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Pemphigoid Gestationis with Oral Manifestations: Case Report and Review of the Literature

SUMMARY

Pemphigoid gestationis (PG) is an autoimmune pregnancy dermatosis that rarely affects the oral mucosa. PG is mediated by an autoimmune response to BP180, a 180-kDa trans-membrane hemidesmosomal glycoprotein. Diagnosis of PG requires careful consideration of clinical signs and symptoms in combination with histopathologic and immunophenotypic analyses. Systemic corticosteroid administration is currently the treatment of choice and lesions usually resolve completely without scarring. We present the second PG case with florid oral involvement to ever be reported in the literature, and we discuss its diagnosis, clinical course and management.

Keywords: Pemphigoid Gestationis; Oral Mucosa; Pregnancy Dermatosis

Eleni Gagari, George Laskaris

Athens University, School of Medicine, Department of Dermatology, Athens, Greece

CASE REPORT (CR)
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Introduction

Pemphigoid gestationis (PG) or herpes gestationis is a rare pregnancy dermatosis of autoimmune etiology[1]. The clinical manifestations of PG usually appear in third trimester of pregnancy or in the immediate postpartum period and consist of a vesiculobullous skin eruption that affects the skin of the periumbilical area, hands and feet[2,3]. Lesions usually resolve with a course of systemic steroids and recurrences are uncommon[4-6].

PG is caused by an autoimmune response to BP180, an 180-kDa trans-membrane hemidesmosomal glycoprotein[7-9]. Linear deposition of C3 and/or IgG in the basement membrane area results in the formation of a subepithelial vesicle[10]. Circulating autoantibodies are usually present in most of PG patients and there is an association between the incidence of PG and HLA class II antigens DR3 and DR4[11]. However, oral manifestations of PG are distinctly rare. We present the second case of PG with oral manifestations to ever be reported in the literature[12].

Case History

A 26-year-old woman presented to the A. Syggros Oral Medicine Clinic with a chief complaint of "itchy bleeding sores" on the skin and the oral mucosa that appeared 2 months after she gave birth to a healthy child. There was an abrupt onset of lesions and generalized blistering set in within the first 48 hours. Upon clinical examination, the patient presented with multiple hemorrhagic bullae on the soft palate, buccal mucosa, gingiva and lips (Fig. 1). A vesiculobullous eruption was noted on the scalp, periocular and perinasal folds, as well as on the skin of the trunk, upper and lower extremities (Fig. 2). The patient reported experiencing intense pruritus that followed exacerbations and remissions. A provisional clinical diagnosis of PG was rendered. A CBC with differential demonstrated leukocytosis (WBC 12.6) with increased number of neutrophils (10k/ml) and decreased number of lymphocytes (13 k/ml). Serum albumin was low (55g/l) and serum urea was elevated (55mg/dl). HSVAg I and II were shown to be negative. Serum levels of anti-Ro, anti-La, anti-Sm, ANA, anti-DNA were shown to be below detectable levels.

An intraoral biopsy as well as a skin biopsy was obtained. Histopathologic examination, direct immunofluorescence (DIF) and indirect immunofluorescence (IIF) analyses were performed.

A biopsy was obtained from the right buccal mucosa. Sections showed stratified squamous epithelium and connective tissue. The epithelium exhibited parakeratosis, acanthosis, spongiosis and formation of a subepithelial vesicle. Specifically, the roof of the

vesicle demonstrated an intact basal cell layer and the floor of the vesicle were composed of connective tissue exhibiting a lymphohistiocytic infiltrate (Fig. 3). A similar histopathologic picture was observed from the skin biopsy specimen taken at the same time.

DIF from oral mucosa and skin showed a linear, basement membrane zone deposition of IgG and C3 (Fig. 4). The specimen was negative for IgA deposits. Indirect immunofluorescence (IIF) demonstrated the presence of IgG autoantibodies and C3. There were no circulating IgA autoantibodies detected. Based of the clinical and histopathologic findings the diagnosis of the PG was confirmed.

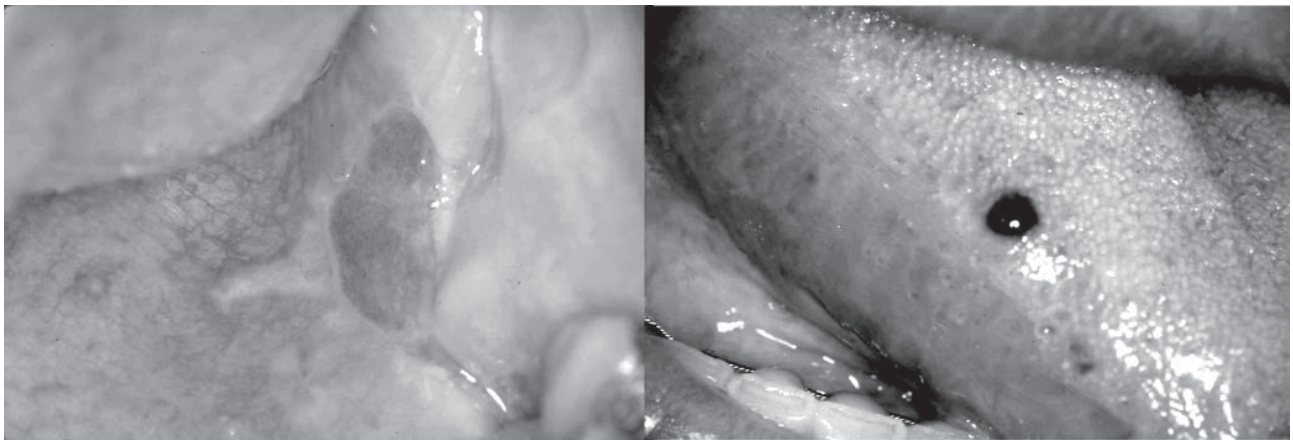

Figure 1. Ruptured bullae on the buccal mucosa (left) and intact bulla on the tongue (right)

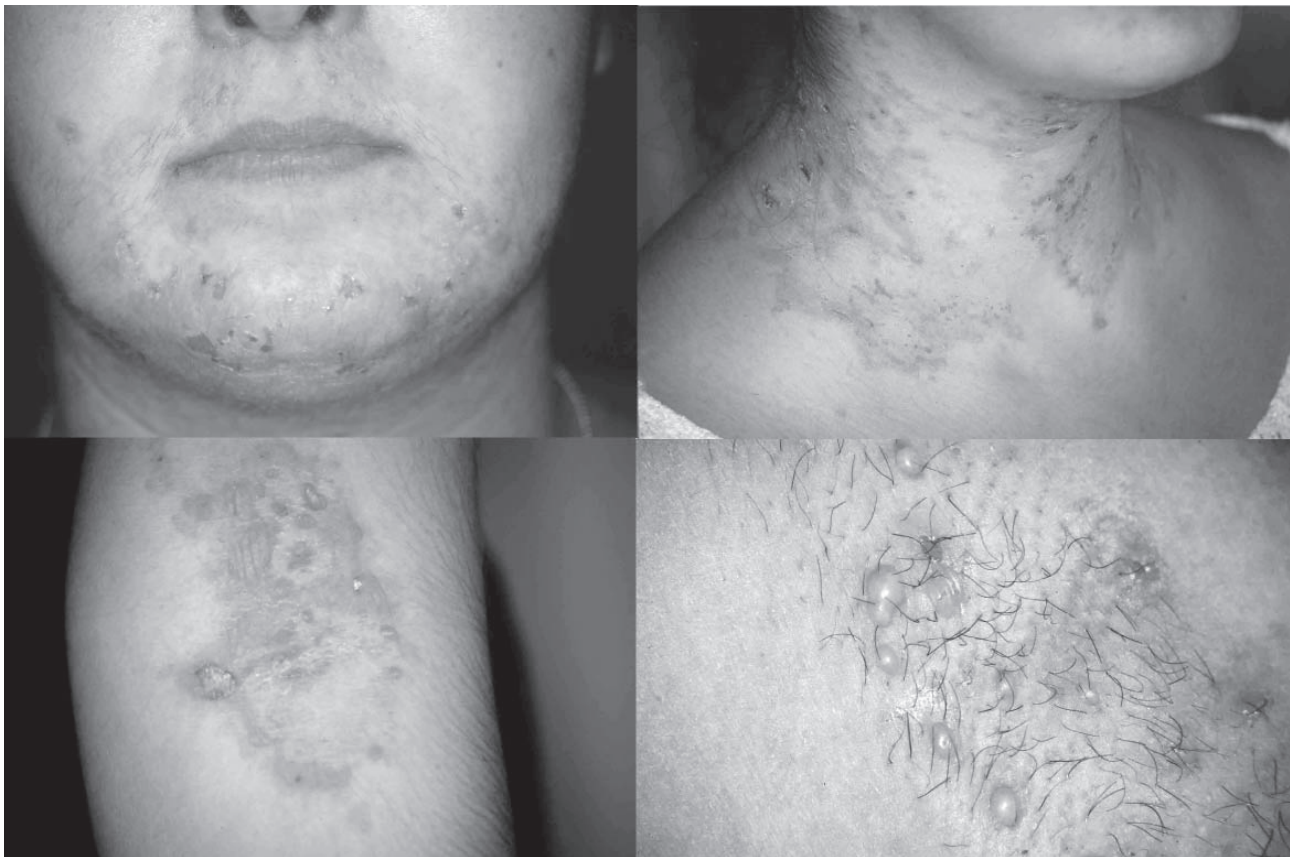

Figure 2. Clockwise from the top, vesiculobullous eruption on the skin of the face, neck, armpit and arm

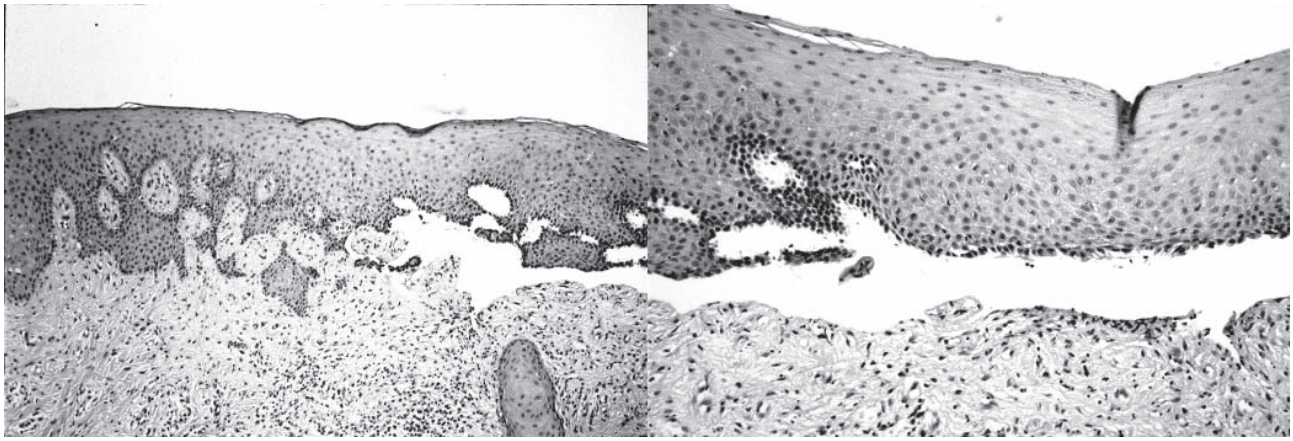

Figure 3. Low power (10x) magnification demonstrates separation of the epithelium from the connective tissue (left). High power magnification (20x) demonstrates the subepithelial nature of the vesicle as well as the intact basal cell layer (right)

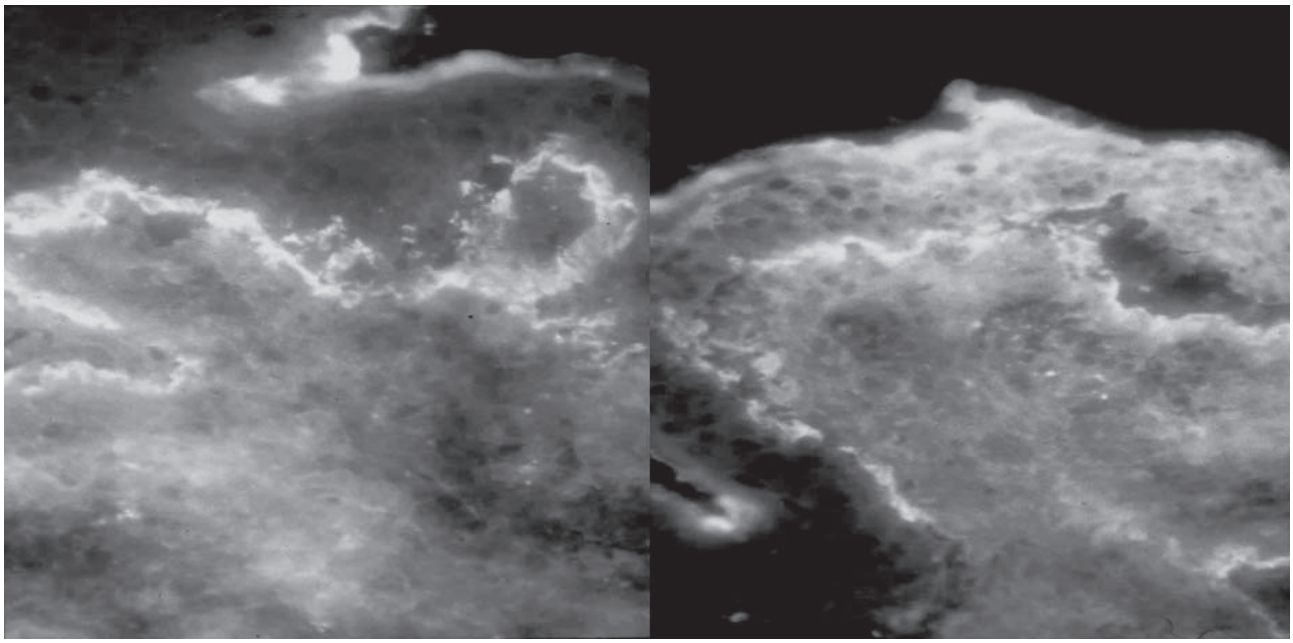

Figure 4. Direct immunofluorescence exhibits a linear deposition of IgG (left) and C3 (right) at the basement membrane zone

The patient was put on a regimen of 60 mg of prednisolone/day. The oral lesions and pruritic skin eruption improved within 6 days of treatment initiation and the skin lesions subsided considerably. Reduction of the prednisolone dosage to 40 mg/day resulted in a severe recurrence of the skin lesions. The prednisolone dosage was escalated up to 85 mg/day accompanied by 100 mg of azathioprine per day for 2 weeks, followed by progressive tapering of the dose. This treatment regimen resulted in complete resolution of oral and skin lesions within a month.

The patient presented with a minor disease recurrence 2 months later and was treated with lower dosages of prednisolone (25 mg/day tapered to 10 mg per day). She experienced complete recovery. At a follow-up visit 3 years later, she demonstrated no evidence of recurrence and remains free of disease to this date.

Discussion

PG is a rare, mucocutaneous vesiculobullous disease of autoimmune pathogenesis that is strongly associated with late pregnancy and the immediate postpartum period[1,8,11]. A relationship of PG with

trophoblastic tumours has also been reported[13]. PG occurs approximately 1:50,000 pregnancies and shares common features with bullous pemphigoid[14,15]. The term "herpes gestationis" has been used synonymously with PG but should be avoided as there is no proven association of this disease with a viral infection or pathogenesis[16].

The clinical signs of PG involve the abrupt onset of intensely pruritic erythema, usually on the trunk and the periumbilical area, which gradually spreads to involve the abdomen, thighs palms and soles[17]. The erythematous lesions progress into urticated papules and plaques, followed by the development of subepidermal blisters in the same areas where the erythema originally appeared[18]. Oral manifestations are distinctly rare[12]. The initial appearance of PG lesions is most likely to occur in the second and third trimester of pregnancy, although they have been reported as early as 5 weeks gestation and as late as 35 days postpartum[15]. In a clinical study of 87 patients with PG[15], parity or paternity change was shown to have no significant effect in the incidence of PG contradicting the evidence from a previous study that suggested that exposure of an antigen derived by the father might play a role in the development of PG. In the same study[15], the collective rate of incidence of spontaneous abortion and ectopic pregnancy was 17.5% compared to 15% noted in the general population. Interestingly, uninvolved or "skip" pregnancies were observed in 8% of the patients reviewed. The incidence of neonates with skin disease was 2.8% compared to 5% previously reported. The neonatal form of PG is mild and self-limited[19]. Increased incidence of prematurity and low birth weight infants has been reported but is controversial[19]. Jenkins et al[15] also observed a significant increase in the incidence of Graves' disease in the population of PG patients[20].

Histopathologic examination of the PG lesions usually discloses a subepithelial vesicle with variable degrees of lymphohistiocytic and eosinophilic infiltrates in the connective tissue[21]. The pathogenesis of PG is defined by the presence of circulating autoantibodies against the 180-kd bullous pemphigoid antigen (BP180). BP 180 is a 180-kDa trans membrane hemidesmosomal glycoprotein that consists of an intracellular N-terminal globular head, a trans membrane region and a C-terminal ectodomain[7,22-24]. Sera from PG patients contain complement-fixing IgG autoantibodies reactive against the membrane-proximal NC16A domain of BP-180. BP 230 is another, less common, target antigen for PG autoantibodies present alone or in conjunction with BP-180 in the serum of PG patients[7]. DIF studies of PG show linear depositions of C3 along the basement membrane zone (BMZ) in 100% of the cases and in 40-50% of the cases an IgG deposit of the same morphology[25,26]. IIF demonstrates in 20-60% of the PG cases circulating IgG autoantibodies against BMZ antigens. The PG autoantibodies are predominantly of the IgG1 subclass but IgG3 and IgA mediated disease has also been reported[25,26]. The immunofluorescence profile of our case is consistent with that customarily observed in PG patients. An immunoblot was not performed as the determination of the auto antigen would not aid any further in the differential diagnosis between PG and bullous pemphigoid. However, the serologic and histologic features of the patient's disease as well as its association with pregnancy and response to treatment are characteristic of PG and clearly distinguish it from bullous pemphigoid.

Oral involvement in patients with PG is an extremely rare clinical manifestation of the disease. Shimanovich et al[27] have so far reported the only case of PG with oral involvement. The patient developed vesiculobullous lesions on oral mucosal membranes during the eighth week of her second pregnancy and skin lesions appeared 1 week after the oral lesions. However, mucosal involvement remained the predominant feature throughout the course of the disease, with skin lesions being fewer and less severe in extent. It is unclear whether the pregnancy resulted in a live birth. A previous pregnancy with the same paternity had been uneventful. Lesions were managed by systemic prednisolone and complete resolution without scarring was achieved only after delivery. Interestingly, the autoimmune response appeared to be mediated primarily by IgA autoantibodies directed against the C-terminal portion of the BP180 ectodomain located 800 amino acids downstream of the NC16A epitope usually recognized by PG patients' sera. IgG immunoreactivity was faint on DIF and non-existent in IIF.

To our knowledge, the case reported in our manuscript is only the second case of PG where the oral mucosa is involved. In the present case, the patient developed mucosal and skin lesions of equal severity in the postpartum period after a live birth. In contrast to the case reported by Shimanovich et al[12], both skin and mucosal lesions appeared at the same time and DIF of lesional tissue demonstrated mainly IgG autoantibodies against BP-180 in the absence of IgA autoantibodies. The same findings were observed in IIF analysis. Complete resolution of the lesions after systemic corticosteroid administration was observed in both cases. In the present case, the distribution of the lesions, histopathologic picture and immunofluorescent profile, as well as the patient's response to systemic corticosteroid administration, are characteristic of PG. The presence of extensive skin lesions weighs against a diagnosis of cicatricial pemphigoid and the complete resolution of the lesions with systemic corticosteroids argues against a diagnosis of bullous pemphigoid, a chronic disease. The immunofluorescent profile in our case is more consistent with that commonly associated with PG, than the one reported by Shimanovich et al[12]. However, PG cases reported in the literature present with a variety of clinical

manifestations and immunologic findings and further investigation would be required in order to clarify the issue.

The differential diagnosis of PG includes bullous pemphigoid, cicatricial pemphigoid, linear IgA disease and pregnancy dermatoses as well as herpetic infection. The latter is easily ruled out by consistently negative viral studies in PG patients. The histologic and DIF features are usually very helpful in ruling out other vesiculobullous diseases, as well as pregnancy dermatoses. Cicatricial pemphigoid affects the oral mucosa but usually does not present with extensive skin lesions and the autoimmune response is directed against miscellaneous epitopes. In addition, circulating autoantibodies are uncommon in cicatricial pemphigoid. The dividing line gets indistinct between bullous pemphigoid and PG as they share many common features including the type of autoimmune response and the antigen to which it is directed. However, the protracted chronic clinical course of bullous pemphigoid as well as its response to corticosteroid administration is different than those observed in PG patients. PG patients may experience complete resolution while bullous pemphigoid patients go through periods of exacerbation and remission that last a long time[18]. Rarely, conversion of PG into bullous pemphigoid has been noted[28]. In the case of PG patients, the striking association with pregnancy, the initial peri-umbilical distribution of the eruption and the high incidence of disease resolution with systemic administration of corticosteroids are reliable features that help establish the diagnosis of PG in the presence of the appropriate serologic and histopathologic findings.

Treatment of PG usually requires systemic administration of corticosteroids[15]. The dosage varies significantly according to the severity of the vesiculobullous eruption. Reported initial doses of prednisolone are in the range of 5-110 mg daily. The therapeutic goal is suppression of blistering and tapering of the regimen to achieve disease-free status. A small number of PG patients (18.8%) have been reported to be successfully treated with topical administration of steroids[15]. Most patients can eventually discontinue corticosteroid treatment while remaining disease-free. A few patients have been reported to be unresponsive to high dose systemic corticosteroids and to present with chronic persistent disease that converts to bullous pemphigoid[1,15,18]. Azathioprine, dapsone, pyridoxine and sulphapyridine are also occasionally used as adjunctive therapy. Treatment with plasmapheresis and IV immunoglobulin has also been reported but the success rate is inferior to that achieved by corticosteroid administration[1,15,18]. Our patient responded well to systemic administration of prednisolone and the vesiculobullous eruption resolved successfully within a few months after initial presentation.

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Correspondence and request for offprints to:

Dr. Eleni Gagari
176 Kifissias Avenue and 1 Veaki Street
Athens, Greece 11525
Email: egagari@med.uoa.gr