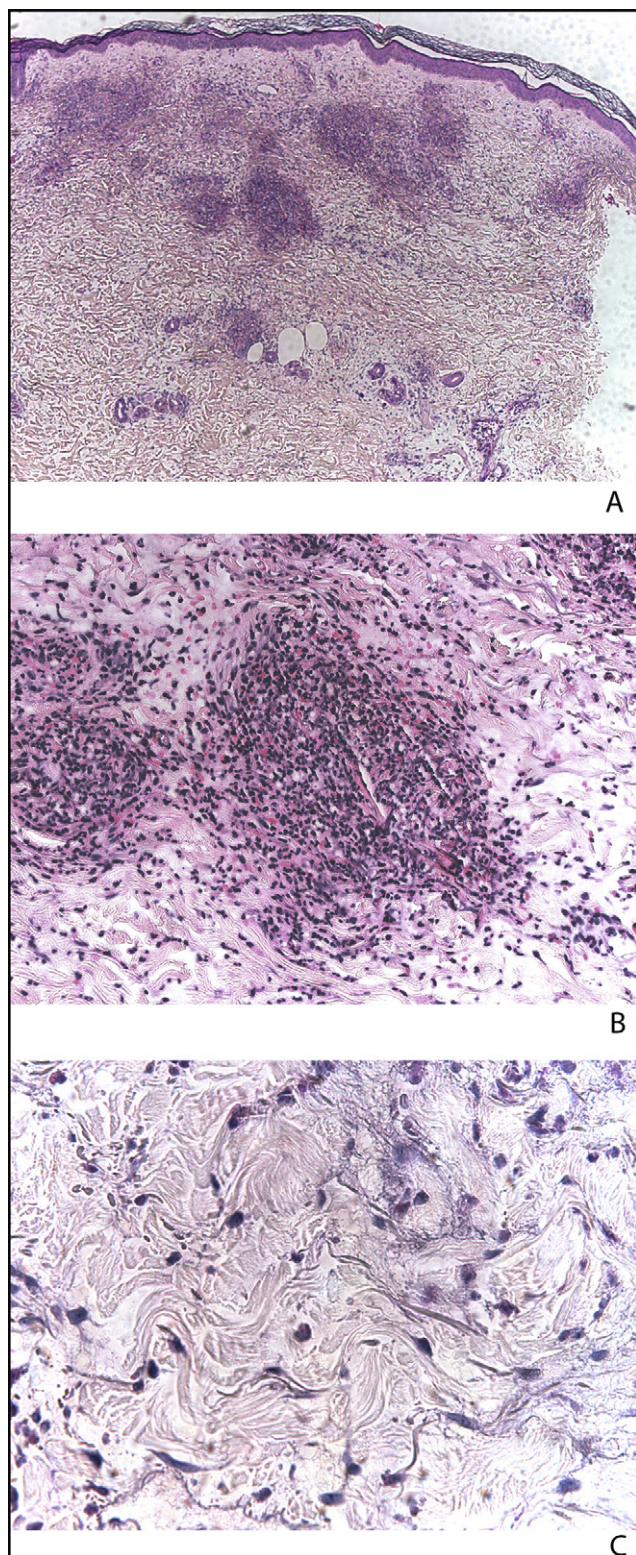


Figure 5 12-hour reactions. (A) There was a vasculitic reaction with striking fibrinoid necrosis and a 4+ infiltrate of neutrophils (100×). (B) There were vesicles with neutrophilic debris, eosinophils, and hemorrhage (200×). Immunofluorescent studies showed 3+ staining for CD68 cells, trace CD4 and CD8 positivity (not shown). (C) There was 3+ mast cell degranulation on CAE (chloroacetate esterase) stain (400×).

Another author reported that repeated bedbug bites in a patient with bullous reactions were associated with febrile episodes, a systemic symptom not noted in IgE-mediated late cutaneous allergic reactions, and one that suggested other mechanisms like those seen here.¹³ Patients with this degree of cutaneous hypersensitivity could be at risk for a syndrome of systemic hypersensitivity with multiple repeated insect bites. Monitoring of patients who develop bullous reactions after bedbug bites for evidence of systemic vasculitis, and extensive efforts to prevent additional bites, seems prudent.

Finally, the findings here suggest that early use of high-potency topical corticosteroids plus oral antihistamines are likely to be the treatment of choice in individuals who develop bullous reactions to bedbug bites. Oral corticosteroids may be required in patients with diffuse bullous reactions.

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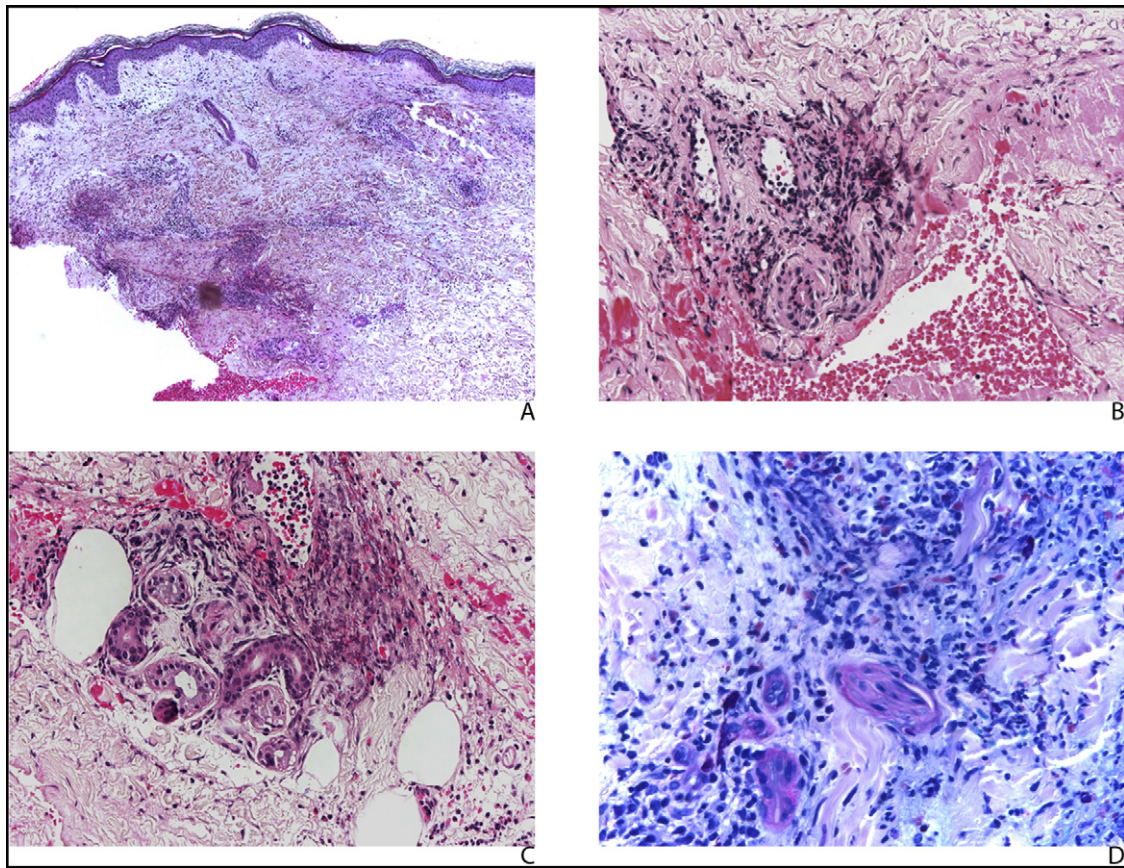


Figure 6 24-hour reactions. (A) There was a striking necrotizing vasculitis with numerous eosinophils (40 $\times$). (B) The perivascular eosinophils were markedly degranulated (200 $\times$). Immunofluorescence staining showed an admixture of eosinophils with a 2+ concentration of CD68 positive histiocytes. There was 1+CD4 and focal 1+ staining for CD8-positive lymphocyte as well. (C) There was a Churg-Strauss-like eosinophilic vasculitis in some areas with eosinophil granules coating collagen fibers surrounded by a palisading histiocytic infiltrate (400 $\times$). (D) Giemsa stains showed focal degranulation of the mast cells and massive degranulation of the eosinophils (400 $\times$).

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