JAMA Dermatology Clinicopathological Challenge

# Vesicles and Bullae on the Right Cheek, Neck, and Both Hands

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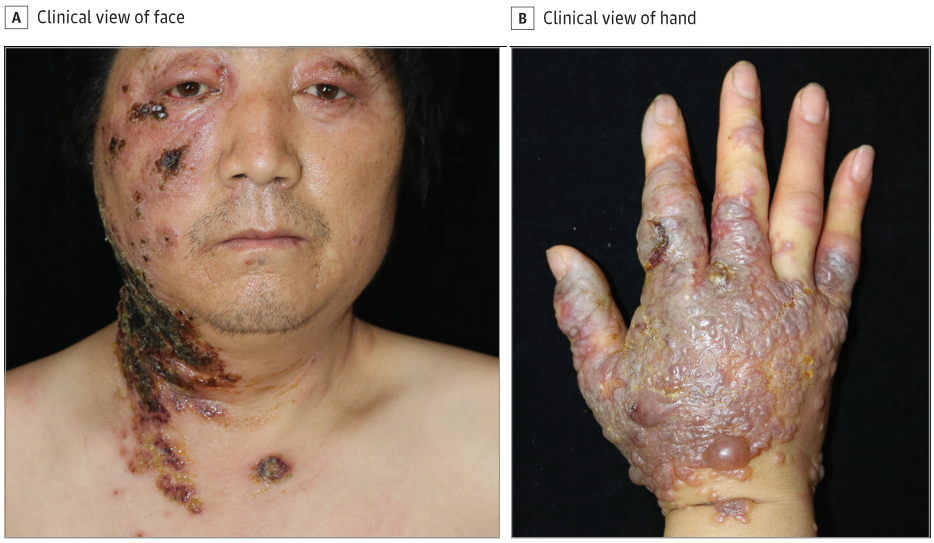



**Figure 1.** A, Edema on both eyelids; multiple papules, blisters, and crusted erosions with thin exudation on right cheek and neck. B, Erythematous plaques, tense blisters, and bullae on both hands (right hand depicted).

**A man in his 40s** was admitted to the hospital with a 10-day history of edema and presented with vesicles and bullae on his right cheek, neck, back, both eyelids, and the dorsal surface of his hands (**Figure 1**A). Prior to presentation, he had been treated for herpes zoster with famciclovir for 1 week, during which the lesions kept developing and were accompanied with irregular fever (maximum temperature, 39°C). Physical examination revealed edema on both eyelids; multiple papules, blisters, and crusted erosions with thin exudation on his right cheek and neck; and erythematous plaques and tense blisters and bullae on his back and on the dorsal surface of both hands (Figure 1B). A full laboratory workup was performed for autoantibodies for systemic lupus erythematosus (SLE), pemphigus, and bullous pemphigoid; skin and bone-marrow biopsies and direct immunofluorescence were performed; and immunohistochemichal analysis, a swab of exudation, and bacterial, fungal, and atypical mycobacterial cultures from blood and tissue were also examined.

**WHAT IS YOUR DIAGNOSIS?**

- **A.** Famciclovir-resistant disseminated herpes zoster
- **B.** Bullous Sweet syndrome
- **C.** Bullous Wells syndrome
- **D.** Bullous pemphigoid

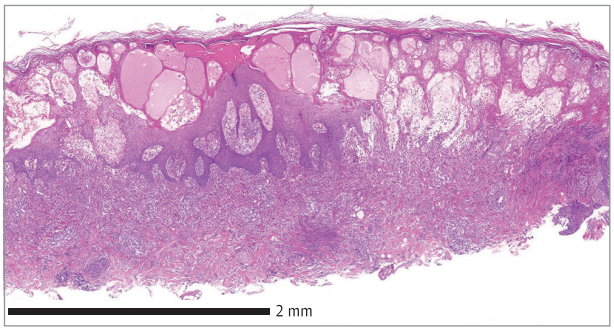
## Diagnosis

**C.** Bullous Wells syndrome

## Microscopic Findings and Clinical Course

The complete blood cell count showed an elevated eosinophil count ($1.36 \times 10^9$/L). No additional anomalies were found besides a mild increase in eosinophil levels in the bone marrow biopsy. *Enterococcus faecalis* was isolated from the exudation swab. Blood and tissue cultures and autoantibody profiles of SLE, pemphigus (Dsg-1 and Dsg-3), and bullous pemphigoid (BP-180 and BP-230) were all negative. Histopathologic examination indicated irregular hyperplasia and spongiosis of the epidermis with hyperkeratosis and localized necrosis (**Figure 2**A). Additionally, extensive edema of dermal papillary and mixed infiltrate of marked diffuse eosinophils and lymphocytes were found in the dermis, accompanied by scattered neutrophils (Figure 2B). Direct immunoflourescence results for IgA, IgG, IgM, and C3 were negative. Initially, the patient was given levofloxacin for 5 days owing to a concern of bacterial infection but did not respond. Following the histopathologic results, the diagnosis of bullous Wells syndrome was made. Intravenous methylprednisolone at 1.5mg/kg/d was given for 1 week, followed by rapid relief of fever and lesions. The lesions completely cleared, and the patient showed no sign of relapse at 12-month follow-up.

A Original magnification ×40




B Original magnification ×200

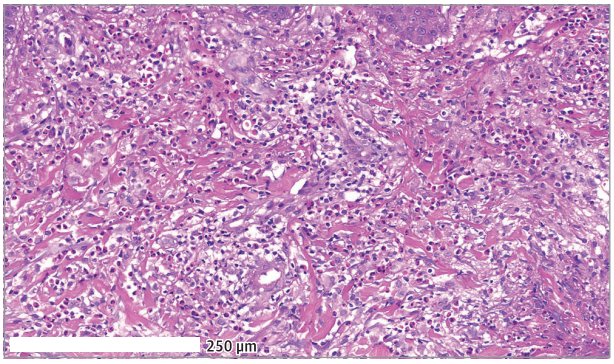



**Figure 2.** Hematoxylin-eosin stained sections. A, Irregular hyperplasia and spongiosis of the epidermis, extensive edema of dermal papillary and massive inflammatory cell infiltration. B, Extensive edema of dermal papillary and mixed infiltrate of marked diffuse eosinophils and lymphocytes in the dermis, accompanied by scattered neutrophils.

## Discussion

Wells syndrome, also known as eosinophilic cellulitis, was first described in 1971.[1] The main clinical variants include plaque type, annular granulomalike, urticarialike, papulovesicular, bullous, papulonodular, and fixed drug eruptionlike, among which the bullous type is quite rare and more likely to affect adults.[2]

The low prevalence of Wells syndrome, along with its variability of manifestation, often delays its diagnosis until a patient does not respond to an initial antimicrobial regimen.[3] Although the onset of Wells syndrome is acute, the systemic symptoms are generally mild. The irregular fever presented in this case is not a common complication. Besides bacterial cellulitis, differential diagnoses of Wells syndrome include, but are not limited to, necrotizing fasciitis, parasitoses, urticaria, Churg-Strauss syndrome, granuloma annulare, and hypereosinophilic syndrome.[4] In patients presenting blisters or bullae, the diagnoses of herpes virus infection, bullous pemphigoid, acute contact dermatitis, bullous SLE, and bullous Sweet syndrome should also be considered. Notably, bullous Sweet syndrome can present symptoms very similar to the present case. However, the histologic traits of Sweet syndrome feature dense neutrophils and nuclear dust in the mid-dermis, with occasional eosinophils or lymphocytes.

A variety of triggers are reported to be associated with Wells syndrome, including drugs, infections, insect bites, cancer, and vaccinations.[5] However, in this case, no obvious triggers could be found. The history, physical examination, and regular laboratory workup excluded systemic diseases. Furthermore, the blood tests and bone-marrow biopsy provided no evidence to indicate either hematological or myeloproliferative diseases. Therefore, this case was diagnosed as idiopathic Wells syndrome.

A gold standard for Wells syndrome diagnostic criteria is currently nonexistent. Heelan et al[6] have proposed a set of diagnostic criteria for Wells syndrome, which include 4 major characteristics (2 of which need to be present) and 4 minor ones (at least 1 of which needs to be present). However, larger patient cohorts are needed for its validation. In a recent review, Räßler et al[5] suggested that the correlation of clinical features, the course of skin lesions, and histopathological examination of a skin biopsy are necessary for a definitive diagnosis of Wells syndrome.

Owing to the benign course and generally good prognosis, local therapy is the main strategy for treating Wells syndrome, whereas systemic treatment is used in cases with widespread lesions or systemic involvement. Topical and systemic glucocorticosteroids are the most common treatments for Wells syndrome and to our knowledge are the only clearly beneficial therapies reported so far.[5] Other treatment options include cyclosporine, dapsone, oral or topical tacrolimus, antihistamines, interferon-α, interferon-γ, tumor necrosis factor inhibitors, sulphone or sulfasalazine, psoralen and UV-A therapy, colchicines, antimalarial drugs, azathioprine, minocycline, and griseofulvin.[5]

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ARTICLE INFORMATION

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