CASE REPORT

UDC: 616.51:616.13/.16
DOI: https://doi.org/10.2298/VSP190525114R

Wells' syndrome associated with eosinophilic granulomatosis with polyangiitis − A case report

Velsov sindrom udružen sa eozinofilnom granulomatozom sa poliangiitisom

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Abstract

Introduction. Wells` syndrome (eosinophilic cellulitis) is a chronic, recurrent disease characterized by episodes of erythematous and edematous plaques or nodules with occasional development of hemorrhagic bullae on the trunk and limbs. Eosinophilic granulomatosis with polyangiitis, formerly known as Churg-Strauss syndrome, is a specific variant of the group of diseases characterized by necrotizing vasculitis of small to medium-sized blood vessels affecting multiple organ systems. The association of Wells` syndrome and eosinophilic granulomatosis with polyangiitis is very rare, and to our knowledge has been reported in only ten patients. **Case report**. We present a case of a 34-year-old woman with a 3-year history of periodical onset of erythematous plaques on the trunk and edematous plaques clinically resembling cellulitis on her lower limbs. The patient reported a one-year history of asthma, rhinosinusitis, and nasal polyposis. Skin biopsy revealed the presence of diffuse eosinophilic infiltrates in the dermis accompanied by characteristic "flame figures". Further investigation showed peripheral blood eosinophilia (22.6%), bilateral maxillary sinusitis, presence of eosinophil infiltrates and microabscesses in the bronchial wall, and pericapillary eosinophil infiltrates in the pulmonary interstitium shown by bronchoscopy and transbronchial biopsy, respectively. Treatment was started with methylprednisolone 0.5 mg/kg/day, and the dose was gradually tapered for the following twelve weeks. Complete remission of skin changes was achieved, but new lesions appeared in the past two years, which required repeated treatment. **Conclusion.** Association of these syndromes is unusual and may be based on the common pathogenetic background. We hypothesize that Wells` syndrome could be a stage preceding eosinophilic granulomatosis with polyangiitis, and that patients should be evaluated for eosinophilic granulomatosis with polyangiitis, since these two diseases overlap in clinical and laboratory findings.

Key words:
biopsy; churg-strauss syndrome; diagnosis; eosinophilia; wells syndrome; therapeutics; treatment outcome.

Apstrakt

Uvod. Velsov sindom (eozinofilni celulitis) je hronično rekurentno oboljenje koje odlikuju epizode eritematoznih i edematoznih plakova ili nodusa, uz povremenu pojavu hemoragičnih bula na trupu i ekstremitetima. Eozinofilna granulomatoza sa poliangiitisom, u ranijoj terminologiji Čarg-Štrausov sindrom, je specifična varijanta grupe bolesti koje se karakterišu nekrotizirajućim vaskulitisom malih i srednjih krvnih sudova. Prema našem saznanju, udruženost Velsovog sindoma i eozinofilne granulomatoze sa poliangiitisom je retka, do sada opisana kod deset bolesnika. **Prikaz bolesnika.** Prikazana je bolesnica, stara 34 godine, sa trogodišnjom istorijom periodične pojave eritematoznih plakova na trupu i edematoznih plakova nalik celulitisu na donjim ekstremitetima. U ličnoj anamnezi navela je astmu u prethodnih godinu dana, rinosinuzitis i nazalnu polipozu. Biopsijom kože uočeno je prisustvo difuznog eozinofilnog infiltrata u dermu sa karakterističnim "plamenim figurama". Daljim pretragama evidentirana je eozinofilija u perifernoj krvi (22,6%), obostrani maksilarni sinuzitis, eozinofilni infiltrati i mikroapcesi u bronhijalnom zidu i perikapilarni eozinofilni infiltrati u intersticijumu pluća, uočeni brohoskopijom, kao i transbronhijalnom biopsijom. Lečenje je započeto metilprednizolonom 0,5 mg/kg/dan uz postepeno snižavanje doze narednih 12 nedelja. Postignuta je kompletna remisija promena na koži, uz ponovnu pojavu u poslednje dve godine, što je zahtevalo ponavljanje terapije. **Zaključak.** Udruženost ova dva sindroma je neuobičajena, sa mogućom zajedničkom patogenetskom osnovom. Pretpostavljamo da Velsov sindrom može biti prethodni stadijum eozinofilne granulomatoze sa poli

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angiitisom i mišljenja smo da bolesnike treba ispitati u smislu postojanja eozinofilne granulomatoze sa poliangiitisom s obzirom na to da ove bolesti mogu imati klinička i laboratorijska preklapanja.

Ključne reči:
biopsija; angiitis, alergijski, granulomatozni; dijagnoza; eozinofilija; vels sindrom; lečenje; lečenje, ishod.

Introduction

Wells' syndrome (WS) or eosinophilic cellulitis, described by Wells in 1971, is a rare inflammatory dermatosis with episodes of erythematous urticarial plaques [1]. It may also manifest itself as the development of vesicles and bullae or nodules and granulomatous eosinophilic infiltrates in the dermis. WS is characterized by benign disease course with lesions usually located on the head, trunk and limbs. Seven clinical variants have been described [2]. The classic plaque- type variant is the most common in children, while the granuloma-like variant is more common in adults. To date, approximately 200 cases of WS have been reported.

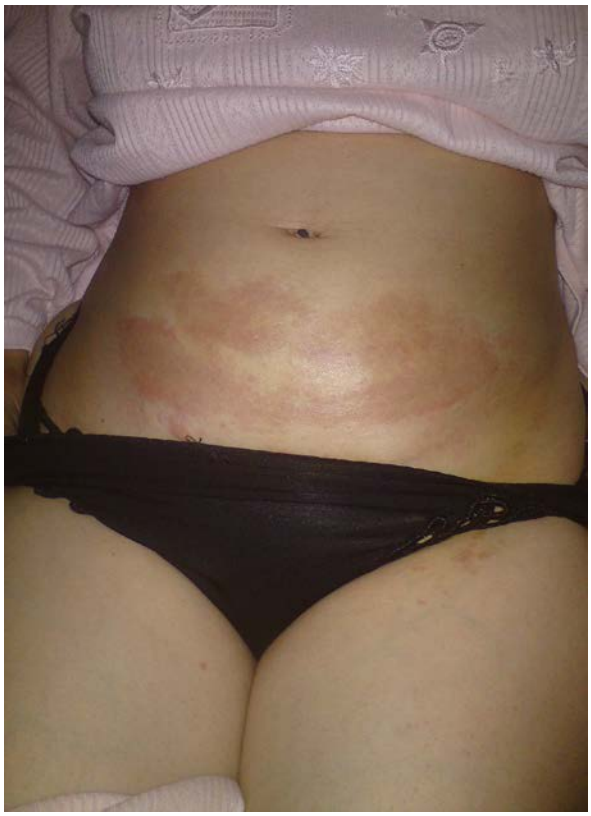
Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome (CSS), is a rare, systemic small to medium sized vasculitis associated with asthma and eosinophilia. The manifestation of the disease depends on the systems involved [3].

To our knowledge, the association between WS and EGPA has been reported in ten patients. These syndromes may have a common pathogenetic mechanism with hypersensitive reaction to the underlying cause including allergens, insect bites, infections, vaccinations, medications, and malignancy [4–12].

Case report

A 34-year-old woman with a 3-year history of periodical onset of erythematous plaques on the trunk and edematous plaques clinically resembling cellulitis on the lower limbs was admitted to our Department (Figure 1). At the time, the lesions were extremely pruritic and occasionally accompanied by burning sensation. Previously, the patient had been treated with antihistamines and occasionally with short-term administration of prednisone. However, she had had several exacerbations following each discontinuation of prednisone. The patient denied taking any additional medications, presence of fever, weight loss, or joint pain. She reported a one-year history of asthma, rhinosinusitis, and nasal polyposis. To treat asthma, she had been taking inhaled corticosteroids and beta-2-agonists.

Histopathologic examination of the skin lesions demonstrated abundant lymphocytic and eosinophilic infiltrates in the dermis, with characteristic eosinophilic staining in the form of "flame figures", which was consistent with the diagnosis of WS (Figure 2). Direct immunofluorescence microscopy did not reveal any deposits of immunoglobulin or complement in the skin biopsy.



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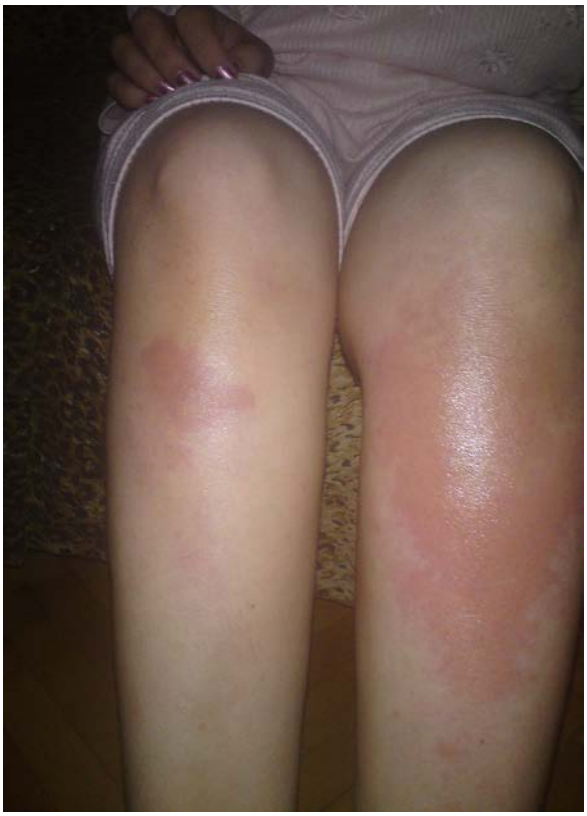

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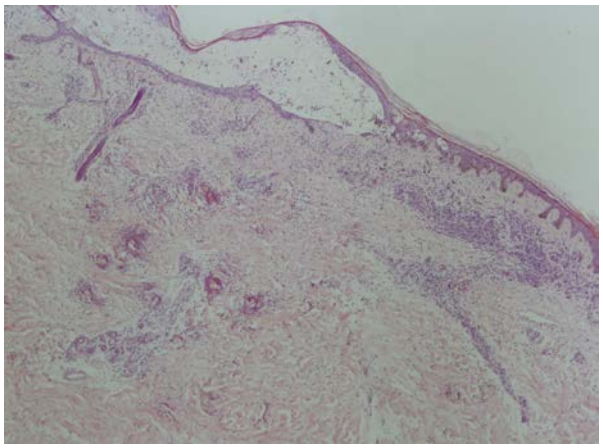
Fig. 1 – a) Widespread erythematous plaques with sharp borders and central regression on the abdomen; b) Urticarial plaques on the lower extremities, clinically resembling cellulitis.



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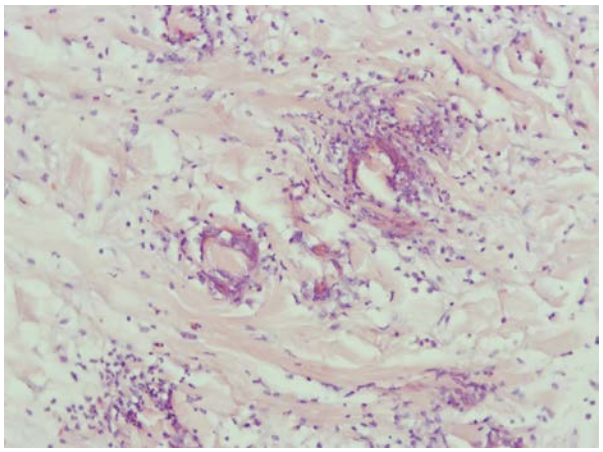

b)

Fig. 2 – a) Histology of the skin biopsy shows an intraepidermal vesicle in the spinous layer and abundant eosinophilic and lymphocytic infiltrates with degeneration of collagen surrounded by eosinophils in the dermis (hematoxylin and eosin, ×40); b) "Flame figures" with surrounding dense eosinophilic infiltration (hematoxylin and eosin, ×200).

Laboratory investigation showed eosinophilia (22.6%). Erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, liver and renal tests and immunoglobulin E (IgE) were within normal ranges. Cytoplasmic and perinuclear antineutrophil cytoplasmic antibody (c- and p-ANCA), antinuclear antibodies (ANA), ENA (extractable nuclear antigen) screening, cryoglobulins and immune complexes were negative. Enzyme-linked immunosorbent assay (ELISA) for *Toxocara*, *Toxoplasma*, *Echinococcus*, *Cysticercosis*, *Strongyloides*, anti HIV 1/2, HBsAg and HCV antibodies were negative. Other infective causes of eosinophilia were also ruled out: stool sample test for intestinal parasites, sputum for acid-resistant bacilli (ARB) direct examination and Löwenstein cultivation and bacterial swabs were negative. Prick tests with the standard battery of inhaled allergens were negative. Pulmonary function tests showed normal spirometry finding, transfer factor for carbon monoxide (70% normal range 50%–80%) and transfer coefficient (72%) were reduced; oxygen saturation was 97% (normal range ≥ 97%).

Radiological examination revealed bilateral maxillary sinusitis (Figure 3). The electromyoneurographic examination was performed and neuropathy was excluded. Peripheral blood smear and bone marrow biopsy ruled out a hematological disorder. Chest radiography and heart ultrasonography were normal. However, microscopic examination of bronchoalveolar lavage confirmed eosinophilia (63%). Histopathologic findings of bronchoscopic biopsy revealed fragments with abundant eosinophilic and lymphocytic infiltrates as well as the foci of eosinophilic microabscesses. Pericapillary eosinophilic infiltrates affecting the lung interstitial were observed with transbronchial biopsy which could be a histologic sign of vasculitis.

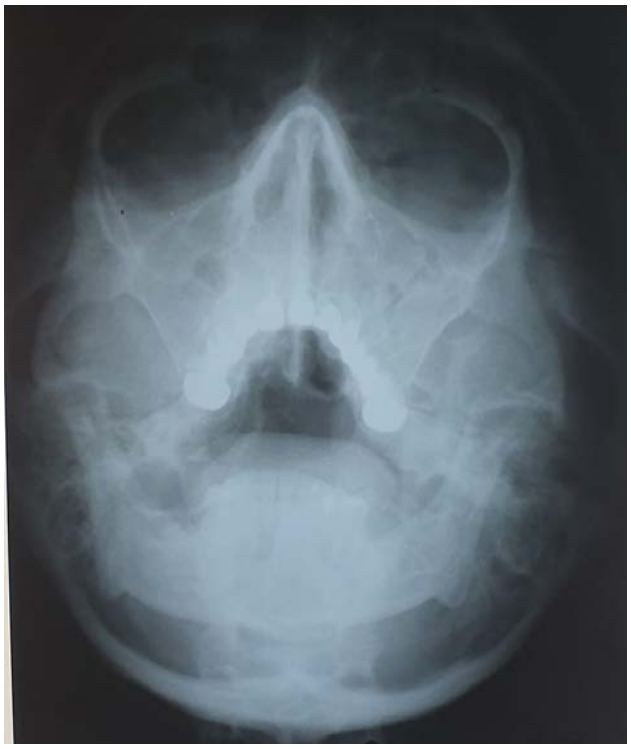

Fig. 3 – Radiological examination revealed bilateral maxillary sinusitis.

WS associated with EGPA was confirmed and the initial treatment with methylprednisolone was introduced at a dose of 0.5 mg/kg/day. For the following 12 weeks, the dose was gradually reduced to the maintenance dose of 5 mg every other day that was prescribed for the period of one year. The administered therapy was sufficient to manage the condition for the subsequent six years, after which the lesions appeared again and the treatment was reintroduced. Any attempt to discontinue the treatment led to reappearance of skin changes.

In the last two years skin lesions have reappeared, and methylprednisolone was reintroduced with tapering to 5 mg every other day, up until now. Nevertheless, any attempt to discontinue the drug led to reappearance of skin lesions that were mild compared to the initial presentation of the disease. Additional treatment with inhaled budesonide/formoterol and supplementation with calcium 1,000 mg/day and vitamin D at the dosage of 800 IU/day was prescribed.

Discussion

WS is a rare inflammatory dermatosis with spontaneous remission but frequent recurrence [1]. It is characterized by pruritic, urticarial plaques, vesicles, bullae or nodules during the acute phase, and indurated morphea-like lesions in later stages. Skin symptoms are accompanied with peripheral blood eosinophilia in almost half of the patients [1, 2, 4].

Indicative of this disease are the histopathologic "flame figures", which can also be observed in EGPA associated with WS, hypereosinophilic syndrome, cutaneous eosinophilic vasculitis, insect bite reactions, cutaneous parasitic infections, bullous pemphigoid and herpes gestationis [12, 13].

EGPA is a disorder that may affect multiple organ systems. It has been found that EGPA evolves through three phases. The prodromal phase, characterized by asthma and rhinosinusitis is followed by the eosinophilic phase with peripheral eosinophilia and eosinophil infiltrations in various organs, the lung, heart and gastrointestinal tract being most commonly affected. The third, vasculitic phase is marked by small vessel vasculitis, fever, fatigue, and improvement of asthma as a cardinal feature of this phase [3, 14]. Skin lesions are variable, appearing as palpable purpura, nodules, erythematous, maculopapular, and rarely as bullous lesions [15]. Although etiopathogenesis of the disease is still considered to be unclear, the infiltration by eosinophils and ANCA are likely the most important mechanisms [3]. WS and EGPA display involvement of abnormal Th2 cells, increased production of IL-5, and consequently, activated eosinophilic granulocytes driving nonspecific hypersensitivity response to exogenous or endogenous stimuli. The pathogenic T-helper cells present in skin lesions display memory Th cells phenotype (CD4+CD7-)[16], but it is still unclear what their activation mechanisms are. A correlation has been found between clinical parameters of EGPA disease activity (Birmingham Vasculitis Activity Score – BVAS, eosinophilia) and expression of IL4, IL5, IL10 and STAT5A [17]. Considering that myeloid cells, particularly dendritic cells (DC), are most potent Th polarizing cells which drive their differentiation towards Th2 or Th1717, it is of great importance to study the functions of DC from patients with WS and EGPA.

Patients with ANCA-positive EGPA more frequently had peripheral neuropathy, glomerulonephritis and palpable purpura due to small-vessel vasculitis [18, 19]. In contrast, patients with ANCA-negative EGPA experience erythematous plaques, urticarial lesions and eosinophilic infiltration of the lung, myocardial and gastrointestinal tissue, as in our case [3, 18, 19]. Since WS is characterized by eosinophilic infiltration without vasculitis, the authors point out that EGPA with WS would be ANCA-negative [20], which we confirmed, in contrast to three other reported cases [5, 8, 12]. This is the case of ANCA negative EGPA associated with WS.

The most commonly used criteria for diagnosing EGPA are defined by the American College of Rheumatology with 85% of sensitivity and 99.7% specificity [21]. The affected patients should meet four out of the following six criteria: asthma, eosinophilia of $>10\%$ in differential white blood cell counts, mononeuropathy or polyneuropathy, migratory or transient pulmonary infiltrates, paranasal sinus abnormalities on radiography, and extravascular eosinophil infiltration on biopsy findings [21]. In case of our patient, four criteria were met: the presence of eosinophilia, asthma, paranasal sinus abnormalities, and pericapillary eosinophilic infiltrates affecting the lung interstitium observed with transbronchial biopsy as the key histologic characteristic of vasculitis. The key histological characteristics of EGPA are eosinophilic tissue infiltration and/or vasculitis and/or extravascular eosinophilic granulomas. Mononeuropathy and migratory pulmonary infiltrates were not present.

In addition to the presence of distinct EGPA diagnostic criteria, the IgE levels were normal, ANCA and rheumatoid factor were negative, and immune complexes were undetectable, classifying the case of our patient in the group of ANCA-negative EGPA, which may be present in one third of the patients [3, 18, 19]. The association between these two diseases is unusual; Lee et al. [8] published a case where EGPA preceded WS, suggesting that EGPA may induce WS through the pathogenetic effect of eosinophils infiltration of the skin. In contrast, in our patient and other reported cases, WS was a prodromal manifestation and it developed after EGPA [11, 12]. Some authors also propose that WS should be considered in the differential diagnosis of patients with EGPA whose clinical presentation includes erythematous urticarial plaques [9].

These diseases share common features including blood and/or tissue eosinophilia, abnormal eosinophilic reactions to underlying factors, similar skin manifestations, and good therapeutic response to systemic corticosteroids [2, 3, 11]. The severity of the disease can be determined based on the presence of poor prognostic factors for EGPA according to French Vasculitis Study Group [22]. The presence of each factor is allocated 1 point. For patients with a score equal to or greater than 1, treatment with corticosteroids and cyclophosphamide is recommended. Our patient had no poor prognostic factors, no evidence of proteinuria, cardiomyopathy or involvement of the gastrointestinal tract or central nervous system, with normal values of serum creatinine; such cases are usually treated with glucocorticoids. Current treatment options for WS include topical and systemic corticosteroids, antihistamines, cyclosporine, azathioprine, griseofulvin, doxycycline, minocycline, antimalarials, oral tacrolimus/topical tacrolimus, sulfasalazine, interferon alpha and gamma, TNF-alpha inhibitors, colchicine and psoralen and ultraviolet A (PUVA) therapy [23]. Although multiple treatment modalities have been used with variable success rates, the first-line treatment option should be topical and/or systemic corticosteroids. Since long-term systemic corticosteroid therapy can have a wide range of side effects, careful monitoring and using appropriate preventive strategies may minimize them [24].

Regarding treatment, our patient had a favorable response to methylprednisolone, and remission was achieved and maintained for six years. However, due to relapse, additional treatment was necessary.

Conclusion

Association of these syndromes is unusual and may be based on the common pathogenetic background. We hypothesize that WS could be a prior stage of EGPA and that patients should be evaluated for EGPA since these two diseases overlap in clinical and laboratory findings. Corticosteroids are the first line of treatment and usually sufficient for patients who do not have severe organ involvement as in the case of our patient, where we achieved long-term remission. Additional immunosuppressive or biological agents may be necessary in cases of severe organ damage, treatment failure, and frequent relapses.

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Received on May 25, 2019
Revised on September 30, 2019
Accepted October 7, 2019
Online First October, 2019