CASE REPORT

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Pemphigus herpetiformis – A case report of a rare form of pemphigus and review of the literature

Pemphigus herpetiformis – prikaz bolesnika sa retkom formom pemfigusa i pregled literature

Jelena Stojković-Filipović*†, Branislav Lekić*, Danijela Milčić*†, Mirjana V. Milinković*†

***Clinic of Dermatovenerology, Clinical Center of Serbia, Belgrade, Serbia;**
†Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Abstract

Introduction. *Pemphigus herpetiformis* is the rare variant of pemphigus with characteristic clinical features, histopathological findings different from the convectional pemphigus, and immunological findings consistent with pemphigus. **Case report.** We presented a 65-year-old woman with initial pruritus followed by pruritic urticarial papules and plaques, some with annular rings of tense vesicles on the periphery, on the trunk and extremities, with no mucous lesions. Histopathological examination demonstrated spongiosis and intraepidermal vesicles in the mid or subcorneal epidermis in some biopsy specimen, with neutrophil and eosinophil infiltrate. Direct immunoflorescent microscopy revealed intercellular IgG deposition, most prominent in the upper layers of epidermis. Indirect immunoflorescent microscopy showed intercellular binding of IgG autoantibodies in the patient's sera. Initially the patient was threated with systemic corticosteroids and azathioprine, but dapson provided complete clinical remission. **Conclusion.** This entity was established 40 years ago, and around 100 patients have been reported worldwide. It is important to be aware of this particular form of pemphigus because clinical presentation, course of the disease and therapeutic approach are different from conventional forms of pemphigus.

Key words:
pemphigus; rare diseases; diagnosis; drug therapy; treatment outcome.

Apstrakt

Uvod. *Pemphigus herpetiformis* predstavlja retku varijantu pemfigusa, sa karakterističnom kliničkom prezentacijom i patohistološkim nalazom koji se razlikuju od klasičnih formi pemfigusa, i imunološkim karakteristikama koje odgovaraju pemfigusu. **Prikaz bolesnika.** U radu je prikazana bolesnica stara 65 godina sa početnim pruritusom, a potom pojavom pruritičnih papula i plakova, sa mestimično anularno raspoređenim vezikulama na periferiji pojedinih lezija, na trupu i ekstremitetima. Na mukozama nije bilo patoloških promena. Patohistološkim pregledom utvrđena je spongioza i intraepidermalne vezikule u srednjim slojevima epiderma i supkornealno, uz ćelijski infiltrat sačinjen od neutrofila i eozinofila. Direktnom imunoflorescentnom mikroskopijom uočeni su intercelularni depoziti IgG autoantitela, izraženije u gornjim slojevima epiderma. Indirektnom imunoflorescentnom mikroskopijom u serumu bolesnika dokazana su autoantitela IgG klase. Bolesnica je inicijalno lečena opštom kortikosteroidnom terapijom i azatioprinom, ali je do kompletne kliničke remisije dovela terapija dapsonom. **Zaključak.** Od kada je ovaj entitet prvi put opisan pre 40 godina, u literaturi je prikazano oko 100 bolesnika. Pemfigus *herpetiformis* je važno prepoznati s obzirom na drugačiju kliničku prezentaciju, tok bolesti i terapijski pristup u odnosu na konvencionalne forme pemfigusa.

Ključne reči:
pemfigus; retke bolesti; dijagnoza; lečenje lekovima; lečenje, ishod.

Introduction

Pemphigus represents a group of potentially life-threatening autoimmune blistering diseases affecting the skin and mucous membranes [1]. It is characterized by intraepdermal blisters due to achantholyslis, separation of the epidermal cells from each other caused by the antibody-induced disruption of the structural components of keratinocytes, cell-cell anchoring complex, desmosomes [1]. Pathophysiologically, the underling intraepithelial blister formation is caused by immunoglobulin G (IgG) antibodies against desmosomal adhesion proteins desmoglein 3 (Dsg3) and/or desmoglein 1 (Dsg 1)

Correspondence to: Mirjana V. Milinković, Clinic of Dermatovenereology, Clinical Center of Serbia, Faculty of Medicine, University of Belgrade, Pasterova 2, 11 000 Belgrade, Seriba. Phone: +381 11 36 62 483. E-mail: milinm@eunet.rs

on the epidermal keratinocyte cell surface [1]. They can be detected in tissue by direct immunofluorescent microcopy (DIF) of the perilesional skin, in circulation by indirect immunofluorescent microscopy (IIF), as serological detection of antibodies against epidermal components, or specific target antigen, by enzyme-linked immunosorbent assay (ELISA) or immunobloting [1–3].

Pemphigus can be divided into three major forms: pemphigus *vulgaris* (with its localized form pemphigus *vegetans*), pemphigus *foliaceus* (with its localized form pemphigus erythematous and endemic form *fogo selvagem*) and paraneoplastic pemphigus [4]. Pemphigus *vulgaris* (PV) and pemphigus *foliaceus* (PF) are originally characterized as classic or main types of pemphigus [1, 3–5]. In addition, rare forms are included: pemphigus *herpetiformis* (PH), IgA pemphigus [3–6], drug-induced pemphigus, [4, 6] neonatal pemphigus [6] and IgA/IgG pemphigus [5].

In general, pemphigus is uncommon disease. The epidemiology is dependent on the area of the world that is studied as well as the ethnic population in that area. In Europe, the incidence has been reported as 0.5–1.0 [1] up to 2.0 [2] new cases *per* one million inhabitants *per* year.

Pemphigus *herpetiformis* is one of the rare subtypes of pemphigus. It was first introduced by Jablonska et al. [7] in 1975. With the clinical presentation atypical for the most common types of pemphigus, but the immunologic characteristics of pemphigus, this entity presents challenges in the diagnosis. Therefore, a delay in the diagnosis is common. Also, the treatment may be puzzling.

Case report

A 65-year-old Caucasian female was admitted to the Clinic for pruritic urticarial eruption of 3 months duration. Her initial symptom was pruritus, started few weeks before skin changes that initially emerged on the trunk. Physical examination revealed pruritic urticarial papules and plaques, some with annular rings of small or abortive vesicles frequently in herpetiform pattern (Figure 1). The lesions were scattered on the trunk (Figure 2a) and, more prominent, on the extremities (Figures 2b and 2c). Mucous lesions were not present. The patient complained of mild pruritus during the course of skin changes. Histopathological examination of the lesonal skin demonstrated eosinophilic spongiosis with

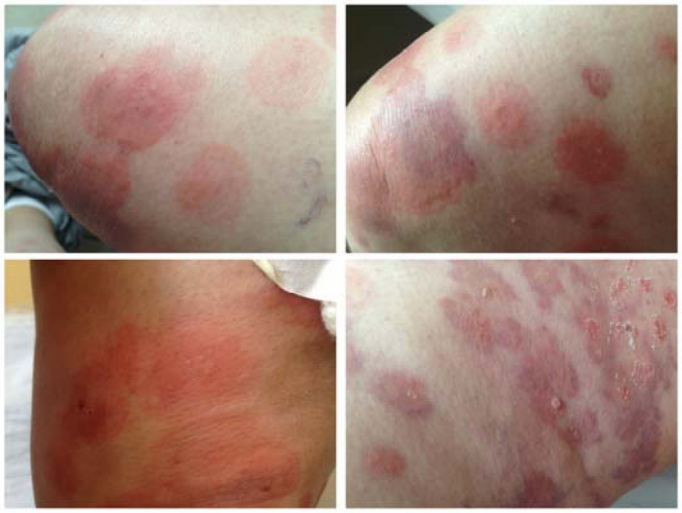

Fig. 1 − Pemphigus *herpetiformis* − groups of small and abortive vesicles, in herpetiform pattern, on erythematous plaques.

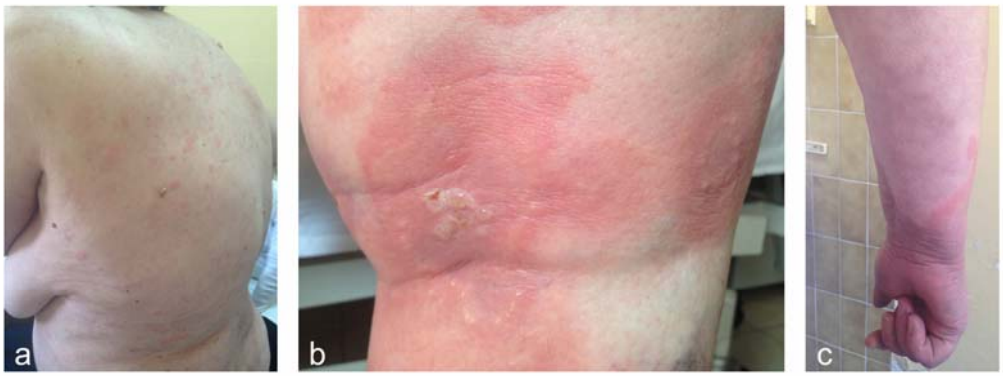

Fig. 2 − Pemphigus *herpetiformis*: a) Erythematous, urticarial plaques on the trunk; b) Tense, vesicles on erythematous base on the leg; c) Annular erythematous, edematous plaques on the distal arm.

formation of intraepidermal vesicles in the mid or subcorneal epidermis and perivascular and interstitial infiltration of eosinophils and lymphocytes in the dermis. (Figures 3a, 3b and 3c) A perilesional skin biopsy for DIF revealed intercellular IgG deposition, most prominent in the upper layers of epidermis (Figure 3d); IgA, IgM and C3 were negative. IIF, using the monkey esophagus as the supstrate, shows intercellular binding of IgG (Figure 3e). Laboratory examination showed slightly elevated levels of urea (9.8 U/L), creatinine (101 U/L) proteins (51 U/L) and gamma-glutamyl transferase (GGT − 49 U/L), while other serum parameters, complete blood count, and tumor markers were within normal limits; urinalysis was normal. The patient had been taking antihypertensive medications for years. Based on clinicopathological and immunological features the diagnosis of pemphigus *herpetiformis* was made. Chest X-ray, computed tomography (CT) scan of the thorax and abdominal ultrasonography were normal, as well as gynecological examination. Oral prednisone in a dosage of 0.59 mg/kg daily was started, as well as topical corticosteroids (fluocinonide 0.05%, clobetasole-propionate 0.05%). In addition, azathioprine 100 mg daily has been administered achieving significant improvement. In further course the prednisone dosage was slowly reduced to 20 mg daily. After two months of treatment mild flare appeared. Azathioprine was excluded and the dosage of prednisone increased. After serum glucose-6-phosphate delydrogenase (G6PD) activity check, dapson, up to 100 mg daily was initiated, and complete clinical remission was achieved in 15 days. Three months later the patient was still free of lesions.

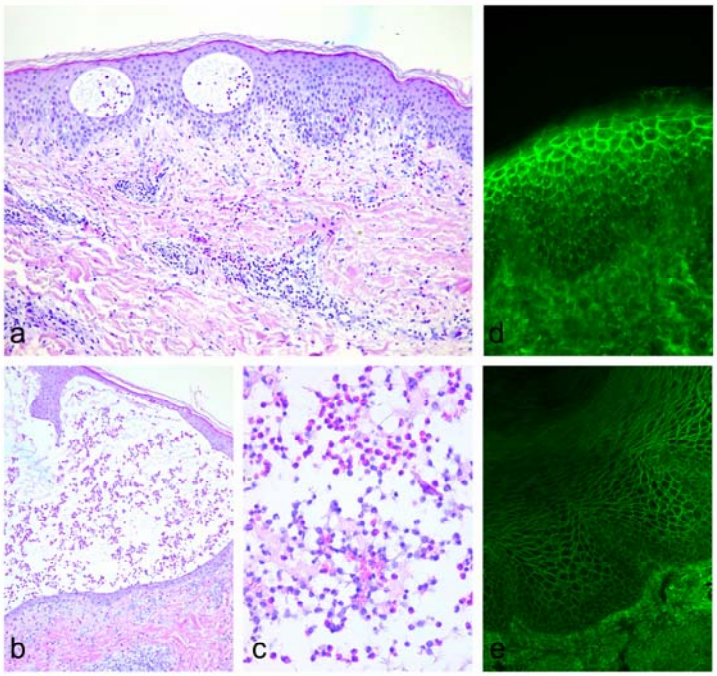

Fig. 3 − Pemphigus *herpetiformis*: a) Spongiosis and intraepidermal vesicles with eosinophils (HE, ×40); b) Spongiotic vesicle containing numerous eosinophils and neutrophils (HE, ×200); c) Numerous eosinophils within vesicle (HE, ×400); d) Direct immunofluorescence of perilesional skin showing intercellular deposits of IgG, more prominent in the upper layers of the epidermis; e) Indirect immunofluorescence on monkey esophagus demonstrating intercellular distribution of anti-IgG antibodies in the patient's sera (1 : 320).

Discussion

Pemphigus *herpetiformis* is a uncommon and sporadic variant of pemphigus with the incidence estimated at 6% [5, 8–10] up to 7.3% [5, 10] of all cases of pemphigus. So far, around 100 patients have been reported [10]. There is no ethnic or gender predilection [5, 10]. Although PH was reported in patients from 5 to 92 years of age, most of the patients were adults [10]. So far, only 4 pediatric patients have been reported [8, 9, 11, 12]. PH is considered to be a distinct entity due to its specific clinical characteristics and distinctive benign course, different from the classical forms of pemphigus. It is characterized by clinical features that resemble dermatitis *herpetiformis* (DH), but immunological findings are consistent with pemphigus [3, 5–7, 9–11]. Although Jablonska et al. [7] established the name of this entity in 1975, similar clinical presentations were described by Floden and Gentele [13] in early 1955, named dermatitis *herpetiformis* with achantolysis. Skin lesions of PH are usually atypical comparing to PV and PF. Erythematous, edematous, vesicular, bullous or papular lesions may be presented [5, 7, 10]. Resulting from centrifugal spread of inflammatory process, the lesions tend to form annular shape [7, 10]. Usually, the groups of small or abortive vesicles, sometimes even pustules, often in herpetiform pattern, are shown on erythematous

base and/or plaques [4–6, 10]. Occasionally, the dominant lesions might be just urticarial erythematous papules and plaques [4, 14]. The lesions frequently affect the trunk and proximal extremities, but they can be shown on other sites as well [7, 10]. Mucous membranes are speared in the majority of the cases [5–7, 10]. Pruritus often accompanies skin lesions, sometimes it might be severe [5, 7, 10], even the initial clinical symptom [14]. Eosinophilia can be found in peripheral blood samples [5], reported in 37.5% cases by Laws et al. [14]. PH may occasionally evolve into PV and PF [4, 7, 15–17], in one case even *fogo selvagem*. Also, the opposite has been reported, PH initially misdiagnosed as other classic variants of pemphigus [4, 5, 7]. Due to the diversity of the clinical presentation, differential diagnosis includes DH, PF, IgA pemphigus, bullous pemphigoid and IgA linear dermatosis [5, 7, 10]. Biopsy findings may also be variable and nonspecific [3, 5, 10]. The eosinophilic spongiosis is the most typical [3–5], but neutrophilic spongiosis or even mixed neutrophilic-eosinophilic spongiosis may be presented, also found in early, urticarial lesions [3, 5]. The assumption is that autoantibody-amplified signaling pathways lead to the secretion of cytokines, chemokines (especially IL8 as potent granulocyte chemoattractant), which cause stimulation and recruitment of eosinophils and neutrophils, resulting in intercellular edema and spongiosis [18], or developed antibodies, despite their minimum acantholytic activity, could activate eosinophils and neutrophils through the Fc portion of IgG [15]. Another characteristic of PH is the presence of intraepidermal bullae [3, 5, 10] or pustules [4–5, 10] variable in composition, in most cases in the subcorneal epidermis, occasionally suprabasally or in the spinous layer [3, 5, 10]. Dermal papillary neutrophilic microabscesses may also be seen [3]. Acatholysis is often absent [3–5, 10]. If present it appears later in the disease process [7, 19]. In practical terms, multiple biopsies are required because of the variable histopathology among patients, even in one patient [3, 5, 7], and the correlation with immunopathology is crucial for final diagnosis. Furthermore, performing direct immunofluorescence (as the gold standard in the diagnosis) when histology reveals neutrophilic and/or eosinophilic spongiosis is recommended. On DIF, intercellular IgG and C3 deposits are most often seen in the superficial layers of the epidermis, less frequently in the lower layers, mainly when circulating anti-Dsg3 antibodies are present [7, 19]. IIF with the monkey/guinea pig esophagus, rat bladder or healthy human skin as substrate can reveal intercellular binding of IgG antibodies [20]. So far, there has not been a clear explanation why autoantibodies produce unusual lesions in PH, different from classic types of pemphigus. The assumption is that the pathogenic blister-inducing activity of the IgG autoantibodies might be weaker [4]. Moreover, the suggested hypothesis is that there is different antibody profiles and broader epitope distribution in patients with PH compared with classic pemphigus [21]. Although ELISA or immunoblotting can show circulating antibodies against epidermal components, usually Dsg1 [4, 5], less commonly Dsg-3 [4, 5], Dsg1 and 3, the same target antigens of the classic pemphigus [5], in PH antibody binding is probably different or target functionally different epitopes of Dsg-1 or 3, therefore do not lead directly to achantolysis, and causing clinicopathological diversity [5, 21]. Furthermore, an epitope spreading phenomenon can be crucial in the pathogenesis, since inflammatory event releases and exposes new antigens inducing autoimmunity to other antigens [22]. Some patients with PH have shown immunoreactivity to 150- and 230-kd antigens [23], 178-kd antigen [24], Dsc3 [25, 26], Dsc1 [20, 27], BP 180 C-terminus and laminin 332 γ2 subunit [20]. PH has been described coexisting with malignances and other diseases. Cases related to malignances are sporadic; to date, five patients with PH and coexisting of lung cancer have been reported [23, 24, 28–30], one esophageal cancer [31], prostate cancer [32] and cutaneous angiosarcoma [33]. In regards to other comorbidities, PH has also been reported in association with another autoimmune diseases, like autoimmune hemolytic anaemia [34], psoriasis [35, 36] and systemic lupus erythematodes [37]. In addition, some cases have been reported with HIV infection [38], drug intake (penicillamine, thiopronine) [39–41] and ultraviolet light exposure [36]. PH generally has an indolent course, good prognosis, [5, 10] and responds well to treatment [5]. It is less life threatening than other types of pemphigus [10]. In this sence, even low doses of systemic corticosteroids can be enough to achieve complete remission [5]. The drug of first choice is dapson (100−300 mg daily), as monotherapy or in combination with systemic steroids [5, 10]. Other therapeutic options are methylprednisolon as puls therapy (1 mg/day for 3 days) together with azathioprine 150 mg/day [5], or azathioprine as monotherapy [19], cyclophosphamide [42, 43], sulfapyridine [7, 44], mycophenol mofetil [45], mycophenolate sodium [46], methotrexate [8], high dose intravenous immunoglobulin [26] and plasmapheresis [26, 42] for more severe cases or cases evolving to classical forms of pemphigus. Recently, the treatment with minocycline and nicotinamide has been published [47].

Conclusion

PH is an uncommon variant of pemphigus with unusual clinical and immunopathological findings, and still unclear underlining pathogenesis. The rarity of this disease and its specificity makes the diagnosis a challenge, so the delay in distinction of this form of pemphigus is often. Therefore, establishing the early diagnosis is important because of the specific course that necessitates a different approach in treatment than for the conventional forms of pemphigus.

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