INTRAVENOUS IMMUNOGLOBULINS IN THE MANAGEMENT OF PEMPHIGUS VULGARIS – CASE PRESENTATION

DANIELA JUGĂNARU*, ANDA NĂSTASE*, DUMITRIȚA-LENUȚA NICHITEAN*, ADINA-CRISTINA AGHEORGHIESEI*, LAURA GHEUCĂ SOLOVĂSTRU*, **

Summary

Pemphigus vulgaris (PV) is a potentially fatal, autoimmune disease, with intraepithelial localization, characterized clinically by flaccid blisters and erosions of the skin and mucous membranes, and histologically by acantholysis. The main goal in the treatment of PV is to control the disease, prevent relapses and avoid side effects associated with prolonged use of systemic corticosteroids (SC) and immunosuppressive agents [1]. To date, SC remain the gold standard and the first therapeutic option in PV, and their association with immunosuppressive agents allows to obtain a better therapeutic effect, also reducing dependence on SC [2]. We report and discuss the case of a female patient aged 42 years with the diagnosis of Pemphigus vulgaris since 2018, confirmed pathologically, under specialized therapy with Medrol 8 mg/day, medication associated with corticotherapy and Imuran (Azathioprine) 150 mg/day, who comes for clinical and biological re-evaluation and specialized therapeutic conduct in the context of persistent bullous eruption.

Keywords: *pemphigus vulgaris, acantholysis, corticotherapy, azathioprine, immunosuppressant.*

Received: 12.11.2020 *Accepted: 9.12.2020*

Introduction

The term pemphigus comes from the Greek "pemphix", meaning blisters or bullae, and describes a group of chronic autoimmune diseases that affect the skin surface and mucous membrane. PV is the most serious and common form, which occurs in subjects aged 40-60 years, involving both sexes. It is characterized histologically by the formation of intraepidermal vesicles, due to the loss of cell adhesion between keratinocytes, and immunopathologically by the formation in vivo of circulating igG auto-antibodies directed to the cell surface of keratinocytes. These IgG autoantibodies (predominantly IgG1 and IgG4) are responsible for the production of acantholysis, being directed to desmoglein 3, desmoglein 1 and plakoglobin, which are the target antigens. Several factors play a role in triggering the disease, such as: UV exposure, burns, ionizing radiation, infections, genetic predisposition, some drugs (captopril, penicillamine, penicillin, rifampicin, etc.) [2, 3].

Lesions usually begin in the oral mucosa by painful post-bullous erosions with a weak tendency to heal, preceding the skin lesions by several months. They may involve any part of the oral mucosa, with possible extension to the pharynx; other mucous membranes (esophageal, laryngeal, ocular, nasal, genitourinary, anal) may also be affected. The skin lesions are expressed by monomorphic bullous rash, consisting of small, flaccid blisters that appear on normal skin, with a tendency to peripheral extension, with a positive Nicolsky's sign, which subsequently rupture, leaving painful erosions, covered with crusts, and

* Dermatological Clinic of the County Emergency Clinical Hospital "St. Spiridon "Iași.
** Discipline of Dermatology, "Grigore T. Popa" University of Medicine and Pharmacy, Iași.

healing is associated with post-inflammatory hyperpigmentation [4].

The clinical aspects presented, biopsy of the skin and mucous membranes (Tzanck cytodiagnosis, histopathological examination), direct immunofluorescence and identification of circulating autoantibodies support the positive diagnosis [5].

Case presentation

We report the case of a 42-year-old female patient with personal pathologic antecedents of cardiovascular nature (Secondary hypertension, Chronic venous insufficiency Class C3 CEAP), endocrinological nature (Iatrogenic Cushing Syndrome) known to the Iași Dermatology Clinic with the diagnosis of Pemphigus vulgaris ever since 2018, confirmed anatomically and pathologically, found under specialized treatment with Medrol 8 mg/day, medication associated with corticotherapy and Imuran 150 mg/day, who comes for clinical and biological re-evaluation and specialized therapeutic conduct in the context of the presence and persistence of the bullous rash. The onset of the disease was in January 2018, the patient being hospitalized in the County Hospital of Botosani, where she received high-dose corticosteroid therapy (initially Prednisone 100 mg/day for 3 weeks, then Medrol 64 mg/day, gradually decreasing the dose) with partial favourable evolution of the disease, which is why she was redirected to our Clinic for the determining of the further therapeutic conduct.

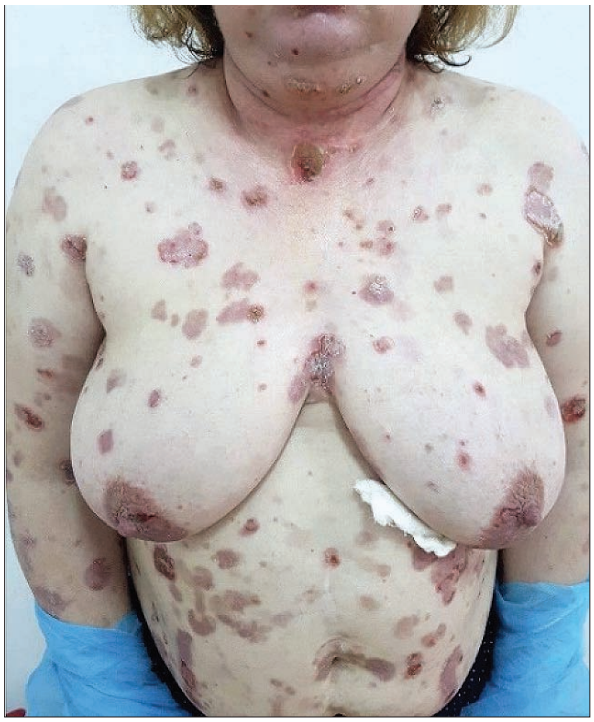
The current clinical examination reveals the presence of well-defined post-bullous erosions, with regular contour, round-oval shape, erythematous nature, covered with adherent, painful sero-hematous crusts, sometimes presenting small, flaccid blisters, with serous citrine content, with positive Nicolsky's sign, located on facies, trunk and limbs (Fig.1, Fig.2); well-defined, round-oval erosions, covered by whitish, painful deposits, located at the level of the jugal mucosa; Cushingoid appearance (centripetal obesity/red-purple stretch marks/plethoric facies, "in the full moon"/skin fragility, telangiectasias). Paraclinical investigations reveal: inflammatory syndrome, normocytic normochromic anaemia; blood glucose, kidney and liver function within normal limits; pathological urine test, urine culture being negative. At the bacteriological examination of the secretions at the level of erosions, overinfection with different pathogens is identified during hospitalization: initially with *Staphylococcus aureus, Enterococcus faecalis*, later with *Pseudomonas Aeruginosa* and *Klebsiella pneumoniae*.

Paraclinical investigations and histopathological examinations support the positive diagnosis.

Given the fact that the patient has a Cushingoid appearance and has been following systemic corticosteroid treatment for 2 years (since 2018), an Endocrinological examination and the profile of the following hormones have been performed: ACTH, TSH, FT4, FT3, cortisol, all with normal values. During hospitalization, the patient presented multiple bursts of new bullous lesions located on the trunk and limbs. She also developed post-bullous erosions on both outer ears and on the right eyelid, which is why she was referred to Otorhinolaryngology and Ophthalmology, which recommended ear instillations with antibiotics and dexamethasone, and at the eye level - lubricated drops, Tobradex ointment at the conjunctival level, and application of low potency dermatocorticoid cream on the eyelid.

During hospitalization, the patient followed the systemic treatment with antihistamines, venotonic drugs, venotropic drugs, vitamin therapy, medication for associated pathologies (antihypertensives). Antibiotic treatment was initiated according to the antibiogram, initially with Ciprofloxacin per os 500 mgx2/day for 10 days, then with Ampicillin per os 1 gx3/day for 10 days.

Regarding the pathogenic treatment, it was decided to replace Imuran with Endoxan (Cyclophosphamide) initially 100 mg/day, later 150 mg/day, but given the renal manifestations (macroscopic haematuria, pathological urine test) and the febrile syndrome, it was decided to stop the latter and increase the dose of Medrol to 32 mg/day in combination with pulse therapy with 5% intravenous immunoglobulin - 4 courses every 7 days. There were 2 courses of Methylprednisolone 250 mg i.v. 10 days each, 2 courses with Hydrocortisone Hemisuccinate 200 mg i.v. of 7 days each. Topically, the following were applied: dryers, re-epithelialization drugs with antibiotics according to the antibiogram at the level of post-bullous erosions, creams with



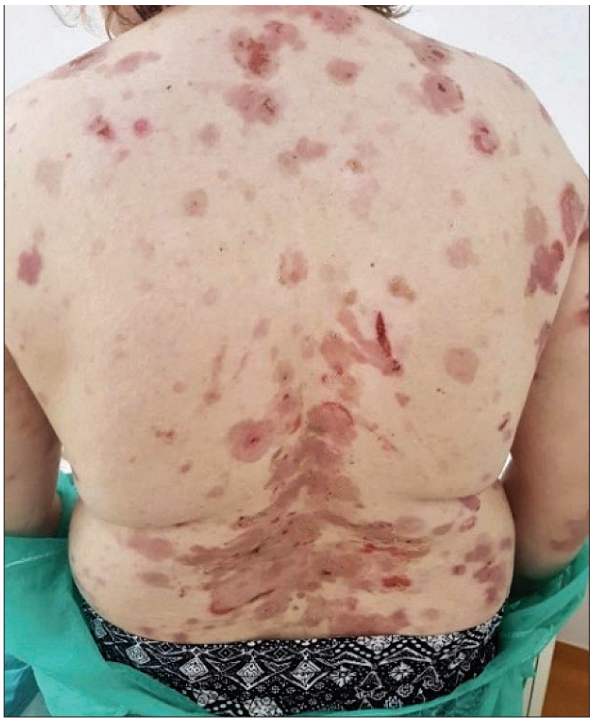
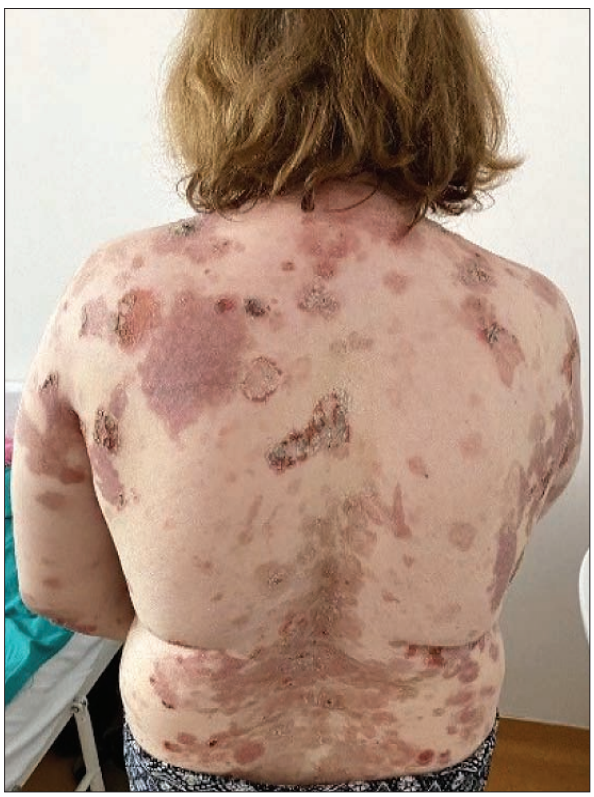


Figure 1 and Figure 2. Clinical appearance of hospitalization lesions (Jan. 2020)



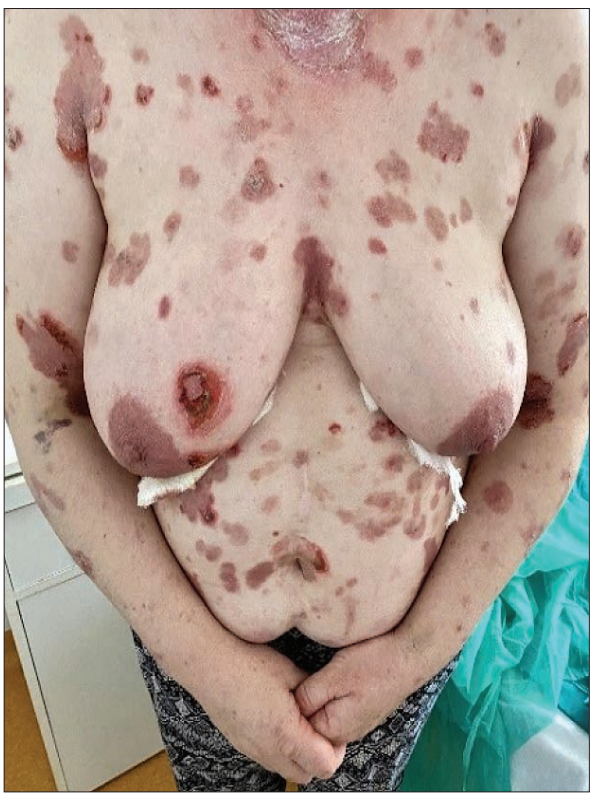
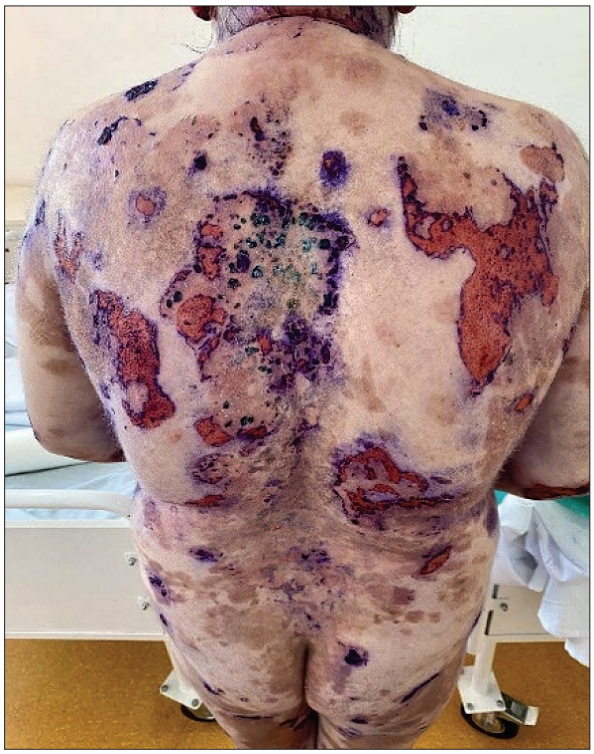


Figure 3 and Figure 4. Clinical appearance of lesions during hospitalization (February 2020)



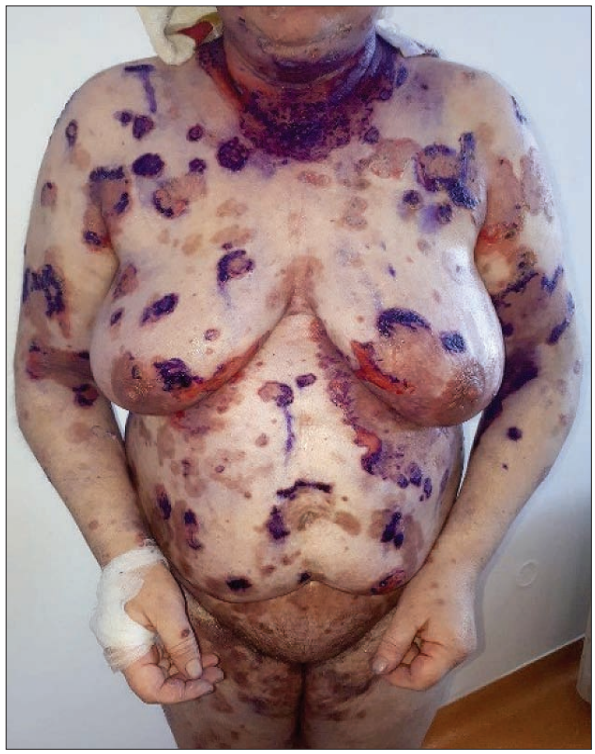
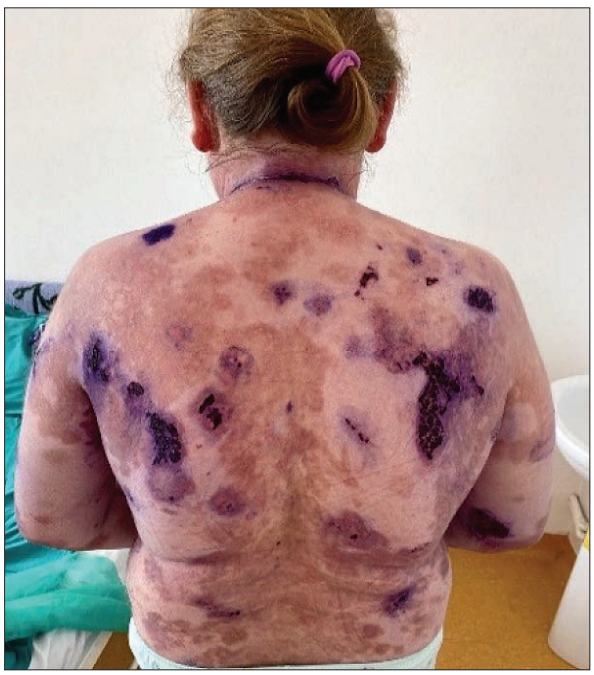


Figure 5 and Figure 6. Clinical appearance of lesions during hospitalization (March 2020)



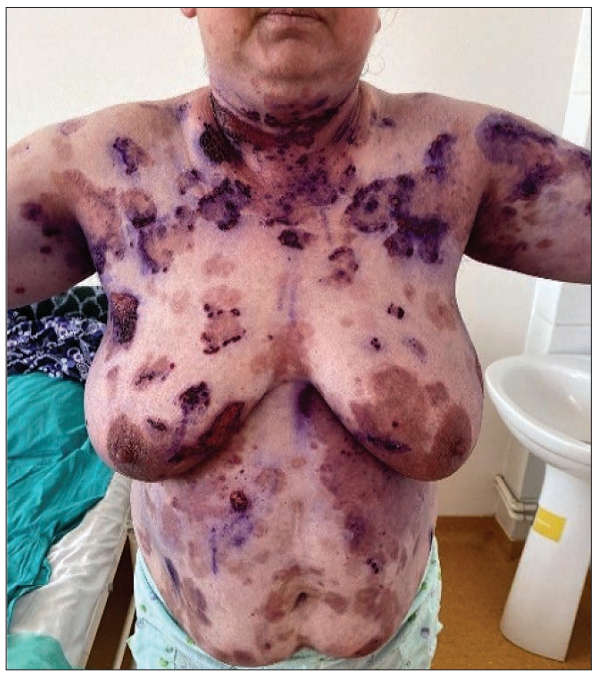


Figure 7 și Figure 8. Clinical appearance of discharge lesions (April 2020)

dermatocorticoids at the level of erythematous lesions, creams with antifungal agent at the level of the folds; given the damage to a large surface of the skin, dressings were tried with Atrauman, Hydroclean Advance to accelerate epithelialization.

The established systemic and topical treatments were associated with the undulating evolution of the disease, with periods of significant alteration of the general condition of the patient, but, after all therapeutic gestures, a slow favourable evolution of the disease was noticed.

Discussions and conclusions

Pemphigus vulgaris is a chronic recurrent dermatosis with no tendency to spontaneous healing. The course and prognosis of the disease remain uncertain, but may vary from patient to patient. Untreated, the disease evolves into successive outbreaks of increasing severity, leading to exitus in 6 months to 2 years, due to infectious, haematological complications, hydroelectrolytic and protein, cachectic, metabolic, neoplastic imbalances, etc. [6]. The use of corticosteroid therapy and immunosuppressants in the management of PV has considerably changed the evolution of the disease: the prognosis depends primarily on the patient's response to corticosteroid therapy and the complications associated with its long-term administration [7].

Systemic corticosteroids (SC) such as Prednisone/prednisolone remain the first-line therapy of choice in the management of pemphigus vulgaris. Prior to the availability of adjuvant immunosuppressive therapy, very high initial doses of Prednisone (> 2.0 mg / kg) were associated with significant morbidity.

Currently, the recommended dose by specialist guides is 1.5 mg/kg daily for 2-3 weeks. In unresponsive patients, a daily fragmentation of the medication into 2-3 doses may be helpful. Once the disease activity is controlled, the minimum effective dose of Prednisone (5-10 mg/day) is used. However, many patients respond favourably to a single dose of 0.5-1 mg/kg body-weight/day, especially if combined with adjuvant immunosuppressive therapy [3, 8].

SC administered in pulse therapy (Methylprednisolone 15-20 mg/kg body-weight/day, for 3 days) can be used for a faster and more effective control of the disease [2]. Specialist studies have shown that this treatment option does not appear to have a benefit over conventional first-line treatment with oral administration of Prednisone/prednisolone per os in combination with immunosuppressive adjuvants. Pulse therapy with SC should be reserved for patients with severe and refractory forms of the disease [9, 10]. Immunosuppressive/ immunomodulatory therapy is an adjuvant corticosteroid therapy used to gradually lower corticosteroid doses and minimize their adverse effects. The following are used as adjuvants in corticosteroid therapy:

- Immunosuppressants: Azathioprine (100-150 mg/day), Mycophenolate mofetil (2-3 g/day), Cyclophosphamide (100-200 mg/day), Methotrexate (25-50 mg/week), Cyclosporine (6 mg/day) kg body-weight/day), Chlorambucil (4 mg/day). In the active and extensive forms of the disease, SC is associated with immuno-suppressants (Azathioprine - the first option). After remission, the dose of Prednisone is gradually decreased. Prednisone 40 mg every 2 days, in combination with Azathioprine (100-150 mg/ day), is recommended as a maintenance treatment;
- Plasmapheresis - 3 sessions/week;
- Extracorporeal photochemotherapy - recom/mended for corticosteroid-resistant forms;
- Immunoadsorption - allows the elimination of pathogenic autoantibodies by adsorption on a ligand, method based on the principle of affinity chromatography [2, 8];
- Biological agents - Rituximab (MABTHERA), anti-CD20+ monoclonal antibody, acts on B lymphocytes, precursors of antibody-producing plasma cells, thus causing a decrease in antidesmoglein 3 antibodies; it is administered intravenously (375mg/m^2) once/week, for 4 weeks, with the repetition of the cure after 6 months or 1g x 2/week, for 2 weeks [2, 8, 11,12];
- Intravenous immunoglobulins (IVIG) are administered at a dose of 2 g/kg body-weight/per course every 2-5 days, a total of 4 courses, per month. They inhibit the synthesis of immunoglobulins and block the production of autoantibodies. Treatment should be carried out over several days to avoid side effects such as

headache and nausea. IVIG therapy may induce aseptic meningitis in patients with frequent migraines and is contraindicated in those with complete IgA deficiency. IVIG have demonstrated their effec-tiveness especially in combination with cortico-steroids and immunosuppressants, in the case of refractory forms of the disease [13, 14, 15].

Topical therapy has no major therapeutic and evolutionary significance, being applied only as additional medication (dryers, disinfectants, epithelializers, topical/intralesional corticos-teroids, antibacterial agents, topical analgesics) [11].

Bibliography

1. Ioannides D, Lazaridou E, Rigopoulos D. Pemphigus. Management of pemphigus vulgaris: challenges and solutions. *J Eur Acad Dermatol Venereol*. 2008, 22:1478–1496.
2. Petrescu Z. Dermatologie și infecții sexual-transmisibile. Junimea, 2008, p.241-250.
3. Pătrașcu V. Boli dermatologice si boli sexual-transmisibile. Diagnostic, tratament, editia a-2-a. Editura Sitech, Craiova, 2006, p.214-219.
4. Amagai M. Pemphigus. In: Dermatology, Fourth Edition, Bolognia JL, Schaffer JV, Cerroni L (Eds) et al, Elsevier Limited, 2018. p. 494-509.
5. Vito Di Lernia, Casanova D.M., Goldust M., Ricci C. Pemphigus Vulgaris and Bullous Pemphigoid: Update on Diagnosis and Treatment. *Dermatol Pract Concept*. 2020 Jul; 10(3): e2020050.
6. Protocole National de diagnostic et de soins les maladies rares. Maladies bulleuses auto-immunes-Pemphigus. Janvier, 2011.
7. M. Saha, B. Bhogal, M.M. Black, D. Cooper, R.W. Vaughan, R.W. Groves,"Prognostic factors in pemphigus vulgaris and pemphigus foliaceus"; *British Journal of Dermatology*; Volume 170, Issue1, pages116–122, January 2014.
8. Payne AS, Stanley JR.Pemphigus. In:Fitzpatrick's Dermatology Ninth Edition, Kang S, Amagai M, Bruckner AL et al (Eds), New York, McGraw-Hill, 2019, p. 909-933.
9. Mentink LF, Mackenzie MW, Toth GG et al. Randomized controlled trial of adjuvant oral dexamethasone pulse therapy in pemphigus vulgaris: PEMPULS trial. *Arch Dermatol* 2006; 142: 570–576.
10. Toth GG, Westerlaken BO, Eilders M, Laseur M, Jonkman MF, Uges DR. Dexamethasone pharmacokinetics after high-dose oral therapy for pemphigus. *Ann Pharmacother* 2002; 36: 1108–1109.
11. Pemphigus. S2 Guideline for diagnosis and treatment – guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). *JEADV* 2015, 29, 405–414.
12. Joly P, Bernard P, Bedane C, Prost C, Ingen-Housz-Oro S. Pemphigus. Guidelines for the diagnosis and treatment. Centres de reference des maladies bulleuses auto-immunes. Societe Française de Dermatologie. *Ann Dermatol Venereol* 2011; 138: 252–258.
13. Czernik A, Toosi S, Bystryn JC, Grando SA. Intravenous immunoglobulin in the treatment of autoimmune bullous dermatoses: an update. *Autoimmunity* 2012; 45:111–118.
14. Amagai M, Ikeda S, Shimizu H, et al, Pemphigus Study Group. A randomized double-blind trial of intravenous immunoglobulin for pemphigus. *J Am Acad Dermatol*. 2009;60:595–603.
15. Arnold DF, Burton J, Shine B, et al. An "n-of-1" placebo-controlled crossover trial of intravenous immunoglobulin as adjuvant therapy in refractory pemphigus vulgaris. *Br J Dermatol*. 2009;160:1098–1102.

Conflict of interest
NONE DECLARED

Correspondance address: Daniela Jugănaru
Dermatological Clinic of the County Emergency Clinical Hospital "St. Spiridon "Iași.
daniela_juganaru@yahoo.com