

## CASE REPORT

# Recurrent wells' syndrome associated with allergic asthma exacerbation

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### Abstract

Wells syndrome is an inflammatory eosinophilic dermatosis of unknown pathogenesis characterized by clinical polymorphism, a suggestive but nonspecific histopathologic traits, usually with a recurrent course and inconstant response to therapy. It seems to be an unspecific hypersensitivity reaction in response to various exogenous and endogenous stimuli, such as insect bites, infections, drug eruption or underlying internal disorders. We present a patient with allergic asthma and atopic dermatitis in whom a skin eruption developed in the sequence of allergic asthma exacerbation, which was clinically and histologically consistent with the diagnosis of eosinophilic cellulitis. The authors discuss the probability of a common pathogenesis and the role of IL-5. To our best knowledge this is the first pediatric case where this association is reported.

**Keywords:** Wells' Syndrome, allergic asthma, eosinophilic cellulitis

## Introduction

Well's syndrome (WS) or eosinophilic cellulitis, first described by Wells in 1971 (1), is a rare, often recurrent, multifaceted dermatosis. It has a wide morphological spectrum, ranging from a characteristic plaque-type variant to more unusual patterns like papulonodular and bullous, occurring with single or multiple lesions and suggestive, however not distinctive, histopathological findings, namely eosinophilic infiltration and flame figures. Associated laboratory findings include elevated white blood cell count and peripheral eosinophilia that occurs in approximately 50% of cases during the active phase of the disease (2). Most cases occur in adults and no more than 33 have been reported in children (3). We describe the case of a pediatric patient with recurrent WS associated with allergic asthma exacerbation episodes.

## Case report

A 2-year-old caucasian boy, with personal history of allergic asthma and atopic dermatitis, presented with acute onset of annular erythematous plaques, pruritic but not

painful, symmetrically distributed over the lower extremities. The lesions were persistent, lasting for more than 48 hours and appeared one week after an allergic asthma exacerbation (Figure 1). His parents denied concomitant fever, a history of insect bites, recent immunizations, medications (except inhaled corticosteroids for asthma), trauma and other previous acute illness. Laboratory evaluation revealed discrete leukocytosis ( $11.84 \times 10^9/L$ ; Normal range  $6-11 \times 10^9/L$ ), with peripheral eosinophilia of 22%. Immunological evaluation showed increased IgE (883 IU/mL; normal range  $<180$  IU/mL) but ANA, ANCA and rheumatoid factor were all negative. Skin prick tests demonstrated sensitization to house dust mite and pollen. Serological testing, blood and stool cultures for the detection of bacterial, parasitic and viral agents were negative. Chest X-ray and abdominal ultrasound were irrelevant. Histological skin examination supported the clinical diagnosis of WS by demonstrating an intense eosinophilic infiltrate at the dermis and the presence of eosinophilic flame figures (Figure 2). Direct immunofluorescence was negative. Oral steroid therapy was started at 1 mg/kg/day with complete remission of the lesions

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after 5 days and with significant reduction in peripheral eosinophilia (8%) after 2 weeks. Nonetheless the lesions recurred 3 times during the following 6 months, 48 to 72 hours after an allergic asthma exacerbation (Figure 3a-c). In all the episodes the lesions had the same clinical appearance of annular erythematous plaques but with a wider distribution than previously observed, involving not only the lower extremities but also the trunk. The respiratory symptoms and cutaneous lesions completely remitted with short courses of systemic and inhaled steroids therapy in all the occasions. The extensive clinical and laboratory investigations undertaken since the first

episode were not helpful in identifying a precipitant factor other than the preceding exacerbation of allergic asthma. After one year of follow-up, allergic asthma has been adequately controlled with inhaled corticosteroids, oral antihistamines and oral leukotriene antagonists. No skin involvement has been recorded since then.

## Discussion

Unlike allergic asthma, the underlying pathogenesis of WS is still unknown but it appears to be a delayed (type IV) hypersensitivity reaction in response to different endogenous and exogenous stimuli in patients with an aberrant and inadequate eosinophil expression (4,5). Very limited data regarding eosinophil pattern expression, adhesion molecules or cytokines profile is reported for this condition. However, two recent publications describe increased levels of IL-5 and ECP in peripheral blood and skin of these patients, with a good correlation with disease severity (6,7). In fact, IL-5 mobilizes eosinophils from the bone marrow to blood and ultimately



Figure 1. Annular erythematous plaques, symmetrically distributed over the lower extremities, 1 week after an allergic asthma exacerbation.

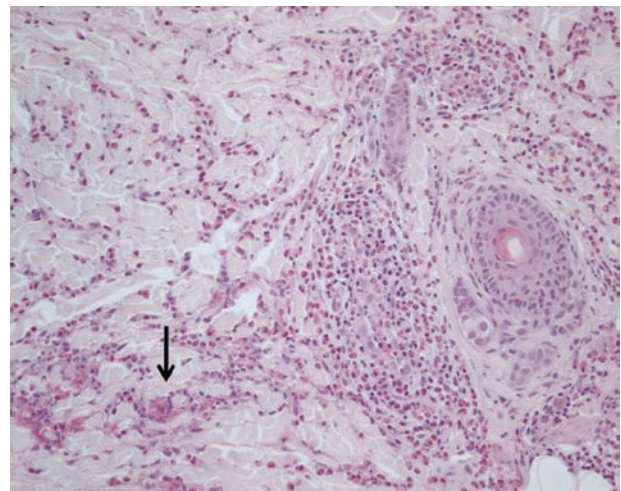


Figure 2. Histological examination of the skin demonstrating an intense eosinophilic infiltrate at the dermis and the presence of eosinophilic flame figures highlighted by the arrow (Hematoxylin-Eosin – magnification 200×).



Figure 3. (a) Recurrent lesions 48 hours after an allergic asthma exacerbation, 2 months after the first episode of WS. (b) Recurrent lesions 72 hours after an allergic asthma exacerbation, 3 months after the first episode of WS. (c) Recurrent lesions 48 hours after an allergic asthma exacerbation, 6 months after the first episode of WS.

promotes their homing in skin and other tissues presumably by altering the expression of adhesion molecules and increasing the expression of CD25, a component of the IL-2 receptor involved on the degranulation of eosinophils. Therefore, ECP is presumably one of the toxic cationic proteins contained in eosinophil granules that mediates toxic tissue damage in WS (8). In the light of this view, it is interesting to observe that Churg–Strauss (CSS) and hypereosinophilic syndromes can occur in association with WS, supporting a proposed hypothesis that all these conditions share the same nosological spectrum, representing WS the most benign cutaneous counterpart (9,10).

Reported trigger factors of this condition include arthropod bites, viral, fungal and parasitic infections, medications, vaccinations, autoimmune diseases, carcinomas, leukaemia and other myeloproliferative disorders (11). To our best knowledge this is the second reported case where allergic asthma and WS are associated and the first in pediatric age (12). In this case, the course of both conditions seems to be strictly related. Although the mechanism leading to WS is not yet fully characterized as stated, it seems to share common features with allergic asthma pathogenesis. In fact, both diseases appear to be triggered by several different stimuli, IL-5 levels and eosinophils are increased in the two conditions and both diseases have a recurrent course. Our hypothesis is that aeroallergens, responsible for asthma exacerbation, were the triggers of an aberrant and inadequate eosinophil expression, with subsequent simultaneous skin and pulmonary homing, in the setting of a genetically susceptible patient. As WS is considered a type IV hypersensitivity reaction, the T cells of our patient became specifically sensitized to a particular antigen, in this case an aeroallergen (probably house dust mite or pollen), which explains the delayed recurrences observed, with a period of 48–72 hours after the allergic asthma exacerbation.

The standard treatment for WS, as for allergic asthma, are corticosteroids which, in this case, resulted in a complete resolution of both cutaneous and respiratory symptoms. The treatment of the underlying associated condition generally leads to resolution of WS. Due to the chronic course of allergic asthma, it is plausible to predict that in our patient both conditions will recur. Other drugs such as cyclosporin A, azathioprine, dapsone, tetracyclins, systemic antihistamines, colchicine, interferon- $\alpha$ 2a and antimalarials have all been reported to be effective in the treatment of WS, either alone or in combination especially in refractory cases (2,11,13). Considering the

putative role of IL-5 as a significant pathogenic factor in WS, it is possible that this cytokine will be an effective therapeutic target as is currently in asthma.

In conclusion, reporting different types, clinical courses and triggers of this condition and their responses to different therapies may provide further clues for clarifying the underlying pathogenesis of WS, a condition probably misdiagnosed in many instances.

## Declaration of interest

The authors declare no conflicts of interest.

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