CLINICAL VIGNETTE

Wells Syndrome: A Rare Dermatologic Complication of Chronic Lymphocytic Leukemia

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Background

Wells Syndrome or Eosinophilic Cellulitis is a rare inflammatory dermatologic disorder first described by the British Dermatologist Dr. GC Wells in 1971 as "recurrent granulomatous dermatitis with eosinophilia".[1] In 1979, the term "Wells Syndrome" was coined by Spiegel and Winkelman to credit Dr. Wells who published eight more cases in one year and simplified the syndrome name to "Eosinophilic Cellulitis".[2,3] Limited prevalence and incidence data are available as it is rare and largely not tracked. Fewer than 200 cases have been published as of the past decade.[4,5] Clinically, it is characterized by recurrent onset of edematous, non-tender, erythematous and pruritic lesions involving the torso and extremities. They can spontaneously resolve without scarring within 2 - 8 weeks.[3–6] Lesion morphologies include vesicles, papules, nodules, plaques and bullae.[3,5–7] Histologically, Wells syndrome is typified by interstitial eosinophilic infiltration with eosinophil major basic protein, collection of eosinophilic granules and nuclear fragments encasing collagen fiber depositions constituting the "flame figures" observed in the dermis.[3,8,9] Superficial and deep non-specific inflammatory infiltrates may be present.[6] Diagnosis of Wells syndrome involves a combination of clinical and histological findings. There is no current consensus on diagnostic criteria given the evolving understanding of the disorder. Diagnosis is often delayed due to the clinical presentation's resemblance to bacterial cellulitis.[6] Despite reports of superinfection of the lesions with gram positive and negative bacterial[7,10] these recurrent lesions usually do not respond to antibiotic regimens. They have negative immunofluorescence and special staining for microorganisms.[3,5,6] The pathophysiology of the aberrant eosinophilic activation or regulation characterizing Wells syndrome is poorly understood, although upregulated interleukin signaling has been observed.[11] Management is primarily topical corticosteroids as first-line therapy with escalation to oral and intravenous anti-inflammatory therapies if topical corticosteroids do not provide adequate control.[5,6,12]. Monoclonal antibodies targeting interleukin-5 (IL-5) and immunoglobulin E (IgE) have been suggested to be effective long-term therapies, but prospective, properly controlled studies are needed for validation.[13–15]

The inflammatory eosinophilic degranulation in Wells syndrome has been reported to be in response to infectious, and non-infectious stimuli. These include parasites, viruses, pharmacological agents, insect bites, and other inflammatory disorders.[4,16] Wells syndrome has also been associated with hematologic malignancies such as chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), non-Hodgkin lymphoma.[17,18] The immune deficits accompanying these hematologic malignancies may contribute to the eosinophilic sensitivity modulations that develop during the course and management of Wells syndrome.[18] We report a patient who developed Eosinophilic cellulitis (Wells syndrome) as a rare dermatologic complication of chronic lymphocytic leukemia.

Clinical Presentation and Course

A 70-year-old male was diagnosed with CLL in 2005. He was started on chemotherapy in 2014 for progressive fatigue, leukocytosis and diffuse adenopathy that developed almost a decade after initial diagnosis. He completed four cycles of Bendamustine and Rituximab with clinical remission and symp-tom improvement. However, a PET/CT four years after starting treatment showed diffuse adenopathy and splenomegaly. He also had leukocytosis of 50,000 / µL with a peripheral monoclonal B cell population. He denied fever, chills, night sweats, weight loss or pain. He was also noted to be hypoimmunoglobulinemic (seral IgG of 485mg/dl, IgA <8 mg/dl, and IgM <6 mg/dl) and received intravenous immunoglobulin transfusions (IVIG). Five years later, he was retreated with five cycles of Bendamustine and Rituximab and has remained free of disease with no symptom progression. His white blood cell count was 3.5 x 10^3/µL with absolute lymphocyte count of 1.55 x10^3 / µL.

Two months later, he developed recurrent, erythematous bullae and papulovesicular pruritic lesions (Figure 1) that were initially thought to be infectious and was referred to an Infectious Disease (ID) specialist. These lesions would occasionally resolve without scarring and involved his bilateral upper (BUE)

and lower extremities (BLE) in addition to his torso. Wound cultures revealed few colonies of Enterococci which were treated with ceftriaxone. Blood cultures showed no growth, and he remained afebrile. He was subsequently thought to have folliculitis and initiated on oral Cephalexin. He then developed more lesions concerning for bullous pemphigoid with older lesions showing slight improvement and scabbing. He developed intolerance after one week of doxycycline and started prednisone. Following prednisone taper, he continued to note new pruritic skin lesions on his extremities and chest that were managed with topical steroid lotions with some improvement of his lower extremity lesions.

One month later, he developed new erythematous skin lesions of BUE, BLE after working in his garden wearing shorts and short sleeves. Insect bite exacerbation was suspected. Following a multidisciplinary conversation, one month later a punch skin biopsy was obtained from the left superior popliteal fossa. It revealed superficial and deep perivascular and interstitial mixed inflammatory infiltrates composed of lymphocytes, neutrophils and abundant eosinophils. The pattern of the infiltrate and the abundance of eosinophils and lymphocytes raised the possibility of Eosinophilic cellulitis (Wells syndrome) likely related to CLL. Immunofluorescence probing revealed weak C3 granular deposition within the walls of superficial dermal vessels – a non-specific finding in areas of inflammation (Figure 2).

Conclusion

Wells syndrome (Eosinophilic cellulitis) is a rare dermatologic inflammatory disorder of unknown incidence and prevalence characterized by recurrent erythematous lesions that can spontaneously heal without scarring with aberrant eosinophilic infiltration and degranulation and presence of dermal flame figures. Presentation may resemble bacterial cellulitis, but consideration for Wells syndrome should arise in patients with recurrent lesions that are refractory to antibiotics. Diagnosis requires a combination of histopathologic features on skin biopsy. Pathophysiology is largely not understood with reports of perturbations in inflammatory signaling and aberrant recruitment of T-cells and interleukin secretion. Associations with hematologic malignancies have been reported and may suggest immune deficits modulating sensitivity pathways. Our patient developed Eosinophilic cellulitis as a rare dermatologic complication of chronic lymphocytic leukemia. These lesions are sporadic and can be difficult to treat. Options include topical or oral steroids, as well as antihistamines.

Figures

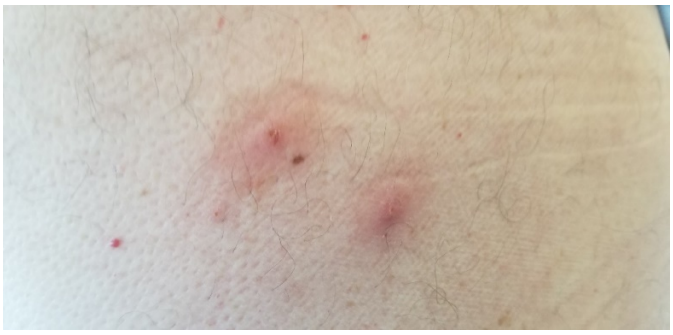

Figure 1. Typical lesions of patient, located on thigh.

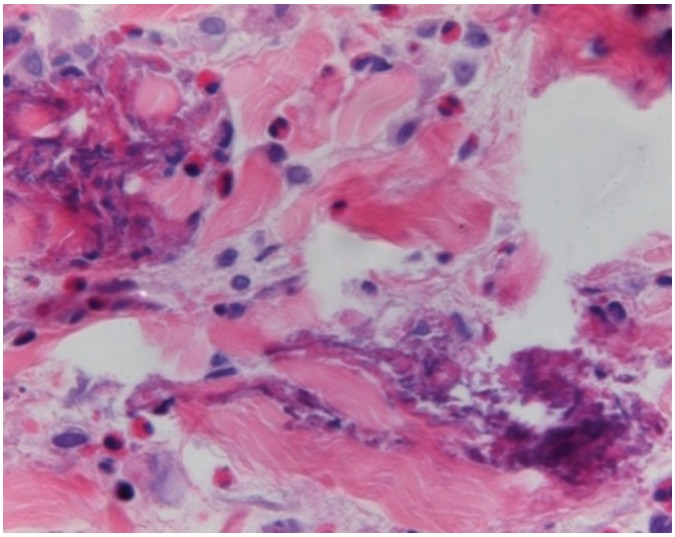

Figure 2. Skin biopsy with flame figure, dermal edema and dermal infiltration by eosinophils.[5]

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