Eosinophilic cellulitis (Wells’ syndrome) in a female pediatric patient

ABSTRACT

Wells’ syndrome, or eosinophilic cellulitis, is an inflammatory disease of unknown origin, uncommon in the pediatric age. It usually appears clinically as erythematous and edematous plaques, nodules, papules, blisters, among other symptoms. Here we describe the case of a female pediatric patient with generalized, asymptomatic subcutaneous nodules associated with severe eosinophilia. The histopathological examination of the lesions was compatible with Wells’ syndrome. An interdisciplinary evaluation was performed to establish the cause and look for associated eosinophilic disorders; the results were negative. Systemic corticosteroids were indicated and the patient had a good response; however, in view of the recurrence of the lesions after treatment discontinuation, dapsone was indicated as a second-line treatment, with subsequent improvement of the lesions and eosinophilia. The aim of this report was to describe the case of a female patient with an atypical manifestation of Wells’ syndrome and the resulting therapeutic challenge.

Keywords: Wells’ syndrome; cellulitis; eosinophilia; dapsone; child.

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INTRODUCTION

Wells’ syndrome (WS), or eosinophilic cellulitis, is an inflammatory disease of unknown origin, first described by Wells in 1971 as a recurrent granulomatous skin disorder associated with eosinophilia.\textsuperscript{1–5} It is a rare disease that presents different clinical forms; the most common is cellulitis. Wells’ syndrome tends to show a spontaneous regression, although sometimes treatment may be necessary; systemic corticosteroids are the first-line of treatment. Here we describe the case of a girl with a rare clinical form of Wells’ syndrome that required a therapeutic alternative to avoid prolonged corticosteroid use.

CASE REPORT

This was a 5-year-old female patient who was receiving follow-up in our hospital due to eosinophilia, who had been previously assessed by our Department on different occasions due to pruritic skin disorder, assumed to be prurigo. She consulted due to the development of multiple asymptomatic nodules for the past month. On physical examination, she had asymptomatic nodules of hard-elastic consistency, with no change in color of the overlying skin, located on her face, upper and lower limbs, trunk, and paravertebral region (Figure 1), and pruritic erythematous micropapules, arranged in cobblestones, located on the knees and dorsum of the feet (Figure 2).

The laboratory tests showed severe eosinophilia (7400 eosinophils/mm\textsuperscript{3}) and slightly elevated immunoglobulin E (54 IU/mL), with normal rheumatology profile screen and negative serologies. In addition, a chest X-ray and an abdominal ultrasound did not show any pathological finding; the tuberculin test (PPD) was negative; and the throat swab was negative. A skin biopsy of one of the lesions of the lower limb was performed. The cultures were negative; the histopathological examination showed eosinophilic dermohypodermitis with areas of degranulation with eosinophilic acellular material and cellular detritus on collagen fibers, called “flame figure,” surrounded by histiocytes and forming granulomas (Figures 3 and 4); the findings were compatible with eosinophilic cellulitis. To rule out associated disorders and due to severe eosinophilia, the patient was assessed by the Departments of Rheumatology, Ophthalmology, Cardiology, and Infectious Diseases; no pathological findings were noted. The Department of Hematology performed a flow cytometry, bone marrow cytogenetic study, and molecular biology studies; the hematologic causes of hypereosinophilia were ruled out.
**Figure 2.** Subcutaneous nodules in the inner side of both knees, which make her knees appear enlarged. Erythematous micropapules in the overlaying skin

**Figure 3.** Histopathology: H&E stain 10X - cellular infiltration in dermis, associated with amorphous material on collagen (“flame figures”)

**Figure 4.** Histopathology: H&E stain 40X - eosinophilic infiltration
The patient started receiving treatment with meprednisone 1 mg/kg/day for 15 days; the dose was down-titrated. The lesions and peripheral eosinophilia resolved after 1 month of treatment. However, 2 months later, nodules reappeared in different areas of the skin; so, to prevent the adverse effects of prolonged corticosteroid use, it was decided to start treatment with dapsone 2 mg/kg/day, with a previous normal glucose-6-phosphate dehydrogenase result. The patient evolved favorably; skin lesions resolved after 4 months and peripheral eosinophilia after 9 months. One year after starting treatment, she began a slow and progressive dose reduction. Currently, she has been receiving a down-titrated dose for 5 months, with no adverse effects and remains lesion free.

DISCUSSION

Wells’ syndrome is an uncommon disease; less than 200 cases have been described in the bibliography and, although it affects patients of any age, it is more frequently observed in adults.\textsuperscript{1,5–9} At present, the etiology of Wells’ syndrome has not been completely elucidated. It has been proposed that it is caused by a type IV hypersensitivity reaction to various exogenous or endogenous triggers (hematological disorders, drugs, vaccines, infections, among others). Fifty percent of cases are idiopathic, as we believe to be the case of our patient.\textsuperscript{1,2,5–11} The drugs include antibiotics (penicillin and derivatives, tetracyclines, clindamycin), diazepam, NSAIDs (aspirin, diclofenac), diuretics, antineoplastic agents, anti-TNF drugs, among others.\textsuperscript{1,2}

Considering its pathophysiology, it has been described that T cells would activate the production of interleukin-5 (IL5), favoring the production, adhesion, and activation of eosinophils in the tissues and inducing the expression of the alpha chain of the interleukin-2 receptor (CD25), and, in the presence of interleukin-2 (IL2), the degranulation of eosinophils with the consequent edema and tissue inflammation.\textsuperscript{1,2,5–11} This mechanism is shared by other eosinophil-mediated conditions, such as hypereosinophilic syndrome, eosinophilic fasciitis, and Churg-Strauss syndrome, which has led several authors to consider Wells’ syndrome as a skin manifestation of the above, rather than as an entity in its own. However, Wells’ syndrome has its own clinical and histological features.\textsuperscript{8}

Its clinical presentation varies greatly; the “cellulitis-like” form is the most frequent. The lesions develop suddenly, are distributed in any site, prevalently in the limbs and, less frequently, the trunk and the face. The lesions may be associated with prodromal symptoms, such as pruritus and burning at the affected sites. Lesions usually present as single or multiple annular erythematous and edematous plaques, with infiltrated borders, mildly pruritic, and without local temperature increase.\textsuperscript{1,2,5,7,10} Although this is the most typical form of presentation, Wells’ syndrome may manifest with nodules, papules, vesicles, blisters, or hives.\textsuperscript{3,6,8,9,11–13} After the acute stage, the lesions involute spontaneously after 2 to 8 weeks, leaving residual hyperpigmentation, morphea-like atrophy, or heal back to normal.\textsuperscript{1,2,7,8,11} However, in 50% of patients, lesion recurrence is observed; the average duration of the disease is between 3 and 4 years.\textsuperscript{1,5,8} Systemic symptoms, such as malaise, fever, arthralgias, or lymphadenopathies, are uncommon and manifest in more severe and chronic forms of the disease.\textsuperscript{1,7–9,11} Peripheral eosinophilia is detected in 50% of patients and has been related to disease activity, as well as increased IL5 levels. Occasionally, some patients show a discrete increase in erythrocyte sedimentation rate and IgE.\textsuperscript{1,4,5,7,8,10}

Our patient had rare features of Wells’ syndrome, manifested by multiple subcutaneous nodules, without systemic repercussion, but associated with severe eosinophilia and elevated IgE levels.

The histological findings vary according to the biopsy study timing. In the acute stage, edema predominates in the dermis, accompanied by a dense infiltrate of eosinophils, without the presence of vasculitis; in the subacute stage, histiocytes and eosinophils are observed degranulating around the collagen bundles, forming the typical flame figures (amorphous material product of eosinophil degranulation on collagen); and in the chronic stage, histiocytes and multinucleated cells are observed forming foreign body-like granulomas surrounding these figures, which tend to disappear. It is worth noting that, although flame figures are very typical of Wells’ syndrome, they are not pathognomonic, as they may be observed in other skin disorders, such as eczema, insect bites, follicular mucinosis, bullous pemphigoid, parasites, among others.\textsuperscript{1,2,4,5,7–9,11–13}

The differential diagnoses of Wells’ syndrome vary according to its form of presentation. First of all, a differential diagnosis with cellulitis of infectious origin, especially bacterial, should be made.\textsuperscript{2,5,12–13} Characteristics such as lesion appearance, the presence of eosinophilia, and the lack of...
response to antibiotics may guide the diagnosis of Wells’ syndrome. Other conditions to take into consideration include contact dermatitis, urticaria, granuloma annulare, viral rash, and insect bites.\textsuperscript{2,7–9}

Several treatments have been described with variable success; they should be tailored to the extent and severity of the condition. The recommendation is to first treat the underlying cause, if identified. Systemic corticosteroids are the treatment of choice: meprednisone 1–2 mg/kg/day with subsequent down-titration.\textsuperscript{1,4,5,7,9} In case of few lesions present, the use of topical corticosteroids is recommended.\textsuperscript{1,7,9,13} In patients with recurrence or poor response to corticosteroids, dapsone has been described as an effective drug.\textsuperscript{1,4,7,9,11} Other treatments used include cyclosporine, minocycline, tetracycline, griseofulvin, azathioprine, anakinra, and benralizumab.\textsuperscript{1,3,4,7,9,11,13} In our patient, although she responded to systemic corticosteroids, due to the recurrence of lesions and to prevent adverse effects, dapsone was used with a very good response. Some authors suggest that antihistamines would be useful for the management of pruritus.\textsuperscript{9,13}

Wells’ syndrome is a rare skin disorder in the pediatric population. Here we report the case of a 5-year-old girl with a rare clinical presentation of Wells’ syndrome who was treated with dapsone as a therapeutic alternative to corticosteroid therapy, with a good response. ■

REFERENCES