

Wells' Syndrome Induced by Ustekinumab

Mati Rozenblat MD¹, Eran Cohen-Barak MD¹, Roni Dodiuk-Gad MD^{1,2} and Michael Ziv MD¹

¹Department of Dermatology, Emek Medical Center, Afula, Israel

²Division of Dermatology, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

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Wells' syndrome is a well-known but infrequent inflammatory eosinophilic dermatosis, first described in 1971 by George Wells. The clinical feature of the disease is a polymorphic eruption. The etiology for Wells' syndrome is unknown, although multiple etiologies have been described, among them drugs, with a number of cases related to tumor necrosis factor-alpha (TNF α) inhibitors and interferons. We present a case with a possible association of ustekinumab, and describe the suggested pathomechanism. We also elaborate on the possible association between immunomodulators and Wells' syndrome.

PATIENT DESCRIPTION

We describe the case of a 58 year old male whose medical history included psoriasis vulgaris for the last 16 years, with no history of arthritis or family history of psoriasis. He was previously treated with acitretin and cyclosporine. During the previous year he had been treated with adalimumab and etanercept. In addition, he was also a hepatitis C carrier and had hyperlipidemia, hypertension and ischemic heart disease.

He was admitted to our department due to a 3 week history of widespread rash, accompanied by purulent discharge from several lesions. The lesions appeared a week after the initial treatment with ustekinumab and were accompanied by mild pruritus. Upon admission, a skin examination revealed a bilateral eruption composed of

erythematous papules, pustules, and annular erythematous plaques covered with a black crust over the face, trunk and limbs. In addition, erythematous plaques and nodules with purplish orange margins and covered by a brown and yellow crust were observed on his arms and the back of his hands [Figure 1]. Laboratory tests demonstrated normal blood count without eosinophilia. Peripheral smear, chemistry, C-reactive protein (CRP), protein electrophoresis, complement, and immunoglobulin E (IgE) were within normal limits. Microbiological tests were taken. Tissue cultures and polymerase chain reaction (PCR) for bacteria, dermatophytes, *Nocardia*, *Mycobacterium*, deep fungal infection and deep mycosis were negative. In addition, a smear and PCR for human immunodeficiency virus (HIV), herpes, and varicella were all negative. Serology for HIV, TPHA, and VDRL was negative. Hepatitis C viral load was 1.3×10^6 IU/ml. A punch biopsy from the dorsal aspect of the hand demonstrated a lymphocytic perivascular infiltrate together with many eosinophils, flame figures, and a few neutrophils along the full thickness of the dermis with no granulomas. Punch biopsy from an erythematous plaque on the left thigh demonstrated edema in the upper dermis and a mixed inflammatory infiltrate along the full thickness of the dermis consisting of eosinophils. In addition, a few torn hair follicles surrounded by eosinophils and neutrophils were observed. In all the biopsies silver and PAS staining were negative. Considering the clinical picture that included a polymorphic eruption consisting of papules, nodules and pustules, and the histological findings comprising eosinophilic infiltrate along the full thickness of the dermis, a diagnosis of eosinophilic cellulitis – Wells' syndrome – was established.

Treatment with topical potent corticosteroids was initiated with no improvement and even continuous spreading. Treatment with prednisone at a dose of 0.5 mg/kg was then begun, which led to an improvement. Later, dapsone was added as steroid sparing, leading to full regression of the rash within 5 days. Subsequent re-administration of ustekinumab 7 weeks after the first dose led to severe exacerbation of the rash 3 days later. During the following year the psoriasis treatment with ustekinumab was replaced by apremilast with poor clinical response, followed by the initiation of secukinumab, achieving full remission. The eosinophilic dermatosis was well controlled with 15 mg prednisone.

COMMENT

In 1971 George Wells described this syndrome, which was renamed eosinophilic cellulitis in 1979. It is an infrequent eosinophilic dermatosis of unknown etiology. The clinical presentation of the disease usually consists of a mildly pruritic polymorphic eruption, including a cellulitis-like eruption as well as annular erythematous plaques. Other clinical presentations such as papules and nodular eruption have also been described. The histological features usually show marked eosinophilia along the dermis and the presence of flame figures.

The etiology of Wells' syndrome is currently unknown; however, many triggering factors have been reported, including malignancy, myeloproliferative disorders, infections, tattoos, and drugs. The latter was reviewed by Heelan et al. [1]. They reported a case of Wells' syndrome triggered by hydrochlorothiazide, and reviewed 24 additional reported cases triggered by antibiotics, non-steroidal anti-inflammatory agents,

Figure 1. Erythematous plaques and nodules with purplish orange margins and covered by brown and yellow crust were observed on arms and the back of the hands



thyroid medications, anesthetics, anticholinergic agent, thiomersal-containing vaccines, and chemotherapeutic agents including 2-chlorodeoxyadenosine, bleomycin, chlorambucil, and pemetrexed. Another class of drugs that has been linked to Wells' syndrome is the immunomodulators.

In this article we suggest ustekinumab as a possible triggering factor as described above. Other immunomodulators that have been described as a possible triggering factor include the association between different TNF α inhibitors: adalimumab [2], etanercept [3], and infliximab [4]. While adalimumab and etanercept caused local reactions, infliximab caused a more generalized eruption that disappeared 8 weeks after drug administration.

The pathomechanism of Wells' syndrome is controversial. There is a dispute over whether Wells' syndrome represents

a hypersensitivity reaction or is a distinct disease entity. The role of the immunomodulators in Wells' syndrome, as mentioned above, can be associated as a triggering factor, possibility tipping the balance towards a TH2 reaction. Another suggested mechanism is that it might solely represent a type of hypersensitivity reaction mediated by eosinophils.

The complex role of immunomodulators is further complicated by the role of TNF α [5]. It can stimulate the Th2 immune response, be released by eosinophils, and stimulate the inflammatory process as demonstrated in the case reported above. Further studies are required in order to reveal the complex elusive interaction between those factors in association with Wells' syndrome.

To improve the diagnosis of this entity, a set of criteria was suggested by Heelan and

co-workers [1] to distinguish Wells' syndrome from different clinical imitators. The four major criteria are: (i) any of the diverse previously reported clinical variants, (ii) a relapsing remitting course, (iii) no evidence of systemic disease, and (iv) histology: eosinophilic infiltrates (no vasculitis). The four minor criteria are: (i) flame figures, (ii) histology: granulomatous change, (iii) peripheral eosinophilia not persistent and not > 1500 μ l, and (iv) a triggering factor. The authors suggested that the diagnosis be based on two major criteria and at least one minor criterion.

In summary, we report a case of Wells' syndrome arising in a patient with psoriasis after treatment with ustekinumab. To the best of our knowledge, this is the first report suggesting an association between the two. We also discuss the possible role of some immunomodulators in the pathomechanism of Wells' syndrome.

Correspondence

Dr. M. Rozenblat

Dept. of Dermatology, Emek Medical Center, Afula 18101, Israel

Phone: (972-4) 649-4255

Fax: (972-4) 649-5137

email: matirozenblat@gmail.com

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“Everything comes to him who hustles while he waits”

Thomas A. Edison (1847–1931), American inventor

“We must be willing to let go of the life we have planned, so as to have the life that is waiting for us”

E.M. Forster (1879–1970), English novelist, short story writer, essayist, and librettist