Wells’ Syndrome Proceeded by Leukocytoclastic Vasculitis: A Discussion with New Insights into Analogous Pathophysiology

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Abstract
Wells’ syndrome, also referred to as eosinophilic cellulitis, is a rare inflammatory dermatosis. Although its etiology is unknown, it is thought to be an abnormal eosinophilic response to one of various causative agents. Its cutaneous manifestations vary in morphology and severity, but the disease often follows a relapsing-remitting course. We report the case of a patient with Wells’ syndrome preceded by leukocytoclastic vasculitis (LCV).

Introduction
Wells’ syndrome, also referred to as eosinophilic cellulitis, is an uncommon inflammatory dermatosis, with fewer than 200 cases reported worldwide.1 It was first described in 1971 by George Wells, noted as a rare entity with an unknown etiology.2 It often presents with a prodromal burning or pruritic sensation, which is followed by a widespread eruption consisting of urticarial erythematous papules, plaques, and bullae of the trunk and upper and lower extremities. Head and neck involvement has also been reported. Often, the cutaneous manifestations recur.1 Although the exact pathophysiology of the disease is unknown, many associations have been reported. A diagnostic criterion has been developed to aid physicians in this uncommon diagnosis, but many cases of Wells’ syndrome are still misdiagnosed.3

Here, we present a patient with a one-year history of LCV who subsequently developed Wells’ syndrome, an association not yet reported in the literature. Whether this case depicts a causal association or reflects a shared pathophysiology is unknown, but it may spur awareness of and further research into Wells’ syndrome in an effort to better understand the disease’s pathophysiology, diagnosis, and treatment options.

Case Report
A 55-year-old African-American female with a past medical history of hypertension presented to our clinic with a two-month history of a purpuric vesicular eruption of the lower extremities that was clinically and pathologically consistent with leukocytoclastic vasculitis (LCV) (Figures 1, 2). Her LCV was thought to be secondary to hydrochlorothiazide (HCTZ) therapy, which she had recently started for hypertension management. She was switched from HCTZ to lisinopril and attained a partial resolution of her symptoms.

At three-month follow-up, the patient presented with a more widespread eruption consisting of scattered urticarial papules, nodules, and plaques involving the trunk and upper and lower extremities, with occasional vesicles and bullae in a similar distribution (Figures 3, 4). The clinical differential was expanded to include bullous pemphigoid, arthropod assault, bullous Sweet’s syndrome, and Wells’ syndrome with or without coexisting LCV. We performed two 4-0 mm punch biopsies: one lesional biopsy from a bulla on the left lateral leg, and one perilesional biopsy from skin directly adjacent to the bulla. They were sent for direct immunofluorescence (DIF), which revealed an overwhelming number of eosinophils in the superficial and deep dermis (Figures 5, 6). The biopsy was read as bullous pemphigoid vs. Wells’ syndrome. The negative DIF together with appropriate clinical and pathologic correlation pointed to Wells’ syndrome. The patient was given a one-month course of prednisone and was free of symptoms at three-month follow-up. She was lost to further follow-up.

Discussion
Clinical Presentation
Wells’ syndrome, first described in 1971 as a “granulomatous dermatitis with eosinophilia,” is commonly referred to as eosinophilic cellulitis and characterized by acute pruritic dermatitis. The clinical appearance can vary depending on the presenting variant. To date, there have been seven clinical variants described in the literature, including plaque, annular granuloma-like, urticaria-like, papulovesicular, bullous, papulonodular, and fixed drug eruption-like.4 Morphologically, one of the most common presentations is a sudden onset of one to several pruritic or painful, edematous, erythematous papules, nodules and/or plaques.1,5,6 Other

Figure 1. Multiple, 2 cm to 3 cm, non-blanchable purpuric vesicular plaques on left lower extremity, clinically and histologically consistent with LCV.

Figure 2. Biopsy of left lateral leg revealing epidermal necrosis with neutrophils and neutrophilic debris in the epidermis. In underlying dermis, neutrophils and eosinophils are present along with significant leukocytoclastic debris, vessel fibrin, and thrombi (H&E, 20x).

Figure 3. Multiple erythematous urticarial plaques on the chest.

Figure 4. Multiple erythematous urticarial plaques on the back.

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presentations include a sudden eruption of cellulitic lesions with blistering, and annular or circinate, erythematous plaques with infiltrated borders. Lesions evolve over two to three days, with complete resolution in about two to eight weeks. The disease recurs in many patients. In a comprehensive review, Sinno et al. calculated a recurrence probability of approximately 56%.

**Etiology**

The etiology of Wells’ syndrome is uncertain; however, some important associations have been documented in the literature. Multiple medications have been cited as causal agents, including antibiotics, anticholinergic agents, anesthetics, non-steroidal anti-inflammatory agents, thyroid medications, chemotherapeutic agents, thiomersal-containing vaccinations, and anti-TNF agents. Of note, the thiazide group of drugs is involved in leukocyte rolling and homing. Thus, while the exact underlying dysregulation involved in leukocyte rolling and homing is not well understood, it is plausible that the processes underlying the dysregulation involved in neutrophil recruitment in LCV could also trigger alterations in IL-5 or other homing signals, leading to inappropriate recruitment of eosinophils to the skin.

Wells’ syndrome has been linked to colonic adenocarcinoma and several hematologic diseases, including chronic lymphoid leukemia, malignant lymphoma, and polycythemia vera. Nakazato et al. reported a case of Wells’ syndrome in a patient with CML. Due to the association between Wells’ syndrome and underlying malignancy, investigation for underlying disorders is warranted in patients diagnosed with Wells’ syndrome. Reports also associate Wells’ syndrome with ascariasis, colon carcinoma, Churg-Strauss, Sweet’s syndrome, STE, HSV type 2, autoimmune disorders, arthropod bites, and viral or bacterial infections. To our knowledge, this is the first published report of a possible association between Wells’ syndrome and leukocytoclastic vasculitis (LCV).

It has been speculated that a hypersensitivity reaction may play a role in the disease process, lending support for arthropod bites as a possible etiology of Wells’ syndrome. Furthermore, there is some evidence that abnormal “homing” of eosinophils to target tissue via abnormal levels of IL-5 is involved in the underlying pathophysiology. Pathophysiology

While the unique presentation of LCV and Wells’ syndrome in this case may not represent associated processes, it may offer insight into the underlying pathophysiology of both diseases. Like Churg-Strauss and Sweet’s syndrome, LCV is a form of vasculitis characterized by inappropriate infiltration of vessels by inflammatory cells such as neutrophils. This process is thought to be due to a dysregulation in the complex process of inflammatory-cell recruitment and homing to specific tissues. In the case of LCV, one of the most common findings is that of immune complex deposition leading to the inappropriate recruitment of neutrophils to a tissue. Some studies also note dysregulation of key integrins and selectins involved in leukocyte rolling and homing.

In the case of Wells’ syndrome, one case study suggests that altered levels of IL-5 are involved in inappropriate recruitment and homing of eosinophils to tissues. Furthermore, an animal study in mice noted the importance of IL-5 and other cytokines in eosinophilia and tissue homing, demonstrating how dysregulation of IL-5 could plausibly lead to eosinophilia and inappropriate recruitment of eosinophils into specific tissues. Thus, while the exact underlying mechanisms of both LCV and Wells’ syndrome are not well understood, it is plausible that the processes underlying the dysregulation involved in neutrophil recruitment in LCV could also trigger alterations in IL-5 or other homing signals, leading to inappropriate recruitment of eosinophils to the skin.

**Diagnosis**

Clinically, diagnosis of Wells’ Syndrome requires certain criteria be met. Caputo et al. describe them as: (1) protein cutaneous manifestations that showed spontaneous resolution or response to nonaggressive treatments; (2) a recurrent course; (3) benign clinical behavior; (4) no evidence of systemic illness; (5) lack of evidence of triggering factors, including insect bites, bacterial, viral, and parasitic infections or infestations, as well as any kind of drug intake; (6) histopathologic changes of eosinophilic dermatosis, with or without granulomatous features, with possible presence of typical flame-shaped figures; (7) negative direct immunofluorescence findings; and (8) inconsistent blood eosinophilia.

Histologically, dermal eosinophilic infiltration and, in the acute phase, peripheral eosinophilia differentiate Wells’ syndrome from infectious cellulitis. During the early phase of disease, dermal edema and diffuse dermal infiltration of eosinophils is seen. In the subacute phase, a characteristic infiltrate of phagocytic histiocytes and flame figures is seen on histopathology. In later phases of disease, fewer eosinophils, histiocytes, giant cells, and flame figures are present. Although important in the histologic diagnosis of Wells’ syndrome, flame figures are not pathognomonic. Flame figures may be present in various other dermatologic conditions including pemphigoid, severe prurigo, eczema, arthropod bites, Churg-Strauss and other inflammatory conditions characterized by eosinophilia. Thus, clinical correlation with histologic findings is essential.

Based on the infiltrate pattern seen on histopathology, a differential diagnosis for Wells’ syndrome may include granuloma annulare, granuloma faciale, urticaria, and, as in this case, leukocytoclastic vasculitis. Histopathologically, both LCV and Wells’ syndrome show eosinophils. LCV can be differentiated by its angiocentric infiltrate, representing fibrin around inflamed vasculature, and the presence of neutrophilic debris (leukocytoclasia), which differs from the diffuse dermal infiltration of eosinophils seen in Wells’ syndrome.

**Treatment**

A variety of treatments has been cited in the literature as possible therapies for Wells’ syndrome, including low-dose oral corticosteroid therapy. Studies report success rates of up to 92% with steroid therapy alone. Other case reports document varying degrees of success with griseofulvin, dapsone, antihistamines (cetirizine), sulphones, interferon-γ, cyclosporine, and antimicrobial agents.

**Conclusion**

Wells’ syndrome is a cutaneous inflammatory syndrome that runs a benign but often relapsing course. A patient with an atypical presentation of cellulitis unresponsive to antibiotic therapy should prompt suspicion of Wells’ syndrome. While Wells’ syndrome has been associated with several diseases, this case report is novel in that it is the first of its kind to present a patient with Wells’ syndrome in the setting of LCV. We hope that this possible association between Wells’ syndrome and LCV leads to further study and insight into this syndrome’s etiology, pathophysiology, and ideal management strategies.
References


