Received: 2021.04.15
Accepted: 2021.06.29
Available online: 2021.07.27
Published: 2021.08.31

Recurrent Cellulitis-Like Episodes of the Lower Limbs and Acute Diarrhea in a 30-Year-Old Woman: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 30-year-old
Final Diagnosis: Wells syndrome
Symptoms: Acute diarrhea • chronic recurrent episodes resembling cellulitis to her lower limbs bs
Medication: —
Clinical Procedure: Skin biopsy
Specialty: Dermatology • Family Medicine

Objective: Unusual clinical course
Background: Wells syndrome is an uncommon inflammatory dermatosis that presents as tender or mildly pruritic cellulitis-like eruptions. The clinical presentation can include papular and nodular eruptions, annular plaques, vesicles, bullae, and urticaria. This syndrome can be promoted by inappropriate eosinophilic stimulation by factors that affect normal eosinophil cellular systems. Histologically, during the acute phase, a dense infiltrate of degranulating eosinophils is located in the epidermis and dermis. Wells syndrome mostly has a benign course; however, its recurrences can be frequent over the years. It can be an imitator of bacterial cellulitis leading to ineffective antibiotic courses, which can promote a *Clostridioides difficile* infection.

Case Report: A 30-year-old woman presented with chronic episodes resembling cellulitis on her lower limbs, for the past 5 years. Her past medical and family history was insignificant. She had been prescribed several courses of antibiotics. At this presentation, she had edema in the lower part of her left foot, erythema and pruritus, mild diarrhea, and fever for 4 days. She was diagnosed with a *Clostridioides difficile* infection with a background of Wells syndrome. She was successfully treated for *Clostridioides difficile* with metronidazole and probiotics, and had complete clinical remission of the Wells syndrome with mometasone furoate cream and levocetirizine.

Conclusions: This report emphasizes the need for greater vigilance by physicians before making a final diagnosis of infectious cellulitis. Thus, excluding from their differential diagnosis, other dermatological diseases mimicking infectious cellulitis and preventing a possible misdiagnosis, delay of appropriate treatment, future antibiotic-associated complications, and the evolution of antimicrobial-resistant microbes in the community.

Keywords: Cellulitis • Eosinophils • Wells syndrome

Full-text PDF: <https://www.amjcaserep.com/abstract/index/idArt/932732>

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Background

Wells syndrome is an uncommon inflammatory dermatosis of unknown etiology defined as eosinophilic cellulitis by Wells and Smith in 1979 [1]. It usually presents as tender or mildly pruritic cellulitis-like eruptions. A burning sensation followed by edema is commonly observed. The clinical presentation can include papular and nodular eruptions, annular plaques, vesicles, bullae, and urticaria [2]. We present the case of a 30-year-old woman with chronic recurrent episodes resembling cellulitis on her lower limbs for the past 5 years. She had been prescribed several courses of antibiotics. She was finally diagnosed with a *Clostridioides difficile* (*C. difficile*) infection with a background of Wells syndrome. This report emphasizes the need for greater vigilance by physicians before making a diagnosis of infectious cellulitis. In their differential diagnosis, they should include other dermatological diseases that can mimic infectious cellulitis.

Case Report

A 30-year-old woman presented to our clinic with erythema, swelling, and moderate pruritus in the lower part of her left foot. In the past 4 days, she had mild diarrhea (3-5 watery bowel movements/day) and her body temperature was 37.7°C. Her past medical history was significant for unilateral pruritic cellulitis-like eruptions on her lower limbs, accompanied by swelling and fever up to 38°C. These episodes began 5 years before her visit to our clinic and had been treated with several courses of antibiotics and topical antibiotic/steroid creams. Moderate improvement was reported 3 weeks to 4 weeks after every attack. The last episode had occurred 3 months before her presentation to our clinic (April 2019). She had been treated with oral clindamycin (300 mg/6 h) and ciprofloxacin (500 mg/12 h) for 10 days and prednisone (30 mg/day for 10 days). Prednisone had been slowly tapered off during the following month. She did not report any joint pain or tenderness. No ocular symptoms suggesting uveitis (dry, painful and/or red eyes, visual impairment, and photophobia) were reported. She did not report any hypersensitivity reactions to medications, metals, or arthropod bites and stings. She had never smoked and had not been prescribed any other medications in the past.

Her physical examination showed that she was in good general health with a respiration rate of 15 breaths/minute, body temperature of 37.5°C, blood pressure of 120/70 mmHg, and heart rate of 98 beats/minute. Generalized erythema with moderate swelling of her left lower foot were observed (Figure 1). All the other clinical examinations (heart, respiratory system, nervous system, and abdomen) were unremarkable. Results of the laboratory investigations showed mild anemia (hemoglobin 11.6 g/dl), a white blood cell count of 9880/mm³

Figure 1. Erythema and swelling in the left lower foot at presentation (ImageJ, LOCI).

(eosinophils 3%), an erythrocyte sedimentation rate of 45 mm/hour, and a C-reactive protein level of 0.61 mg/dl. No peripheral eosinophilia was reported in the earlier cellulitis-like episodes. Blood cultures were negative for bacteria and fungi during her investigations at our clinic. The results for cultures and examinations for ova and parasites in 3 stool samples were normal. However, the 3 stool samples were positive for the *C. difficile* toxin Tcd A test. Serum protein electrophoresis, immunoglobulin E levels, antinuclear and antineutrophil cytoplasmic antibodies, cryoglobulins, hepatitis B surface antigen, human immunodeficiency virus, and hepatitis C virus antibodies were within normal limits. The venereal disease research laboratory test was negative and the angiotensin-converting enzyme was within normal levels. Color Doppler ultrasound imaging excluded any possible lower limb venous disease. The chest radiography disclosed no obvious lung abnormalities and had no hilar lymphadenopathy. A fundus examination was not performed, as it was considered unnecessary. The differential diagnosis of infectious cellulitis includes drug and foreign-body reactions, insect stings, lymphedema, eczema, panniculitis, thrombophlebitis, venous stasis dermatitis, gouty arthritis, carcinoma erysipeloïdes, familial Mediterranean fever, sarcoidosis, lupus erythematosus, Paget's disease, lymphoma, and Wells syndrome.

A skin biopsy showed significant edema and subepidermal intraepithelial blister formation with numerous granulomatous eosinophils. Perivascular chronic inflammatory infiltrates with eosinophils and a few phagocytic histiocytes were found, suggesting Wells syndrome (Figures 2, 3). No histopathological evidence of nodular lymphocytic infiltration, vasculitis, or cancer was observed. She was successfully treated for *C. difficile* infection with oral metronidazole (500 mg/8 h for 10 days) and probiotics. For the treatment of Wells syndrome, she was prescribed mometasone furoate cream (twice daily) for 2 weeks

Figure 2. Histopathological analysis of the skin biopsy showed significant edema and subepidermal intraepithelial blister formation with numerous granulomatous eosinophils (Hematoxylin and eosin stain, original magnification $\times 200$) (ImageJ, LOCI).

Figure 3. Perivascular chronic inflammatory infiltrates with eosinophils and some phagocytic histiocytes were seen (Hematoxylin and eosin stain, original magnification $\times 200$) (ImageJ, LOCI).

and levocetirizine (10 mg daily) for 1 month. She had complete clinical remission of all her symptoms. From April 2019 to-date, she has reported no recurrences. Written informed consent was given by the patient for publication of all her data in this case report on the condition of anonymity. The Institutional Review Board approved the publication of this case report.

Discussion

To the best of our knowledge, this is the first published case of Wells syndrome in Cyprus. A possible explanation for the absence of any other published reports for Wells syndrome from our island, is that the majority of primary health care practitioners are unaware of this entity. This syndrome can be promoted by inappropriate eosinophilic stimulation, which could be a result of the various factors that affect the normal eosinophil cellular systems [2]. These include arthropod bites and stings, medications, metals, as well as bacterial, viral, fungal, parasitic, and helminthic infections [3-5]. It has been associated with leukemia, lymphoma, myeloproliferative syndromes, solid tumors, Churg-Strauss syndrome, and can overlap hypereosinophilic

syndrome [6-8]. A possible type IV hypersensitivity reaction in response to a variety of exogenous and endogenous stimuli has also been suggested [9].

Histologically, during the acute phase, a dense infiltrate of degranulating eosinophils is observed in the epidermis and dermis. Blisters containing eosinophils (predominantly subepidermal) can be found, as seen in our patient. After a few weeks, 'flame figures' can be observed, which correspond to the intense focal eosinophilic degranulation that results in degeneration of the collagen fibers [1,2]. Flame figures are not pathognomonic of Wells syndrome and can be found in spider bites, parasitic infections, follicular mucinosis, herpes gestationis, and Churg-Strauss syndrome [2,9,10]. The final (resolution) stage is characterized by the gradual disappearance of the eosinophils, leaving the histiocytes and giant cells surrounding the flame figures to form granulomas [9,10].

Wells syndrome has a benign course; however, its recurrences can be frequent over the years, with spontaneous remissions between 2 weeks and 8 weeks [2,11,12]. Peripheral blood eosinophilia is reported in 50% of cases during the acute phase, arthralgia and fever are not common although they have been reported [2,11]. The cellulitis-like lesions, the presence of fever, and the absence of peripheral eosinophilia in all her past episodes were some of the main reasons that led to the misdiagnosis of infectious cellulitis in our patient. Wells syndrome can be a clinical imitator of bacterial cellulitis leading to ineffective antibiotic courses and unnecessary hospitalizations. These can harm the patient or even exacerbate the existing skin disease [5,13]. Our patient was treated with unnecessary antibiotics for 5 years, which is the longest published duration in this population. Inappropriate antibiotic administration in the community can lead to the selection of resistant and multi-drug resistant bacteria, which is an evolving global threat to humanity [14]. By changing the community structure of the gut microbiome, inappropriate antibiotic administration alters the intestinal metabolome, which includes host- and microbe-derived metabolites. This can reduce colonization resistance against *C. difficile*, as seen in our patient [15].

Systemic and topical corticosteroids are considered first-line treatment options. Other treatment options are antihistamines, azathioprine, cyclosporine, dapsone, minocycline, antimalarial medications, oral tacrolimus/topical tacrolimus, sulfasalazine, colchicine, tumor necrosis factor alpha inhibitors, interferon alpha, and psoralen and ultraviolet A therapy [2,11,12]. It is important to treat any possible underlying pathology that triggers Wells syndrome, as this can lead to its resolution. Low-dose oral steroids are suggested as the first approach in cases of highly recurrent Wells syndrome [11,12].

Conclusions

This case report emphasizes the need for greater vigilance by physicians before making a final diagnosis of infectious cellulitis. Thus, excluding from their differential diagnosis, any dermatological diseases that mimic infectious cellulitis. This will prevent possible misdiagnosis, delay of appropriate treatment, future antibiotic-associated complications, and the evolution of antimicrobial-resistant microbes in the community. Early suspicion of Wells syndrome is crucial to tailor further diagnostic strategies and provide appropriate therapy and care in this patient population.

Acknowledgements

We would like to thank Kiriaki G. Constantinides for supervising the writing of the text.

Department and Institution Where Work Was Done

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Conflict of Interests

None declared.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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