CASE REPORT

Wells syndrome associated with lung cancer

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SUMMARY

Wells syndrome (WS) or eosinophilic cellulitis is a rare, idiopathic, inflammatory dermatosis. The typical clinical presentation is urticarial plaque without preferential location that usually heals without scarring. We present a 62-year-old man with history of lung cancer that had undergone a right superior lobectomy 12 months previously. The patient had a relapsing dermatosis beginning about 6 months before the diagnosis of the lung cancer, characterised by pruritic, erythematous plaques located on the trunk and arms. These lesions spontaneously resolved within a few weeks without scarring. A skin biopsy revealed findings compatible with WS. Several diseases have been associated with WS. These include haematological diseases, fungal, parasitic and viral infections, drug reactions and rarely non-haematological malignancies. We present a case of this rare syndrome in a patient with history of lung cancer that we believe acted as a triggering event. To our knowledge, this is the second case reporting this association.

BACKGROUND

George Wells was the first to describe, in 1971, a dermatosis that he termed as 'recurrent granulomatous dermatitis with eosinophilia'.¹ Later, in 1979, Wells and Smith proposed the current term 'eosinophilic cellulitis' but the dermatosis is also commonly called as Wells syndrome (WS).²

Eosinophilic cellulitis is a rare inflammatory dermatosis with relatively few cases described in the literature.³ The aetiology of WS is still unknown but several associations and trigger events have been appointed although most of them are based on single clinical cases. The most common trigger events are arthropod bites, drugs, viral and parasitic infections.^{4–6} Although in the majority of cases, no underlying disease can be found, some authors described possible associations with haematological malignancies (like chronic myeloid leukaemia, chronic lymphocytic leukaemia and non-Hodgkin's lymphoma) and rarely with solid malignancies (one case of renal cell cancer, two cases of squamous cell carcinoma—bronchial and anal and one case of colon adenocarcinoma).^{4 7 8}

To the best of our knowledge, we present the second case of possible association between lung cancer and WS and performed a brief revision of the literature on this topic.

CASE PRESENTATION

A 62-year-old man presented to our department with a relapsing pruritic dermatosis with more than 1 year of evolution. The patient had a background remarkable for a non-small cell lung cancer in the upper right lobe (T1aN0M0) that had undergone a right superior lobectomy 12 months previously. The patient was never a smoker and the lung cancer was diagnosed by his pneumologist where he was studied for about a year due to persistent cough with purulent sputum. Other than that, the patient was healthy and without history of regular medication intake.

The cutaneous complaint began about 6 months previous to the diagnosis of the lung cancer. Since then he endorsed a history of a relapsing dermatosis characterised by pruritic, infiltrated and erythematous plaques located on the trunk and arms, predominantly on the right side. These lesions spontaneously resolved within a few weeks without scarring. Even after curative surgery, he maintained the recurrent dermatosis.

On clinical examination, 12 months after the lobectomy, we noticed a well-defined, pink coloured, arcuate oedematous plaque of about 5 cm in diameter located on the right side of the trunk [figure 1](#) and a smaller nummular plaque of similar characteristics on the posterior aspect of the left shoulder [figure 2](#).

INVESTIGATIONS

A skin biopsy was performed and revealed findings compatible with WS (perivascular and interstitial eosinophilic inflammatory infiltrate of the dermis and subcutaneous tissue without evidence of vasculitis) although no 'flame figures' were seen [figures 3 and 4](#).

Laboratory findings, including haemoglobin, total leucocyte counts, glycaemia, protein electrophoresis, erythrocyte sedimentation rate, liver and renal function tests and urinalysis were normal. Maximum absolute eosinophil count was $0.6 \times 10^9/L$ (normal: $0-0.5 \times 10^9/L$).

Tumour markers CEA, CA 15.3 and CYFRA 21–1 were normal. The thorax CT taken 1 year after surgery showed three subpleural nodules in the upper lobe of the left lung with dimensions and characteristics stable with relation to previous exams but no signs of disease relapse.

Although lacking validation, Heelan *et al* proposed, in 2013, a set of diagnostic criteria for WS.⁶ These authors proposed four major criteria (some of the previously described clinical variants of WS; a relapsing disease course; no evidence of systemic disease; histological findings with

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Figure 1 A pink coloured, arcuate, oedematous plaque located on the right side of the trunk.

eosinophilic infiltrates and no evidence of vasculitis) and four minor criteria (presence of 'flame figures'; granulomatous changes; peripheral eosinophilia not persistent and not greater than $>1500/\mu\text{L}$; a triggering factor). A diagnosis of WS should be made in the presence of at least two major and one minor criteria. Our patient met at least three major criteria (plaque-type lesions; relapsing course and histology with eosinophilic infiltrates and no evidence of vasculitis) and two minor criteria

Figure 2 A nummular pink plaque on the posterior aspect of the left shoulder.

Figure 3 Perivascular and interstitial infiltration by inflammatory cells (H&E, 100 $\times$).

(slight peripheral eosinophilia and a presumed triggering factor—lung cancer).

DIFFERENTIAL DIAGNOSIS

Given the clinical manifestations, the recurrent nature of the dermatosis and the histopathological findings, a diagnosis of WS was made.

TREATMENT

As the lesions were few and sparse, the treatment was initiated with clobetasol ointment, topical 0.1% tacrolimus ointment and loratadine 10 mg twice a day for pruritus relief.

OUTCOME AND FOLLOW-UP

The treatment, although effective in resolving the skin lesions did not prevent recurrences as the patient reported three new outbreaks at 6-month follow-up visit.

DISCUSSION

Wells syndrome has no sex or race predilection and affects both adults and children although the paediatric cases are rarer.^{4,9}

Figure 4 Note the predominance of eosinophils. There is no evidence of vasculitis (H&E, 400 $\times$).

Etiopathogenesis is still unknown but it has been hypothesised that WS is a hypersensitivity reaction to an exogenous or endogenous unknown stimulus.¹⁰

It has a pleomorphic clinical presentation but commonly manifests a sudden onset of multiple or single, large, well-defined, oedematous, pink to violaceous plaques that can arise anywhere on the body although more frequently affects the limbs and the extremities.⁴ It is generally accompanied by pruritus or a burning sensation.

The natural history tends to be autoresolution within 2 to 8 weeks without scarring but sometimes leaving some postinflammatory hyperpigmentation.¹¹ Mild systemic symptoms like fever and arthralgia may occur and transient hypereosinophilia is found in about half the cases.¹² When found, peripheral eosinophilia can be correlated with the disease clinical activity.⁶

Least common clinical presentations previously published in the literature includes bullous, nodular or papulonodular lesions.⁶

Histopathological analysis is paramount for the diagnosis of WS. The histological findings depend on the time of evolution of the biopsied lesion.¹³ There are three different stages: acute, subacute and resolution. In the acute stage of WS, dermal oedema and infiltration of granulocytes, predominantly eosinophils, are found.⁴ The subacute stage is characterised by 'flame figures' that represent intense eosinophilic degranulation of major basic protein coating collagen bundles in the dermis.⁴ These 'flame figures' are not pathognomonic of WS but rather can be found in other conditions like bullous pemphigoid, tinea pedis, arthropod bites, Churg-Strauss syndrome or drug eruptions.^{4 11} Finally, in the resolution stage, phagocytic histiocytes form a palisade around the 'flame figures' and granulomas arise in an attempt to eliminate them.¹¹

As the clinical appearance shows great variability, the appropriate diagnosis of WS is based on a proper clinicopathological correlation based on an accurate history. The main differential diagnosis includes bacterial cellulitis, urticaria, contact dermatitis and drug eruptions.⁴ Some authors consider that Churg-Strauss syndrome, characterised by peripheral eosinophilia and eosinophilic infiltration of systemic organs, may be related to WS.^{4 14}

While not common, several malignancies have been associated with WS and so it is highly recommended to obtain an accurate medical history and perform a detailed clinical examination to screen for underlying disorders. If needed, further screening tests should be done accordingly with clinical findings.^{4 7 8} There are several reports addressing the association of WS and haematological malignancies like chronic myeloid leukaemia, chronic lymphocytic leukaemia and non-Hodgkin's lymphocytic lymphoma.^{4 15 16} Rare cases of non-haematological malignancies have been published that included different types of neoplasms like squamous cell carcinoma (bronchial and anal), nasopharyngeal carcinoma, colon adenocarcinoma or renal cell cancer.^{7 8} In our case there is a temporal relationship between the beginning of the dermatosis and the diagnosis of lung cancer. To the best of our knowledge, there has been only one other case describing this particular association.⁸ In 2001, Farrar *et al* published a case of a 79-year-old woman with WS presenting 12 months after a pulmonary lobectomy for a poorly differentiated squamous cell carcinoma of the bronchus. In that case, however, the patient was found to have widespread metastases and eventually died from carcinomatosis. In our patient, there are, for the time being, no signs of metastases or relapse of the neoplasm but the patient is kept under careful follow-up.

Due to the rarity of the disease and the occasional spontaneous resolution, treatments for WS are difficult to evaluate. Most authors agree that, when identified, the treatment of the triggering factor or associated condition is the best approach.¹⁷ If there is no evidence of triggering factors, the first-line therapy should be topical or systemic corticosteroids (depending if the disease is localised or disseminated).¹⁷ Many other therapies have been tried, including dapsons, cyclosporine, antihistamines and oral/topical tacrolimus, but these are generally limited to cases of steroid resistance or steroid contraindications.¹⁷

Wells syndrome is a disease with a benign course although recurrences occur frequently.⁴ The skin lesions resolve without scarring but sometimes leave residual hyperpigmentation.¹¹

We present this case for its rarity and to highlight the possible association with lung cancer that we believe acted as a triggering event. To our knowledge, this is the second case reported with this association.

Learning points

- Wells syndrome (WS) or eosinophilic cellulitis is a rare, idiopathic, inflammatory dermatosis with a pleomorphic clinical presentation and a benign course.
- Etiopathogenesis is still unknown but it has been hypothesised that Wells syndrome is a hypersensitivity reaction to an exogenous or endogenous unknown stimulus.
- Several associations and trigger events have been appointed. The most common trigger events are arthropod bites, drugs, viral and parasitic infections.
- Although in the majority of cases no underlying disease can be found, WS has been occasionally associated with haematological malignancies and, rarely, with solid neoplasms.
- A skin biopsy should always be performed in cases of cellulitis that does not respond to antimicrobial treatment.

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REFERENCES

- 1 Wells GC. Recurrent granulomatous dermatitis with eosinophilia. *Trans St Johns Hosp Dermatol Soc* 1971;57:46–56.
- 2 Wells GC, Smith NP. Eosinophilic cellulitis. *Br J Dermatol* 1979;100:101–9.
- 3 Sinno H, Lacroix JP, Lee J, *et al*. Diagnosis and management of eosinophilic cellulitis (Wells' syndrome): a case series and literature review. *Can J Plast Surg* 2012;20:91–7.
- 4 Long H, Zhang G, Wang L, *et al*. Eosinophilic skin diseases: a comprehensive review. *Clin Rev Allergy Immunol* 2016;50:189–213.
- 5 Schorr WF, Tauscheck AL, Dickson KB, *et al*. Eosinophilic cellulitis (Wells' syndrome): histologic and clinical features in arthropod bite reactions. *J Am Acad Dermatol* 1984;11:1043–9.
- 6 Heelan K, Ryan JF, Shear NH, *et al*. Wells syndrome (eosinophilic cellulitis): proposed diagnostic criteria and a literature review of the drug-induced variant. *J Dermatol Case Rep* 2013;7:113–20.
- 7 Rajpara A, Liolios A, Fraga G, *et al*. Recurrent paraneoplastic wells syndrome in a patient with metastatic renal cell cancer. *Dermatol Online J* 2014;20.
- 8 Farrar CW, Guerin DM, Wilson NJ. Eosinophilic cellulitis associated with squamous cell carcinoma of the bronchus. *Br J Dermatol* 2001;145:678–9.

- 9 Powell JG, Ramsdell A, Rothman IL. Eosinophilic cellulitis (Wells syndrome) in a pediatric patient: a case report and review of the literature. *Cutis* 2012;89:191–4.
- 10 Cormerais M, Poizeau F, Darrieux L, *et al.* Wells' Syndrome Mimicking Facial Cellulitis: A Report of Two Cases. *Case Rep Dermatol* 2015;7:117–22.
- 11 Gandhi RK, Coloe J, Peters S, *et al.* Wells syndrome (eosinophilic cellulitis): a clinical imitator of bacterial cellulitis. *J Clin Aesthet Dermatol* 2011;4:55–7.
- 12 España A, Sanz ML, Sola J, *et al.* Wells' syndrome (eosinophilic cellulitis): correlation between clinical activity, eosinophil levels, eosinophil cation protein and interleukin-5. *Br J Dermatol* 1999;140:127–30.
- 13 Mitchell AJ, Anderson TF, Headington JT, *et al.* Recurrent granulomatous dermatitis with eosinophilia. Wells' syndrome. *Int J Dermatol* 1984;23:198–202.
- 14 Ratzinger G, Zankl J, Zelger B. Wells syndrome and its relationship to Churg-Strauss syndrome. *Int J Dermatol* 2013;52:949–54.
- 15 Stuhr PM, Vale EC. Wells syndrome associated with chronic lymphocytic leukemia. *An Bras Dermatol* 2015;90:571–4.
- 16 Nakazato S, Fujita Y, Hamada Y, *et al.* Wells' syndrome associated with chronic myeloid leukaemia. *Acta Derm Venereol* 2013;93:375–6.
- 17 Rabler F, Lukacs J, Elsner P. Treatment of eosinophilic cellulitis (Wells syndrome) - a systematic review. *J Eur Acad Dermatol Venereol* 2016;30:1465–79.

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