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Wells' syndrome possibly caused by hematologic malignancy, influenza vaccination or ibrutinib: A case report

Mihela Šajn, Boštjan Luzar, Samo Zver

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Abstract

BACKGROUND

Wells' syndrome (eosinophilic cellulitis) is an uncommon eosinophilic dermatosis of uncertain pathogenesis, characterized by clinical polymorphism and suggestive but nonspecific histopathologic traits. Its course is recurrent, and response to therapy is unpredictable. In a case in which the patient has a number of potential triggers for the manifestation of Wells' syndrome skin rash, the treating physician must decide or must make an assumption in order to establish the most likely clinical scenario. This is important for the patient's future treatment plans.

CASE SUMMARY

We describe the clinical case of a 46-year-old female with chronic lymphocytic leukemia who had already received treatment for several months with ibrutinib. She was diagnosed with Wells' syndrome 10 d after an influenza vaccination containing thimerosal. Based on the literature, the patient was treated with a course of oral steroids. Resolution of clinical symptoms and rash were observed in response to the treatment. Ibrutinib was not discontinued.

CONCLUSION

The etiology of Wells' syndrome remains unknown. Clinically, it resembles bacterial cellulitis. Lack of response to antibiotic treatment should lead the physician to consider a diagnosis of Wells' syndrome. Treating the underlying condition is important and may lead to resolution of the syndrome. However, the most common and effective treatment to limit the course of the disease are systemic steroids.

Key Words: Wells' syndrome; Chronic lymphocytic leukemia; Allogenic hematopoietic stem cell transplantation; Ibrutinib; Thimerosal-containing influenza vaccine; Clinical

case; Case report

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Core Tip: Our patient presented with pruritic rash all over her body. Based on the pathohistological features, a diagnosis of Wells' syndrome (eosinophilic cellulitis) was established. We considered hematological malignancy, ibrutinib and influenza vaccine as possible triggers. The only new event and therefore most probable trigger for Wells' syndrome was an influenza vaccination with a vaccine containing thimerosal. Clinically, this is a relatively rare case.

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INTRODUCTION

Classic eosinophilic dermatoses include eosinophilic cellulitis (Wells' syndrome), granuloma faciale, eosinophilic fasciitis (Shulman syndrome) and eosinophilic folliculitis (Ofuji disease). Even though these disorders share the common characteristic of tissue eosinophilia, they have a variety of clinical presentations[1]. Fewer than 200 cases of Wells' syndrome have been reported in the literature[2]. It is characterized by protean cutaneous manifestations with prominent eosinophilia[3]. The diagnosis is corroborated by histopathological findings from a skin biopsy specimen.

The cause of Wells' syndrome is not known. In literature specific triggers were implicated, including drugs such as penicillin or infliximab, thimerosal-containing vaccines, and hematological malignancies, such as chronic lymphocytic leukemia (CLL), non-Hodgkin's lymphoma, chronic myeloid leukemia and polycythemia rubra vera[1,2,4]. The most common and effective treatment is oral steroids. Topical corticosteroids are less effective and should be considered in cases of limited disease or persistent residual lesions[2].

In this case report, a female patient with CLL receiving ibrutinib and recently receiving an influenza vaccination at the time of diagnosis of Wells' syndrome is presented.

CASE PRESENTATION

Chief complaints

A 46-year-old Caucasian woman presented at the Haematology Outpatient Department with pruritic rash all over her body. Prior to this visit, she had been examined by an infectious diseases specialist at her local hospital, who suspected a scabies-related rash.

History of present illness

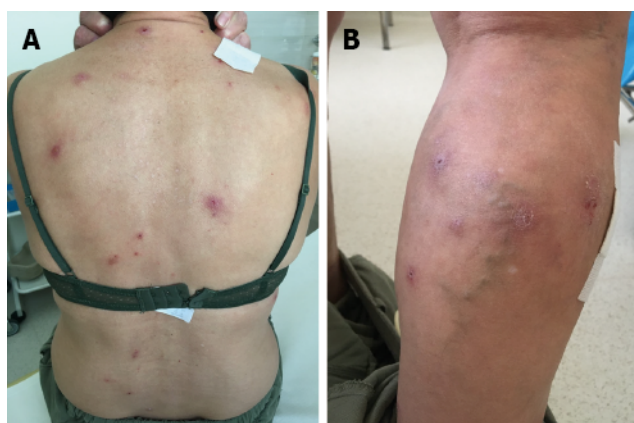
The patient complained of pruritic, erythematous, blister-like lesions that had arose over the past 14 d. Because of scrubbing, the blisters were soon replaced with crusts (Figure 1). She reported having noticed no signs of infection, no fevers or chills, and no B-symptoms, and denied having been bitten by an insect or close contact with domestic animals. She was not receiving any medical drugs, with the exception of ibrutinib (started 18 mo earlier) but remembered having received a thimerosal-containing influenza vaccination (VaxigripTetra®, Sanofi Pasteur, Lyon, France) 10 d prior to the first skin lesions appearing. She reported never having experienced a similar rash.

History of past illness

The patient had been diagnosed with CLL and treated with allogeneic hematopoietic stem cell transplantation (allo-HSCT) in 2017. To address a persistent CLL clone with bone marrow infiltration of 5%, she had received the above-mentioned ibrutinib. More than 3 years after the allo-HSCT, she had presented for an extra outpatient visit to address the itchy rash.

Personal and family history

There is no personal and family history.



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Figure 1 Surgical image. A: Skin rash on the patient's back at presentation; B: Skin rash on the patient's leg at presentation.

Physical examination

On admission, the patient was afebrile. Papulonodular, crusted skin eruptions (2-3 mm in diameter) were prominent on her neck, back, arms and legs. An enlarged painful lymph node (3 cm in diameter) was palpable under the left armpit. The influenza vaccination had been given on that same side.

Laboratory examinations

The patient's white blood cell and absolute eosinophil counts in the peripheral blood were within normal ranges ($7.94 \times 10^9/L$ and $0.27 \times 10^9/L$, respectively). Serological and PCR-based testing ruled out reactivation of herpes simplex virus 1 and 2, varicella zoster virus, cytomegalovirus, and Epstein-Barr virus.

Imaging examinations

No image inspections are involved.

Pathohistological examination

Since the clinical and laboratory examinations did not establish a diagnosis, we opted for skin biopsy. The skin biopsy from the right thigh revealed irregular acanthosis of the epidermis, associated with diffuse superficial and deep perivascular and interstitial inflammatory cell infiltrates composed predominantly of eosinophilic granulocytes admixed with lymphocytes and histiocytes. The inflammatory cell infiltration extended into the septa and lobuli of the subcutaneous fatty tissue (Figure 2).

FINAL DIAGNOSIS

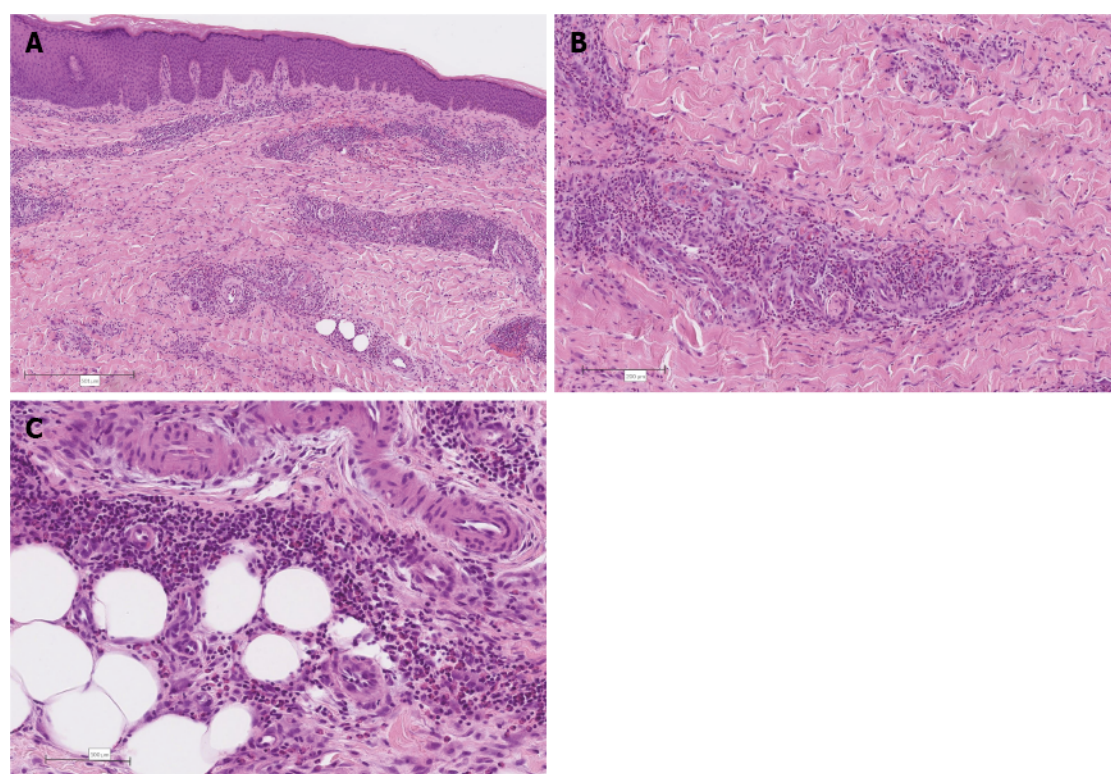
Wells' syndrome (eosinophilic cellulitis).

TREATMENT

Based on the overall and up-to-date literature, the patient was treated with a course of oral steroid (methylprednisolone 48 mg at 1 mg/kg), administered daily for 1 wk and followed by a rapid tapering until discontinuation within 4 wk.

OUTCOME AND FOLLOW-UP

With the steroid treatment, resolution of the clinical symptoms and rash was observed. The ibrutinib was not discontinued at any point. Repeat bone marrow aspiration flow cytometry and histology findings were consistent with 5% residual infiltration of a CLL clone.



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Figure 2 Histological evidence of Wells' syndrome in skin from the right thigh. A: Psoriasiform hyperplasia and moderately intense superficial and deep perivascular and interstitial inflammatory cell infiltrate are evident, extending into the subcutis (magnification: 40 ×); B: Eosinophilic granulocytes as the main component of the inflammatory cell infiltrate. Here, they are seen in perivascular areas but also within the interstitium between collagen bundles (magnification: 100 ×); C: Inflammatory cell infiltrate mainly composed of eosinophilic granulocytes extending into the subcutaneous fatty tissue (magnification: 200 ×).

DISCUSSION

Wells' syndrome, a recurrent granulomatous dermatitis with eosinophilia was first described by Wells in 1971. It also goes by the name eosinophilic cellulitis and eosinophilic dermatosis. Clinically, the syndrome resembles bacterial cellulitis because patients usually present with a warm erythematous skin lesion. Cellulitis not responding to antibiotic treatment should lead the physician to suspect Well's syndrome[2,3]. The classic, plaque-type variant has been shown to be the most common clinical presentation form among children but not among adults. In the latter group, erythematous annular lesions resembling annular granuloma are most frequently recognized, as was the case in our patient[3]; moreover, the pathohistological features were consistent with Wells' syndrome (Figure 2).

The cause of Well's syndrome is not known. In literature possible triggers were implicated in the syndrome development: insect bites, viral or bacterial infections, drugs, thimerosal-containing vaccines, hematological malignancies and carcinoma. Most of the reported cases suggest a certain trigger, such as an underlying disorder, and rarely does the syndrome appear to be idiopathic in origin. Although the pathogenesis is not well defined, a type IV hypersensitivity reaction to various stimuli may be involved [2,4].

CLL is the most common leukemia in adults in Western countries, with the average age of diagnosis being 72 years. The disease is characterized by an accumulation of monoclonal, mature, CD5+ B cells in the peripheral blood, bone marrow and secondary lymphoid organs[5]. CLL is accompanied by an increased incidence of other malignancies, and patients are prone to cutaneous infections, particularly viral ones, and have exaggerated, vivid reactions to insect bites[6]. Although overall leukemic skin infiltration occurs in 3%-50% of patients within the entire spectrum of leukemias or lymphomas, it is a rare event among patients with CLL[7].

Eosinophilic dermatosis of hematologic malignancy (EDHM) and/or insect bite-like reactions are a rare event, particularly in association with CLL[8]. There has been debate about whether this phenomenon is due to a delayed hypersensitivity reaction to insect bites, particularly mosquitoes. However, most patients with lymphoproliferative disease presenting with this reaction cannot recall any bite. The condition has therefore been described with many terms, such as (exaggerated) insect bite-like reaction, eosinophilic dermatosis of myeloproliferative disease, and exaggerated arthropod-bite reaction[9]. EDHM has a pleomorphic presentation. The condition is presented by erythematous, urticarial eruptions of papules, nodules, vesicles, or the formation of plaques[10]. Histology reveals the presence of a superficial and deep, dense perivascular lymphocytic and eosinophilic infiltrate[11]. The

pathogenesis of EDHM is not known[10]. It has been suggested that the leukemic cells may cause an excess of interleukin (IL)-4 and (IL)-5 and consequently a proliferation of neoplastic B cells. The fact is that IL-5 is the major eosinophil-recruiting cytokine and neoplastic B cells are thought to be the major driver of the eruption[10,11]. Some authors have considered EDHM and eosinophilic cellulitis in patients with hematologic disorders to be the same entity[12]. Indeed, there is an overlap in clinical and pathological features between EDHM and eosinophilic cellulitis, as follows: (1) Polymorphisms in the clinical features have been described in these two conditions; and (2) Both disorders are pathologically characterized by an eosinophilic infiltration, mainly in the dermis[10].

Our case is unique because a patient who had undergone treatment with allo-HSCT was involved. This had been performed in the context of CLL treatment with adverse prognostic factors (del17, TP53 mutation; IgHV mutation status was not performed) in the young female[13]. However, the treatment was ultimately not curative, and residual disease was still present after immunosuppression withdrawal after the allo-HSCT. The patient was afraid of graft *vs* host disease[14] and refused a donor lymphocyte infusion, which had been proposed to enhance immune-mediated antitumor activity[15].

Because residual disease is widely associated with a significant risk of CLL progression, ibrutinib, a potent and irreversible small-molecule inhibitor of both Bruton's tyrosine kinase and IL-2 inducible kinase as well as several other tyrosine kinases, was instituted. Ibrutinib should provide effective CLL treatment of residual disease after allo-HSCT[13,16]. Since a reduced dose of ibrutinib proved effective [17], the initial dosage of 420 mg daily was reduced to 120 mg daily after 1 mo due to severe neutropenia. Our main goal with ibrutinib treatment is to prevent CLL progression. Apart from being a Bruton's tyrosine kinase inhibitor, ibrutinib has been shown to effectively inhibit epidermal growth factor receptor (EGFR) in a dose-dependent manner. Inhibition of EGFR is known to stimulate apoptosis and inflammation and to inhibit cell cycle progression. Cutaneous eruptions are a well-known adverse effect to EGFR inhibition by other tyrosine kinase inhibitors, and similarly ibrutinib-induced rash may be related to EGFR inhibition[14,18-20].

EGFR inhibitor-induced toxic effects of the skin are well described and are claimed to be a class effect of this substance group. Patients present with macular, papular or pustular lesions in an acneiform distribution, mainly localized in cosmetically-sensitive areas (*e.g.*, regions rich in sebaceous glands, such as the face and upper trunk) but can also extend to the extremities. Severe acute skin reactions show massive neutrophilic infiltration of the epidermis and profound apoptosis[19]. Cutaneous manifestations, including purpuric eruptions, have been reported in 8%-27% of patients receiving ibrutinib, sometimes resulting in treatment delays or even drug discontinuation[21]. The time of rash onset is highly variable, with onset as late as 300-400 d after the ibrutinib initiation in some patients[21,22].

In our case, if ibrutinib was the trigger, then the rash had appeared more than 600 d after the treatment was begun. In a single-center review of patients with ibrutinib-associated rash performed by Iberri *et al*[21], 4 patients with grade 3 rash underwent biopsy, demonstrating perivascular infiltration of lymphocytes, neutrophils and eosinophils involving the papillary dermis. However, Bullock *et al*[23] reported a clinical case of eosinophilic skin rash in a patient with CLL who had recently started ibrutinib. The patient presented to the emergency department with a 4-d history of a severely pruritic, eruptive full-body rash. The clinical differential was among EDHM *vs* drug eruption, given that she had recently started ibrutinib. After treatment with prednisone, topical corticosteroids and antihistamines, the skin lesions resolved. The patient continued to have complete resolution of her cutaneous eruption despite continuing ibrutinib therapy.

In the case of our patient, the only new event was an influenza vaccination 10 d before the clinical presentation of Wells' syndrome. A case of Wells' syndrome in an adult 13 d after influenza vaccination was described by Masckauchan *et al*[24]. There are also some cases of children being diagnosed with Wells' syndrome post-influenza vaccination and 1 case of an adult being diagnosed after receiving a tetanus vaccination[25-27]. Indeed, all the vaccinations described in the literature include thimerosal, a common preservative[24-27]. In the case of the patient with Wells' syndrome post-tetanus vaccination, a skin test with thimerosal was found to be positive, demonstrating the possibility that part of the pathophysiology of Wells' syndrome is related to hypersensitivity reactions[27].

CONCLUSION

To conclude, in our case of a patient with Wells' syndrome, we first hypothesized that the cause was EDHM. Prior to the allo-HSCT when the bone marrow infiltration was higher than 5%, she did not experience skin changes associated with EDHM. Next, we considered ibrutinib to be a possible trigger. She had been receiving the drug for more than 2 years and had not develop any skin changes during that period. The only new event, and therefore the most probable trigger of Wells' syndrome, was an influenza vaccination with a vaccine containing thimerosal. We have no specific or reliable evidence to state that this was the definite triggering event. It is also possible that there was an intertwining of all three reasons: hematological malignancy, ibrutinib and influenza vaccine. However, the skin rash resolution after treatment with methylprednisolone despite ibrutinib continuation and persistent CLL burden in our case, provides evidence that the influenza vaccination was the most likely factor in the

appearance of Wells' syndrome.

FOOTNOTES

Author contributions: Šajn M and Zver S designed the manuscript; Šajn M and Luzar B collected the patient's clinical data; Šajn M, Luzar B and Zver S contributed to the analysis and interpretation of the data, and participated in drafting of the manuscript; Zver S critically revised the manuscript; all authors read and approved the final version of the manuscript.

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