Wells syndrome as a presenting sign of COVID-19 in the setting of allergic rhinitis and iron deficiency anemia

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INTRODUCTION

Wells syndrome (eosinophilic cellulitis) is an uncommon inflammatory dermatosis characterized by urticarial plaques often admixed with papulonodules or vesiculobullae; systemic features include fever, malaise, and arthralgias with peripheral eosinophilia in 50% of the cases.[1] Wells syndrome is thought to be a type IV hypersensitivity reaction; multiple implicated triggers and associations include arthropod assault, infection, medication, hematologic disorders, and solid organ malignancies.[1-4] Pathogenesis involves eosinophil degranulation, and histologic correlations are identified.[1] We present a patient who experienced Wells syndrome in response to a novel trigger, COVID-19.

Abbreviation used:

IDA: iron deficiency anemia

CASE REPORT

A 51-year-old woman with a history of biopsy-proven Wells syndrome, allergic rhinitis, and iron deficiency anemia (IDA), presented for painful edema in the right arm. She reported 2 weeks of dry cough, mild wheezing, and dyspnea and 3 days of an evolving dermatosis. She denied new medications, affected household members, travel, arthropod exposure, or sick contacts. Her previous Wells syndrome occurred 18 months previously, lacked respiratory symptoms, was preceded by *Cimex lectularius* exposure and characterized by painful right-arm edema, vesiculobullae, and pruritic extremity plaques. A left thigh skin biopsy of an erythematous plaque had revealed superficial and deep perivascular and interstitial eosinophils (Fig 1); blood work demonstrated peripheral eosinophilia (range, 1.5-6.3 K/μL; reference value, <0.5 K/μL). Clinicopathologic correlation rendered a diagnosis of Wells syndrome secondary to arthropod assault, and oral prednisone taper achieved resolution. On re-presentation, the patient was afebrile, normotensive, with mild tachycardia (106 beats/min) and 100% oxygen saturation on room air. Physical examination revealed scattered vesiculobullae overlying edematous erythematous plaques covering 10% of body surface area (Fig 2, ***A, B***). Laboratory testing revealed absolute peripheral eosinophilia (1.0 K/μL), elevated C-reactive protein (16.5 mg/L; reference value, <10 mg/L), and normal total peripheral leukocytes, hemoglobin, and erythrocyte sedimentation rate. Cutaneous swab was negative for herpes simplex virus/varicella zoster virus by polymerase chain reaction; a nasopharyngeal polymerase chain reaction swab was negative for SARS-CoV-2, respiratory syncytial virus, and influenza A/B virus; chest x-ray was unremarkable. Overnight, the patient became febrile (38.3 °C; reference range, 36.1-37.2 °C) with leukocytosis (13.4 $\times$ 10^9/L; reference range, 4.5-11.0 $\times$ 10^9/L), persistent eosinophilia (0.8 K/μL), and increasing C-reactive protein (35.65 mg/L) and

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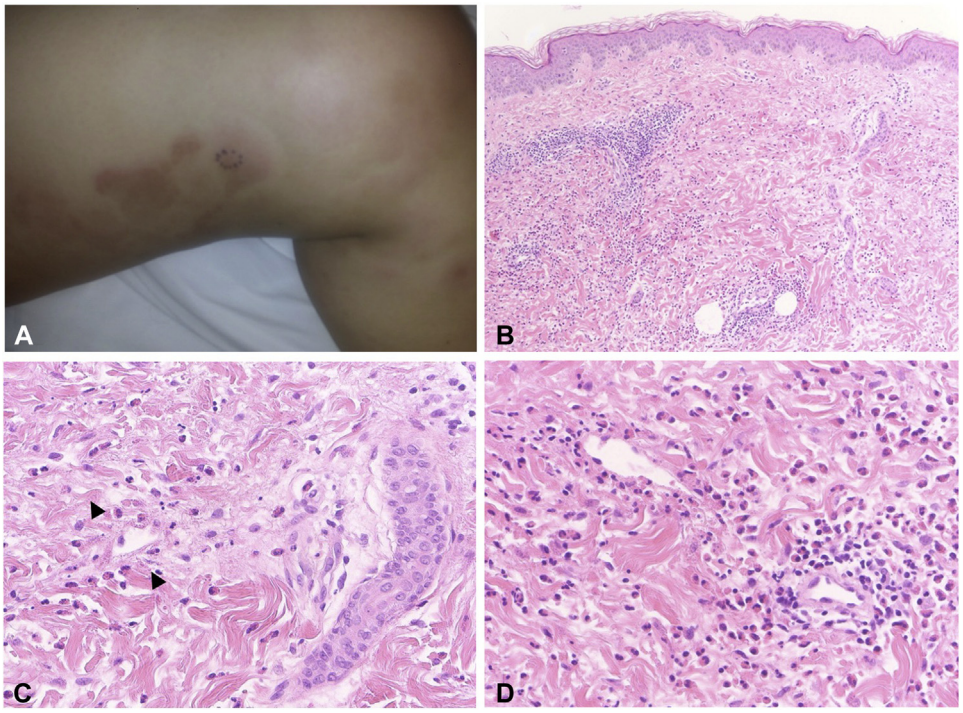

Fig 1. Preceding episode of Wells syndrome with pink edematous plaques of the medial aspect of the left thigh and punch biopsy demarcation (**A**); corresponding histopathologic sections demonstrated superficial and deep perivascular and interstitial inflammation with many eosinophils (hematoxylin-eosin stain, original magnification ×100 [**B**], ×400 [**C, D**]); eosinophil degranulation was present with close approximation of granules to collagen fibers (*arrows*).

erythrocyte sedimentation rate (130 mm/h; reference value, <29 mm/h). Despite empiric intravenous vancomycin and piperacillin/tazobactam, fevers (maximum temperature, 38.8 °C) persisted with worsening tachycardia (125 beats/min); oxygen saturation remained stable on room air. Periorbital edema (Fig 2, ***C***) coincided with worsening leukocytosis (15.9 × 10^9/L) and peripheral eosinophilia (2.9 K/μL). Oral prednisone (0.5 mg/kg per day) for recurrent Wells syndrome achieved cutaneous improvement within 48 hours. Persistent dry cough prompted repeat SARS-CoV-2 testing, and 4 days after initial negative results, SARS-CoV-2 polymerase chain reaction was positive. Three days of prednisone transformed erythematous plaques to violaceous and hyperpigmented patches, and peripheral eosinophilia improved (maximum range, 5 K/μL-1.9 K/μL) (Fig 2, ***D***). The patient underwent home quarantine, completely recovered, and after 11 days of antibiotic therapy and 4 weeks of oral prednisone, the cutaneous lesions had resolved without additional recurrence. Notably, a history of mild baseline peripheral eosinophilia (range, 0.7-1.3 K/μL) coincided with her diagnosis of IDA 2 years prior to her initial diagnosis of Wells syndrome. Three weeks after completing prednisone for recurrent Wells syndrome, laboratory tests revealed persistent eosinophilia (1.6 K/μL), normal hemoglobin, iron deficiency (25 μg/dL; reference range, 60-179 μg/dL), low-to-normal ferritin (11 ng/mL; reference range, 10-120 ng/mL), normal serum immunoglobulins, tryptase, and vitamin B12, and seronegativity for IgG antibodies against *Helicobacter pylori, Schistosoma,* and *Strongyloides*. Four weeks after restarting oral ferrous sulfate, her iron levels normalized (40 μg/dL), ferritin improved (23 ng/mL), and the peripheral eosinophilia resolved.

DISCUSSION

We report Wells syndrome as the presenting sign of COVID-19 in a patient with a history of Wells syndrome, allergic rhinitis, IDA, and baseline mild peripheral eosinophilia. Proposed diagnostic criteria for Wells syndrome require 2 major and 1 minor criteria.[4] Our patient demonstrated the following 3 major and 1 minor criteria: Clinical presentation reflective of reported variants (classic plaque-type with papulovesicular features), a relapsing/remitting course (second presentation), histologic eosinophilic infiltrates without vasculitis (Fig 1, ***B-D***), and a triggering factor (temporal relationship and lack of other triggers suggested COVID-19).

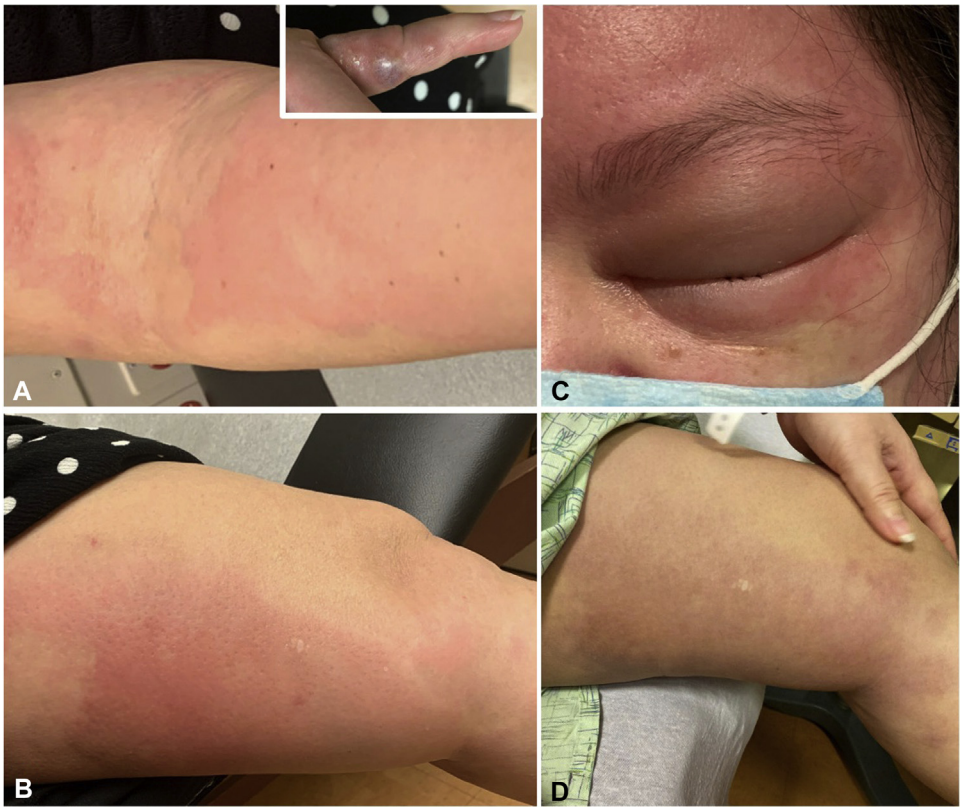

Fig 2. Subsequent episode of Well syndrome: edematous pink plaques on the volar aspect of the left upper extremity (**A**) and medial aspect of the left thigh (**B**), vesicles with a surrounding pink rim on the left 5th finger (*inset*), and edematous pink plaques of the left forehead and eyelids with marked periorbital edema (**C**); subsequent evolution to violaceous and hyperpigmented patches of the left thigh after 3 days of prednisone (**D**).

Regarding other criteria, histologic granulomas and flame figures were not observed; yet, an exhaustive workup failed to demonstrate an underlying systemic disease. Hypereosinophilic syndrome was excluded due to mild baseline eosinophilia and limited duration of hypereosinophilia.

Hospitalized patients with COVID-19 demonstrate variable peripheral eosinophil levels; nearly one-third present with eosinophilia, and one-third develop delayed eosinophilia.[5] In contrast, various reports indicate that a large proportion of patients with COVID-19 present with eosinopenia (absolute eosinophil count <0.02 K/μL), which may portend a more severe disease course.[6] Most COVID-19 patients with peripheral eosinophilia do not develop an erythematous cutaneous eruption.[5] Cutaneous eruptions with peripheral eosinophilia in COVID-19 patients were often attributed to adverse drug reactions upon hospital admission.[5] Here, Wells syndrome recurrence preceded hospital admission.

Peripheral eosinophilia may be incidental (5% of the population);[7] primary pathologies include atopy, infection, malignancy, eosinophilic disorders, and immunodeficiency. Our patient's baseline eosinophilia was attributed to allergic rhinitis; yet, resolution of peripheral eosinophilia following oral iron supplementation suggests a potential contributory role for IDA. Increased prevalence of IDA is reported in patients with atopy,[7] and functional iron deficiency has been demonstrated in women with allergic rhinitis.[8] The potential relationship between atopy, IDA, and peripheral eosinophilia remains elusive.

We found no previous descriptions of eosinophilic cellulitis as the presenting sign of COVID-19 in the medical literature in English language. Known associations between Wells syndrome and viruses, including herpes simplex virus 2, parvovirus, and coxsackievirus A6 support the hypothesis that COVID-19 triggered eosinophilic cellulitis recurrence in our patient.[2-4] Cutaneous manifestations of COVID-19 include the following: Morbilliform, vesicles, urticaria, pseudo-chilblain, livedo, purpura fulminans, and erythema multiforme-like.[9] A single case of eosinophilic panniculitis associated with COVID-19 was reported.[10] Despite a predominantly

lobular panniculitis, the limited distribution is suggestive of erythema nodosum associated with COVID-19 rather than eosinophilic cellulitis.[10] Dermatologic findings of COVID-19 may reflect severity; pernio and retiform purpura have been associated with mild and severe disease, respectively.[9] Other type IV hypersensitivity reactions have been associated with a range of COVID-19 severity.[9] The present case of Wells syndrome as a type IV hypersensitivity reaction in the setting of COVID-19 correlated with mild severity. This case emphasizes the importance of peripheral eosinophilia workup, expands Wells syndrome triggers to include SARS-CoV-2, and suggests an association with a mild disease course.

Conflicts of interest

None disclosed.

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