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Wells syndrome (eosinophilic cellulitis): Proposed diagnostic criteria and a literature review of the drug-induced variant

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Abstract

Background: Wells syndrome is an uncommon inflammatory dermatosis first described in 1971 by Wells. The clinical eruption is characterized by varying morphology and severity and usually follows a relapsing remitting course. The majority of the reported cases are of unknown etiology, drug induced Wells syndrome has rarely been reported. A literature search using MEDLINE was performed. We recorded the features of our case and of the additional cases of drug induced Wells syndrome in the literature.

Main observations: Including our case there are 25 cases of drug-induced Wells syndrome reported. Causative drugs include antibiotics, anticholinergic agents, anaesthetics, non-steroidal anti-inflammatory agents, thyroid medications, chemotherapeutic agents, thiomersal containing vaccinations, anti-tumor necrosis factor agents and thiazide diuretics.

Conclusions: To the authors knowledge this is the first reported case of drug-induced Wells syndrome from thiazide diuretics. The diagnosis of Wells syndrome is often controversial and we propose a set of diagnostic criteria. (*J Dermatol Case Rep*. 2013; 7(4): 113-120)

Introduction

Wells syndrome (WS) is an uncommon inflammatory dermatosis first described in 1971 by Wells.[1] The clinical eruption commences with a prodromal burning or pruritic sensation, followed by urticarial or infiltrative erythema which spreads centrifugally and clears centrally. It is characterized by varying severity and usually follows a relapsing remitting course. The etiology is unknown, however drugs have been associated with onset of this disorder. We recorded the features of our case and of the additional cases of drug induced WS in the literature.

Case Report

We report a 61-year-old male with a longstanding history of biopsy proven eczema. A new extensive eruption with erythematous swollen plaques on the forearms and back developed (Fig. 1 and 2). Blood tests demonstrated raised eosinophils 12%, 1.00 (0.04-0.4), IgE 65 (2-100 U/ml), normal ESR, renal and liver function. ANA and ENA were negative. Creatinine kinase (CK) was persistently raised (436 U/L), aldolase was normal. Systemic examination revealed no lymphadenopathy, organomegaly or proximal muscle weakness. A CT-thorax, abdomen and pelvis was normal. Metachronous biopsies were performed, the first showed a mild spongiotic dermatitis, the second revealed a spongiotic epidermis, dermal eosinophils and flame figures (Fig. 3). WS was considered as a diagnosis. Treatment was instituted with topical betamethasone valerate. However, as the rash continued to relapse and remit oral steroids were commenced. Treatment yielded only temporary improvement with a flare on discontinuation of oral steroids. Medical history included hypertension, medications were tamsulosin, lercandipine and a combination drug (Rasilez®) of a direct rennin inhibitor (aliskiren) and hydrochlorothiazide diuretic. Lymphocyte transformation testing (LTT) to all medications

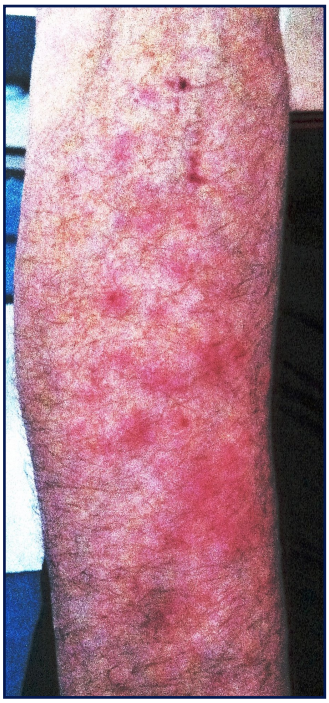

Figure 1
Erythematous swollen plaques on right forearm.

was performed. Results revealed a stimulation index (SI) 3.5 to hydrochlorothiazide indicating type IV sensitization. All other drugs tested demonstrated SI < 1, (normal = SI < 2). Rasilez® was discontinued and the rash resolved. CK levels normalized after discontinuation of the drug. Follow-up histopathology 3 months later revealed background changes of eczema and no evidence of flame figures.

Discussion

Wells in 1971 first described "granulomatous dermatitis with eosinophilia",[1] it was later named eosinophilic cellulitis and over the years became known as WS.[2] Typical rashes cross a varied spectrum from a sudden eruption of cellulitic lesions, sometimes associated with blistering to a more milder form with annular or circinate erythematous plaques with infiltrated borders persisting or recurring over months to years,[3] spontaneous resolution being the rule. The stages of histopathological changes described include an early phase exhibiting dermal oedema, and diffuse dermal infiltration of eosinophils, a subacute phase with a characteristic infiltrate of phagocytic histiocytes together with flame figures where amorphous or granular eosinophilic material adheres to collagen and an older phase showing fewer eosinophils, histiocytes, giant cells between collagen bundles along with remaining flame figures.[4]

Flame figures are not pathognomic and may be detected in other inflammatory dermatoses and also in dermatoses associated with eosinophilia e.g. pemphigoid and its variants, severe prurigo, eczema and follicular mucinoses. In a case series by Caputo *et al.*,[5] approximately 50% of patients showed evidence of flame figures. Treatment is generally with low dose oral steroids, which is not always effective and management with other agents including griseofulvin, dapsone, antihistamines and sulphones have been endeavoured with varying success.[6]

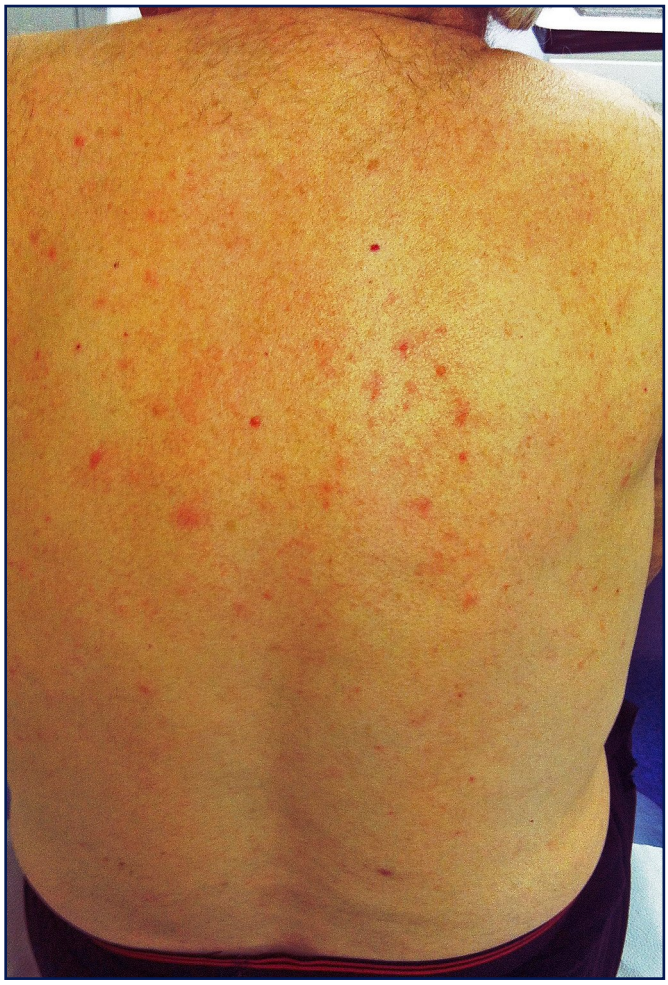

Figure 2
Erythematous lesions on the back.

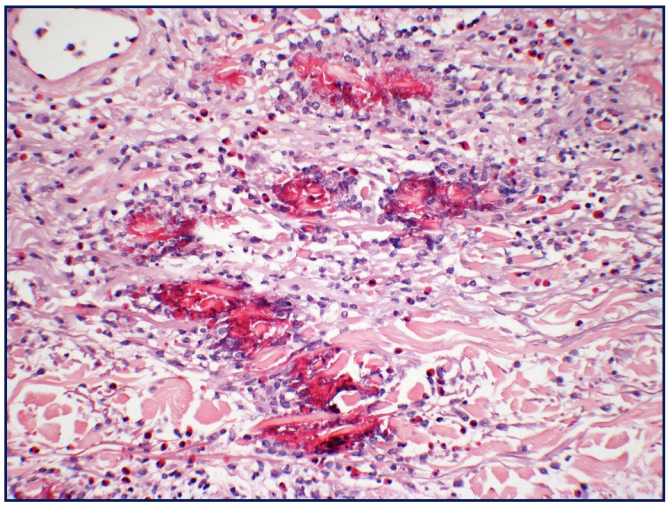

Figure 3
Hematoxylin and eosin (400 x) stain showing flame figures.

The differential diagnosis of WS is broad and includes infections, such as bacterial cellulitis, Toxocara canis, erythema chronicum migrans, arthropod bites and hypereosinophilc syndrome, chronic idiopathic urticaria and Churg-Strauss syndrome.[6] The etiology remains unknown, but reported triggering factors have been reported including infection, arthropod bites, haematological disorders and drugs.[6] The role of a hypersensitivity reaction has been suggested due to the common association between atopic disorders, drug precipitation of the disorder and the frequent occurrence of peripheral eosinophilia.[4]

A Medline search was performed and we recorded the features both in our case and of the twenty-four additional cases of drug-induced WS in the English literature (Table 1). Drugs which have been reported to have a causal relationship with WS include antibiotics,[1-3,7-12] anticholinergic agents,[2] anaesthetics,[2,7,9] non-steroidal anti-inflammatory agents,[2,9,12] thyroid medications,[2,11] chemotherapeutic agents,[8,13] thiomersal containing vaccinations[14-16] and anti-TNF agents.[17-19] Of the twenty-five reported cases eighteen were female and the ages of onset ranged from 3.5 years to 85 years old. Peripheral eosinophilia was reported in 17 cases, this was normal in 4 cases and not reported in 4 other cases. Increased IgE was described in 4 cases. Morphology and sites of the described associated rashes exhibited many variations. In 2 cases flame figures were not seen. A further case while not deemed to be induced by drugs was associated with Danazol induced exacerbations of flare ups.[20]

Thiazide diuretics or aliskiren have not previously been reported to be associated with WS. LTT has been used for over 30 years as part of the diagnosis of possible drug allergies. A population of the patients' peripheral blood lymphocytes is co-cultured, together with non-toxic concentrations of the suspected drug. An enhanced proliferative response in the presence of the suspected drug is interpreted as a sign of a drug-specific T cell sensitization. Proliferative responses are calculated as SI. SI > 2 is the cut-off widely utilized to indicate a positive test.[21] The potential of the thiazide group of drugs to cause cutaneous reactions is well recognized.[22] Rasilez® has been associated with increased CK levels.[23] The diagnosis of WS has been controversial over the years. Whether eosinophilic cellulitis constitutes a disease entity or merely represents a hypersensitivity reaction to different stimuli is still debated.[11]

El-Khalawany *et al.* presented the long-term follow-up of 10 patients with the annular variant of WS.[24] Seven patients had associated systemic disease. Recently Sinnoi *et al.* published a literature review of all reported cases of idiopathic WS.[25] Thirty-two patients were described and an algorithm to decipher it from infectious cellulitis was illustrated. We examined the diagnostic criteria of potential differential diagnosis including; Hypereosinophilic syndrome, Churg-Strauss syndrome and Chronic idiopathic urticaria. Based on these and using the available level 4 evidence we have proposed a set of diagnostic criteria for WS in an aim to improve diagnostic accuracy. The sensitivity and specificity are attributed to the cases which we have reviewed. We included four major (two of which need to be present) and four minor criteria (at least one of which needs to be present). These are pertaining to factors which exclude other potential diagnosis particularly from our proposed most common differentials (Table 2).

Conclusions

The combination of a typical history, a striking clinical picture, characteristic histologic findings and elimination of other possible causes by a thorough history and laboratory examination ostensibly permits a diagnosis of WS.[6] We propose that this is a case of WS developing after treatment with thiazide diuretic in a patient with a history of eczema. This is substantiated by our patient showing the classic histopathologic findings of eosinophilic cellulitis, his skin lesions being typical of a milder subtype which varied in duration of persistence, disappearing while on oral steroids and resolving on discontinuation of thiazide. Hypersensitivity to thiazide was confirmed by LTT and repeat histology after resolution of the Wells rash revealed chronic eczematous changes. We suggest that WS with typical clinical and histopathologic findings may be a side effect of the thiazide subgroup of diuretics.

Table 1. Summary of literature review of cases of drug-induced Wells Syndrome.

Case	Sex	Age	Morphology	Sites	Pathology	Potential Implicated Drug/s	Peripheral Eosinophilia	IgE	Authors
1	F	28	Generalized plaques with greenish oedema Erythematous borders Drying central blisters	Lower limbs Trunk	Dermal infiltration with eosinophils Many flame figures	Ampicillin	2300/mm^3		Wells *et al.*[3]
2	M	12	Infiltrated pruritic lesions widespread	Trunk Thighs	Dermal oedema, eosinophils and phagocytic histiocytes Flame figures	Penicillin	44%		Wells *et al.*[3]

Case	Sex	Age	Morphology	Sites	Pathology	Potential Implicated Drug/s	Peripheral Eosinophilia	IgE	Authors
3	M	11	Urticarial lesions and turgid erythematous plaques. Some blisters	Wide-spread 1/3 of body	Dermal oedema, eosinophils and phagocytic histiocytes Flame figures	Penicillin			Wells *et al.*[3]
4	F	56	Tender plaques of "cellulitis"	Trunk Extremities	Dermal infiltrate of eosinophils and histiocytes Flame figures Focal micrograNulomas	Anticholinergics Antibiotics Anaesthetics	19.5%		Spiegel et al.[2]
5	F	66	Cellulitic, erythematous lesions and erythematous infiltrative lesions	Right arm Trunk Extremities	Diffuse eosinophilc infiltrate of upper dermis with oedema formation Flame figures	Probable penicillin Other possibilities: (Thyroglobulin, Aspirin Chlorodiazepoxide, diazepam, Clidinium bromide, estrogen, Acetaminophen)	34%		Spiegel *et al.*[2]
6	F	26	Recurrent papulovesicular eruption with associated oedema and erythema	Limbs Back Forehead	Dermal eosinophilia Flame figures Histiocytes palisading around areas of altered collagen	Erythromycin	548/mm^3		Peters *et al.*[7]
7	F	56	Pruritic and painful urticarial plaques	Trunk, thighs, neck, axillae, forehead	Dermal eosinophilia Flame figures Histiocytes palisading around areas of altered collagen	Xylocaine, Carbocaine Valium, Penicillin	1406/mm^3		Peters *et al.*[7]
8	M	26	Scattered target and urticarial lesions Papules and follicular pustules	Trunk Face	Eosinophilia Flame figures (on third biopsy)	Tetracycline	6%	Slightly elevated	Brehmer-Andersson *et al.*[8]
9	F	42	Papulovesicular, urticarial infiltrations Oedema	Trunk, limbs Periorbital	Dermal eosinophilia Flame figures	Bleomycin	6%		Brehmer-Andersson *et al.*[8]
10	F	56	Erythematous, oedematous lesions	Face trunk, extremities	Dermal eosinophilia Flame figures	Chlorambucil	10.0 - 11.5%		Brehmer-Andersson *et al.*[8]

Case	Sex	Age	Morphology	Sites	Pathology	Potential Implicated Drug/s	Peripheral Eosinophilia	IgE	Authors
11	F	42	Itchy erythematous, infiltrated plaques with greenish centres and erythematous borders Some bullous lesions	Limbs, trunk, face	Dense inflammatory infiltrate eosinophils and macrophages Flame figures Oedema	Lincomycin, Thiopental, Acetyl salicyclic acid, pholcodin	1460/mm^3	570 µg/L (n=<350 µg/L)	Ferrier *et al.*[9]
12	M	60	Pruritic, erythematous papules and vesicles	Trunk Extremities	Dermal infiltrate eosinophils & neutrophils Flame figures	Minocycline	6%, 1490/µL	2327 U/ml (n=up to 260 U/ml)	Andreano *et al.*[10]
13	F	69	Erythematous indurated pruritic plaques	Buttocks Left groin	Dermal and subcutaneous Eosinophils and lymphocytes. Histiocytes and clusters of eosinophilic granules on collagen fibers No flame figures	Tetanus vaccination	Normal		Moreno *et al.*[16]
14	M	85	Erythematous, oedematous plaques	Left posterior arm and hand	Superficial and mid-dermal perivascular and interstitial pattern of inflammation Eosinophils Flame figures	Clindamycin			Moossavi *et al.*[11]
15	F	57	Erythematous, indurated plaques	Posterior neck, trunk, extremities	Dermal eosinophils Flame figures	Thyroxine	15%		Moossavi *et al.*[11]
16	F	28	Erythematous, papular lesions Bullous lesions Vesiculop apules Erythematous plaque	Dorsal feet Right wrist Fingers Left foot, right ankle	Eosinophilic infiltrate dermis and subcutaneous tissue Flame figures	Tenoxicam and diclofenac sodium and/or amoxicillin	16.5%		Seckin *et al.*[12]
17	M	3.5	**Episode 1**. Rapid onset erythema, ulceration and swelling. Blisters **Episode 2.** Vesicular annular plaques with yellowish centre and erythematous border **Episode 3.** Similar Inflammatory lesions	Left foot Right heel Upper and lower limbs	**Episode 1.** Prominent dermal infiltrate of eosinophils. Prominent flame figures **Episode 2**. Dermal infiltrate, eosinophils and flame figures	Thiomersal containing vaccinations (Episode 1 and 2: Hepatitis B vaccination, Episode 3: Triple Antigen vaccine)	**Episode 1.** 0.62 X10^9/L **Episode 2.** 0.57 X10^9/L (n=0.04-0.40)		Koh *et al.*[15]

Case	Sex	Age	Morphology	Sites	Pathology	Potential Implicated Drug/s	Peripheral Eosinophilia	IgE	Authors
18	F	67	Ulcerated papules and plaques	Trunk	Eosinophilia Perivascular & interstitial infiltrate Flame figures	2-Chlorode-oxyadeno-sine	Normal		Rossini *et al.*[13]
19	F	59	Papules and crusts	Face and legs	Eosinophilia Perivascular der-matitits Flame figures	2-Chlorode-oxyadeno-sine	Normal		Rossini *et al.*[13]
20	F	62	Erythematous, ulcerated vesicular, pruritic lesions	Generali-zed	Epidermal necrosis, panniculitis, dermal oedema Flame figures	2-Chlorode-oxyadeno-sine	Normal		Rossini *et al.*[13]
21	F	57	Erythematous plaques at injection site	Right thigh	Dermal oedema and eosinophilic infiltrate Flame figures	Etanercept			Winfield *et al.*[18]
22	F	72	Urticarial plaques at injection site	Left thigh	Dermal eosinophilic infiltrate Flame figures	Adalimu-mab			Boura *et al.*[19]
23	F	7	Erythematous, vesicular oedematous, plaques	Feet, upper limbs	Dermal eosinophilic infiltrates Flame figures	Tetanusdi-phtheria vaccine	16% 976/mm^3		Calvert *et al.*[14]
24	F	68	Extensive skin-coloured papules with erythematous rim	Back and ab-domen	Dense lymphocytic infiltrate, eosinophils	Infliximab	5.3%, 0.67x10^9		Tugnet *et al.*[17]
25	M	61	Erythematous oedematous plaques	Forearms Back	Dermal eosinophils and flame figures	Hydrochlo-rothiazide	12%,1.00 x 10^9	IgE 65 (2-100 U/ml)	Current case

Table 2. Criteria for Hypereosinophilic Syndrome, Churg-Strauss Syndrome, Chronic idiopathic urticaria, Proposed diagnostic criteria for Wells syndrome.

Chusid criteria for hypereosinophilic syndrome[26]	ACR criteria for Churg-Strauss syndrome[27]	Chronic idiopathic urticaria[28]	Proposed diagnostic criteria for Wells syndrome
A sustained absolute eosinophil count (AEC) greater than >1500/µl is present, which persists for longer than 6 months No identifiable etiology for eosinophilia present Patients must have signs and symptoms of organ involvement	Asthma (wheezing, expiratory rhonchi) Eosinophilia of more than 10% in peripheral blood Paranasal sinusitis Pulmonary infiltrates (may be transient) Histological proof of vasculitis with extravascular eosinophils Mononeuritis multiplex or polyneuropathy	Spontaneous wheals and/or angioedema > 6 weeks Differential blood count and ESR or CRP omission of suspected drugs (e.g. NSAID) Test for: — infectious diseases (e.g. Helicobacter pylori); — type I allergy; — functional autoantibodies; — thyroid hormones and autoantibodies; — skin tests including physical tests; — pseudoallergen-free diet for 3 weeks and tryptase; — autologous serum skin test, lesional skin biopsy	**Major (2 of 4 required)** Diverse clinical picture to include any of the previously reported variants[5] — Plaque-type — Annular-granuloma-like — Urticaria-like — Papulovesicular — Bullous — Papulonodular — Fixed-Drug Eruption-like Relapsing, remitting course No evidence systemic disease Histology: eosinophilic infiltrates, no vasculitis **Minor (at least 1 required)** Flame figures Histology: Granulomatous change Peripheral eosinophila not persistent and not greater than >1500/µl Triggering factor (e.g. drug)

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