Dermatology | Case Report

Cushings syndrome complicating pemphigoid gestationis

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Cushings syndrome complicating pemphigoid gestationis

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Abstract: Purpose: The aims are to assess the clinical and demographic features of bullous pemphigoid in a pregnant women (Pemphigoid Gestationis) that has been complicated by Cushing syndrome after treatment, and compare it to the available literature. Materials and Methods: Case study and literature review in the Hospital of Skin and Venereal diseases named after V.A. Rakhmanov; We assessed a case of pemphigoid in a pregnant woman which was complicated by the appearance of Cushing syndrome due to the administration of steroids. A follow-up was performed. Results: Generally, steroid complications arise as a result of increasing steroid dose, but on the other hand treating a condition like bullous pemphigoid without using steroids can cause relapse or have poor prognosis. Conclusions: Bullous pemphigoid in pregnancy requires careful attention. In addition, considering the complications due to steroid treatment is vital to aid in the prognosis.

Subjects: General Medicine; Immunology; Obstetrics; Physiology; Pharmaceutical Medicine; Dermatology

Keywords: immunobullous skin diseases; pemphigoid; vesiculobullous disease of pregnancy; cushing syndrome and bullous

1. Introduction
Bullous pemphigoid (BP) is an autoimmune blistering disease characterized by autoantibody deposition in the epithelial basement membrane zone. The main presentation of BP is in the elderly with generalized pruritic urticarial plaques and tense subepithelial blisters. The main treatment for this

ABOUT THE AUTHORS
For more than a decade, this team’s clinical research has been focused on diagnosing rare dermatological case presentations and the approach to them, by means of investigating the skin and the body as a whole to come up with the correct diagnosis and best management plan. The majority of our current research however focuses on immunobullous diseases and their management approach and complications by integrating a full team of dermatologist in addition to a multidisciplinary team that helps from various other specialties. The present study reporting on the approach for steroid complication in a pregnant woman with bullous pemphigoid is a part of larger and more comprehensive research, which investigated the steroid resistance and complications in autoimmune diseases.

PUBLIC INTEREST STATEMENT
Bullous pemphigoid is an autoimmune disease which primarily presents in the elderly with generalized rashes and blisters. The main treatment is corticosteroids. Pemphigoid gestationis is when these blisters occur during pregnancy, usually in the second or third trimester. Symptoms usually resolve or lessen towards the end of pregnancy or after delivery. This article describes the importance of continuous monitoring and evaluation of patients presenting with bullous pemphigoid especially in pregnancy and how to manage the steroid complications if present. It is necessary to explain to the patient the importance of treatment with steroids and its side effects, and the need to use minimum effective dose by clinician's in order to reduce the risk to the both the mother and fetus. Good insight about the disease can improve the effectiveness of medical therapy.

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disease is topical or systemic application of corticosteroids in combination with an immunosuppres-
sant, usually azathioprine. In some cases, due to the treatment with steroids, patients can develop
one of its main side effects which is Cushing syndrome. Cushing syndrome, was first described by
Harvey in 1912. It is a group of signs and symptoms that appear as a result of excess of free plasma
glucocorticoids, which is either from an increase in endogenous production or exogenous use of
glucocorticoids. Drugs that have been shown to cause hypercortisolism are glucocorticoids,
megestrol acetate, and herbal preparations that contain glucocorticoids (Murrell & Ramirez-Quizon,
2014; Nguyen & Khardori, 2017).

Pemphigoid gestationis (PG) is thought to arise when BP occurs during pregnancy, usually in the
second or third trimester. Symptoms usually resolve or lesson towards the end of pregnancy or after
delivery, although 70–80% of women have flare ups in at time of delivery for unknown reasons. In
some cases, the symptoms will remain active for months after delivery. Complications are uncom-
mon but they include a slight increase risk of premature delivery and transient blistering on the in-
fants skin (Kelly et al., 1990).

2. Case study
On 7 March 2017, A.A, a 23 year old resident of Odessa region, Ukraine, presented to V.A. Rahmanov
Clinic of Skin and Venereal Diseases at I.M. Sechenov First MSMU. The patient complained of periodi-
cal rash on the skin of hands and forearms, accompanied by pain, weight gain, delay of menstrua-
tion, hypertrichosis, and pain in the chest and lumbar sections of the vertebral column (due to
fractures, resulting from steroid osteoporosis). These symptoms developed in the process of taking
systemic glucocorticoids for the treatment of bullous pemphigoid. The patients’ skin problems ini-
tially started from August 2016, when she was 27 weeks pregnant and she developed a rash in the
form of multiforme exudative erythema on the abdominal skin (see Figure 1). At that time the pa-
tient was only given multivitamins. Within two days, strained vesicles with transparent content on
an erythematous background started to appear on the skin of hands and thighs. She was admitted
to Odessa Regional Clinical Hospital and given the diagnosis of an acute exacerbation of Pemphigoid
gestationis. Within a month she received dexamethasone 8 mg with positive effect until she had a
C-section on September 29. Immediately after childbirth, her skin began to show deterioration, mul-
tiple strained vesicles on the skin of the body, upper and lower extremities began to appear again
(see Figure 2). While staying in the maternity ward she received therapy with methylprednisolone
(see Figure 3) intravenously daily for two weeks, after which the rash regressed. In October she was
further diagnosed with residual effects of the polymorphic erythema and received dexamethasone

Figure 1. Multiform exudative erythematous rash on the skin of the abdomen at 27 weeks of pregnancy.
8 mg i/v and Prednisolone 80 mg a day. After 1 month dexamethasone 8 mg was stopped, Prednisolone 80 mg me daily was continued till the middle of January for approximately 45 days. At this time the patient started to develop steroid-dependent complications (see Table 1). In the middle of January 2017 within a 2 week period, the Prednisolone dosage was reduced from 80 to 40 mg a day, causing the aggravation of the disease again in the form of minor tense vesicles over the whole skin. The Prednisolone dosage was then increased to 50 mg.
In the beginning of March 2017, the time when she presented to our practice, the differential diagnosis we had in mind was bullous pemphigoid, Duhring dermatitis, and erythema multiform. Based on the clinical presentation, as well as on results of the histologic examination and of the indirect immunofluorescence test (IIFT) the patient was given the diagnosis of erythema multiforme. She was administered Dapson 100 mg a day and Prednisolone was reduced by 5 mg a week. The patient was hospitalized for further examination and management.

At admission there were features of the iatrogenic Cushing syndrome: turgor and elasticity of the skin drastically reduced; dysplastic adiposis was present on the face, neck, abdomen, chest and back with symptoms of muscle atrophy of the hands and feet. The face was moon shaped, skin purplish-red in color, with pronounced hypertrichosis mainly on the chin area, which also had many small follicular pustules and yellowish crusts. On the skin of the trunk, especially the abdomen, hyperemia

| Table 1. Complications of steroid therapy |
|----------------------------------------|
| **The complications from steroid therapy** |
| Violation of water-salt balance in the body | • Hypokalemia is manifested in violation conductivity of the heart muscle  
• Hypocalcemia (paresthesias, cramps of striated muscles, osteoporosis, and osteomalacia)  
• Delay solen sodium contributes to the development of steroid hypertension and edema  |
| Hypoproteinemia | As a result of the catabolism of protein there is occurrence of protein-free edema from decreased oncotic pressure of plasma  |
| Gastritis, esophagitis, gastric ulcer and 12 duodenal ulcer. Mental disorders (insomnia, euphoria, excitation, occasionally steroid psychosis)  |
| Muscle atrophy, vascular fragility (purpura), hypercoagulability and less - hypo coagulation) syndrome, atrophic streaks on skin, steroid acne, etc  |

Figure 4. patient before and after being diagnosed with Cushings.
showed abundant striae (see Figure 4). On the skin of the head, trunk, and the right hand, the rash showed single tense blisters with tight covering and serous component, with a diameter from 0.5 to 2 cm, located on the background of erythema. There are restricted erosions at the place of opened vesicles, with no tendency for peripheral growth, the surface is bright pink, with fragments of epidermis peripherally. The Nikolsky sign was negative. The nails and mucous membranes were not affected. The hair did not present any changes. Lymph-nodes were not enlarged. Subjectively, she said that minimal movement caused unbearable pain in the back (steroid osteoporosis and multiple fractures of the spine); and that she had general weakness, weakness while moving (steroid myopathy).
In our clinic, a biopsy was taken from intact skin of the shoulder and examined by direct immuno-fluorescence in order to clarify the diagnosis. IIFT revealed TH + C3 fixation of the complement component and hence immunohistochemical changes corresponding to the diagnosis of bullous pemphigoid (see Figures 5 and 6).

At the time of hospitalization the patient was receiving 30 mg of Prednisolone daily (see Figure 7). Due to the absence of new rashes, long term absence of positive dynamics with administration of high dosages of Prednisolone, growing complications stimulated by the administered steroid therapy, and the confirmation of diagnosis by the direct IIFT, the patient started to receive lower doses of Prednisolone 5 mg a week, Dapson 100 mg/day was replaced by azathioprine 100 mg/day. On the third day after Dapson withdrawal we noticed the appearance of several strained minor vesicles on the body skin and on the hairy part of the head. Dapson 50 mg was again administered and azathioprine withdrawn.

In addition to corrective therapy, the patient was given Miacalcic (calcitonin) 200 mg twice a day, (influencing the bone reabsorption process and stimulating the bone formation) and Retabolil (Nandrolone, anabolic steroid) 100 mg IM, 1 vial a week.

It is assumed that anabolic steroids reduce the bone reabsorption and induce positive calcium balance due to the increased calcium absorption from the intestine and calcium reabsorption by kidneys. Besides that, according to some data it stimulates the osteoblasts activity and increases muscular weight.

Quick improvement with the resolution of vesicles, absence of development of new rashes, and regression of vesicular elements and active epithelialization of erosions was observed. Weight loss of approximately 4 kg from 81 to 78 kg was witnessed, and she was able to move without help in 2 weeks. In order to treat complications, as well as to exclude the primary hypoadrenocorticism, the patient was then transferred to the endocrinology department were we recommended to reduce Prednisolone administration dosage (see Table 2). The patient was followed up and in September 2017, her weight reached 62 kg, and she didn’t have any complains (see Figure 8). The patient signed two informed consents, one for treatment and management and the other for publication of this case report.
3. Discussion

Bullous pemphigoid is an autoimmune subepidermal blistering disease. When it occurs in pregnancy it is called Pemphigoid gestationis (PG) and it usually presents during the second or third trimester. It presents with a rash that quickly develops into blisters. In PG, patients immune system develops antibodies against hemidesmosomal protein BP180 (BPAG2, collagen XVII) or more rarely against BP230. These antibodies are part of the immunoglobulin G1 class, which binds to the basement membrane at the dermoepidermal junction and results in triggering of the immune system by the aid of neutrophils and eosinophils. As a result of this activation of the immune system, there is formation of vesicles and blisters (Kelly et al., 1990).

In 1999, it was demonstrated that PG may have five distinct epitopes within BP180 NC16A, four of which have been reported as major antigenic sites targeted by bullous pemphigoid antibodies. There are many theories for the reason for developing autoantibodies, however the cause remains unknown. Cross-reactivity between placental tissue and skin is a proposed theory. Pemphigoid gestationis has a strong association with HLA-DR3 (61%) and HLA-DR4 (52%), or both (43%), and nearly all patients have shown to demonstrate anti-HLA antibodies. The placenta is known to be the main source of disparate antigens and can thus present an immunologic target during gestation.

BP180 is expressed on both amniotic epithelial cells of the placenta and keratinocytes at the dermoepidermal junction. It may be presented to maternal histocompatibility complex (MHC-II) in the presence of paternal MHC-II and recognized as a foreign antigen (due to expression of fetal major MHC-II on trophoblasts and amnichorionic stromal cells that permits maternal detection of paternal MHC-II), leading to the formation of antibodies that are cross-reactive toward BP180 in the
epidermis (Chimanovitch et al., 1999; Fairlky, Heintz, Neuburg, Diaz, & Giudice, 1995; Kelly, Fleming, Bhogal, Wojnarowska, & Black, 1989; Shornick, Stastny, & Gilliam, 1981).

BP is a disease that appears in old age, but this case is a young woman and the reason is thought to be mainly due to the effect of pregnancy on her body. In literature it has been observed that BP can occur rarely in younger age groups, but is usually more severe, aggressive and active with worse prognosis due higher expression of anti BP180 autoantibodies. In addition, it has been seen to be associated with higher pathological association and physical treatments (Bourdon et al., 2005).

### 3.1. Investigations and differential diagnostics of BP

The BP diagnosis is based on clinical and laboratory data. The main investigation for its diagnosis is based on the direct immunofluorescent test, as well as the enzyme linked immunosorbent assay (ELISA) test, which reveals circulating IgG-antibodies to BP180 or to BPAG2. Key diagnostic criteria are given in the Table 3.

Diseases within the group of bullous dermatoses can be differentiated on the basis of clinical hallmarks and laboratory analysis (see Table 4). As pemphigoid can be a manifestation of the paraneoplastic process, before initiating treatment it is necessary to carefully examine the patient in order to exclude conditions like leucosis, malignant tumors, and Hodgkins disease. In one study it has been shown that up to 47% of the patient group developed malignant tumours (Teplyuk, Nyquist, Grabovskaya, et al., 2013).

One of first descriptions of the bullous dermatoses as of the paraneoplastic process was presented in 1909, when lip carcinoma developed 2 months after the bullous rash appeared in a 28 year old Russian woman. However, 3 days after the tumor has been excised rashes resolved naturally (Bogrow, 1909).
| Feature                        | Pemphigoid vera | Bullous pemphigoid | Hydrodynamic pressure | Bullous form of toxicoderma |
|-------------------------------|----------------|--------------------|-----------------------|---------------------------|
| Paraneoplastic syndrome       | +              | +                  | +                     | −                         |
| Subjective sensations         | Tenderness, burning, pruritus | +/-               | Pruritus              | Burning, pruritus          |
| Localization: Blennosis       | + (vulgar, paraneoplastic) | −/+ (rare)         | −                     | −/+                       |
| Initial element               | Vesicle        | Vesicle            | Polymorphism: spots, urtica-like rashes, papules, plaques, vesicles | Polymorphism; at some patients the vesicle is the only dermatosis manifestation |
| Tectum                        | Soft, strained in the beginning of the process | Strained           | Strained              | Strained                  |
| Content                       | Serous, hemorrhagic | Serous, hemorrhagic | Serous                | Serous                    |
| Skin around vesicle           | Unchanged      | Probable erythema  | Erythema              | Erythema                  |
| Nickolsky symptom             | +              | −                  | −                     | −/+                       |
| Asbo-Hansen symptom           | +              | +                  | −                     | −                         |
| Yadasson symptom              | −              | −                  | +                     | −                         |
| Impression smears (acantholytic cells) | + | − | − | −/+ (Layell syndrome) |
| Vesicular liquid (eosinophils) | −/+ (in small amounts) | − | A lot of eosinophils | −/+ (in small amounts) |
| Histological studies          | Inter-epidermal acantholysis | Sub-epidermal vesicle at the basal membrane level | Sub-epidermal vesicle, located in the dermal papillae area | Intra-and subepidermal vesicle at the expense of spongiosis, ballooning and hydropic degeneration |
| Direct IIFT                   | IgG glow in the intercellular substance of the spinous layer | IgG glow at the level of the basal epidermis membrane | Glow in the form of IgA accumulation in the dermal papillae | − |
The treatment of autoimmune vesicular dermatoses remains a challenge due to few therapeutic studies and is mainly based on clinical experience rather than on controlled researches. To successfully treat the bullous pemphigoid, the therapy is aimed at termination of the disease progress and induction of remission.

3.2. Treatment

Treatment options for BP in order of most frequently used are topical and systemic corticosteroids, immuno-suppressive agents such as Mycophenolate Mofetil, Azathioprine, Dapsone, Methotrexate, Tetracycline-class antibiotics, Cyclosporine, and novel therapies such as intravenous Ig (ivIg), biological agents targeting CD20 and TNF-α, and plasmapheresis. The aims of these therapies are to reduce inflammation and autoantibody production (Murrell & Ramirez-Quizon, 2014).

Oral corticosteroids are the main treatment for BP and the efficacy is reflected by the drop in mortality by almost 50% (Fine, 1995; Rosenberg, Sanders, & Nelson, 1976). Clinical improvement is generally seen in the first weeks of treatment with systemic corticosteroids, therefore it has to be slowly tapered from 20 mg/day downward (Murrell & Ramirez-Quizon, 2014). Prednisone is usually used at a dose of 0.25–1 mg/kg/day and this is the most common dosage range in literature, doses above 0.75 mg/kg/day are less effective and are associated with more side effects (Khumalo, Murrell, Wojnarowska, & Kirtschig, 2002; Morel & Guillaume, 1984; Mutasim, 2004). Clinical improvements are seen in 1–4 weeks after the beginning of the therapy, then the Prednisolone dosage can be reduced, initially by 5 mg, then by 2.5–5 mg.

For restricted forms of BP, it is recommended to treat with topical steroids of the 3–4 class according to the European classification. Generalized BP in most patients requires systemic therapy. The gold standard for treatment however remains oral prednisolone (Church, 1960).

Oral immunosuppressive agents are used for severe BP in combination with steroids. These include Azathioprine (2–3 mg/kg/day), Methotrexate (10–25 mg/week), Cyclophosphamide (1–2 mg/kg/day), Mycophenolate Mofetil (1–2 g/day), Dapsone (1–1.5 mg/kg/day), and Tetracyclines (Kasperkiewicz & Schmidt, 2009). The use of immunosuppressive agents in the treatment remains a point of debate. Some doctors prefer to use it only as secondary line management approach, when corticosteroids do not control the disease or if there are contraindications for their use, as well as if the maintenance dosage of corticosteroids is unacceptably high. About half of the patients require combined treatment with immunosuppressive therapy. The Azathioprine dosage should be selected in conformity with the thiopurinmethyltransferase level in order to increase the efficiency and to reduce toxicity.

Plasmapheresis, typically used in combination with either corticosteroid therapy or other immunosuppressive medications, has been shown to be successful in BP, but researchers were unable to confirm the success of this therapy in a double-blind study (Guillaume et al., 1988).

IVIG has been used at varying dosages; usually more than one cycle is required in order to avoid recurrence. It has been associated with fluctuating opinions on the success rate of such approach in the treatment of BP (Edhegard & Hall, 2011).

Treating BP with steroid may lead to a well-known side effect of steroid which is the development of exogenous Cushing’s syndrome (CS). The main presentation is with a rounded facial like structure “moon face”, central weight gain and subcutaneous fat in the upper neck and back “buffalo hump”, skin atrophy, easy bruising, striae, and hyperglycemia and muscle weakness. Patients are generally prone to infections and have a greater susceptibility to develop poor wound healing and atherosclerotic heart disease. CS is similarly associated with severe psychological adverse effects and has a great impact on the quality of life. Well known psychological conditions seen in such patients including anxiety, depression and psychosis (Lenung, 2015).
In the case of BP, we cannot stop giving the steroids at once even if the patient develops side effects such as cushings and that’s because of the high likelihood of relapsing symptoms of the original disease we are treating. In such cases it is necessary to reduce the manifestation of further complications associated with Cushing’s itself. These include:

- Monitoring/Treating high blood sugar.
- Monitoring/Treating high cholesterol.
- Administration of vitamin D and calcium to prevent bone loss and monitor for osteoporosis (Ferri, 2016; Nieman et al., 2015; Stewart & Newell-Price, 2016).

The mainstay treatment approach in exogenous Cushing syndrome is steady removal of the contributing drug, preferably with the goal of ceasing the causative drug. An important consideration is to give stress dose steroids should be given to avoid adrenal crisis (Nguyen & Khardori, 2017).

3.3. Prognosis and follow up
BP is usually considered a disease with a chronic relapsing course. Long term remissions have been documented for months and years after successful therapy (Bernard et al., 2009; Murrell & Ramirez-Quizon, 2014; Parker et al., 2008; Risser, Lewis, & Weinstock, 2009; Roujeau et al., 1998). In modern times, approximately 50% of treated patients reach remission in 2.5–6 years, but others have been noted to have active disease for 10 or more years (Hadi et al., 1988; Person & Rogers, 1977).

The mortality rate over one year period is reported to be from 25 to 40%. There are few risk factors that have been shown to increase the risk of death, these include older age >80, extensive disease, high dose steroid, poor general condition, high erythrocyte sedimentation rate, low albumin, and female gender. In a study done in Kaplan-Meier it has been shown that the overall survival rate for patient with BP was 61% for patients aged >83 years, and 85% for patients aged <83 years (Bernard, Bedane, & Bonnetblanc, 1997; Colbert, Allen, Eastwood, & Fairley, 2004; Joly, Roujeau, Benichou, et al., 2002; Joly et al., 2005; Parker et al., 2008; Rzany et al., 2002).

4. Conclusion
This report underscores the importance of continuous monitoring and evaluation in patients presenting with bullous pemphigoid. Moreover, it highlights the necessity of explaining to the patient the importance of treatment with steroids and its side effects, and the need to use minimum effective dose by clinician’s in order to reduce the risk to both the mother and fetus. Good insight about the pathogenesis and the clinical presentation can improve the effectiveness of medical therapy. Further research is needed in this field regarding the approach to patients with severe pemphigoid who develop Cushing’s and its complications especially in pregnant women. Additionally, the availability and effectiveness of a multidisciplinary approach to these patients should be studied in order to provide definite evidence for implementation in clinical practice.
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