



Case Report

New onset pemphigus foliaceus during pregnancy: A rare case[☆]

M. Kokolios, MD^{*}, F. Lamprou, MD, MSc, D. Stylianidou, MD,
D. Sotiriadis, MD, PhD, A. Patsatsi, MD, MSc, PhD

Second Department of Dermatology, Aristotle University School of Medicine, Papageorgiou General Hospital, Thessaloniki, Greece

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ABSTRACT

Pemphigus is a rare autoimmune disease during pregnancy. Among the different pemphigus types, pemphigus foliaceus (PF) is even rarer than pemphigus vulgaris. We present a case of PF in a 36-year-old female patient who presented with PF onset during pregnancy in the form of a disseminated, erythematous squamous rash. A diagnosis was made on the basis of histologic, immunofluorescence, and enzyme-linked immunosorbent assay results. A complete remission was recorded a month after steroid treatment initiation. The patient delivered a premature (33 weeks) but otherwise healthy baby girl. Only three cases of PF have been reported in two retrospective studies found in the English-language bibliography. Although pemphigus during pregnancy is a rare disease and treatment guidelines have not yet been elucidated, the management of these cases is individually evaluated. In all cases, the primary goal should be the control of the maternal disease along with the safety of the fetus.

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Introduction

Pemphigus affects the skin and/or mucosa and is characterized by the production of antidesmoglein (anti-Dsg) 1 and/or 3 autoantibodies, which results in the loss of cell-to-cell adhesion in the superficial and deep epidermis. Pemphigus in all forms is a rare autoimmune disease during pregnancy (Daneshpazhooh et al., 2011; Fainaru et al., 2000; Goldberg et al., 1993). In the current bibliography, a number of case reports of pemphigus vulgaris (PV) are documented during pregnancy. After an extended research, pemphigus foliaceus (PF) was observed to be even rarer than PV during pregnancy. Herein, we present a case of PF with onset during pregnancy and we further discuss the related bibliography.

Case report

A 36-year-old female patient was admitted to the Department of Dermatology at the Papageorgiou General Hospital in Thessaloniki, Greece during week 14 of her pregnancy, which was achieved through in vitro fertilization but otherwise healthy, with a nonpruritic erythematous squamous rash on the face and confluent crusted lesions

on the anterior chest wall and abdomen (Fig. 1). Flaccid small bullae were ruptured on both forearms and the lower extremities along with superficial erosions that were surrounded by an erythematous collarette (Fig. 2). The eruption extended to the upper and lower back (Fig. 3) and the Nikolsky sign tested positive. The disease onset was 3 months prior to admission and coincided with the start of the pregnancy. The initial lesion was a solitary hyperkeratotic lesion on the nose.

To ascertain the diagnosis, a Tzanck smear was performed and groups of acantholytic keratinocytes were observed. Biopsy specimens were obtained from a recent lesion on the right arm and revealed a subcorneal serum collection, eosinophilic spongiosis in the epidermis, and inflammatory infiltrates of the lymphocytes and eosinophils in the dermis (Fig. 4). A second biopsy specimen showed typical subcorneal acantholysis. Direct immunofluorescence revealed an intercellular deposition of immunoglobulin (Ig) G and C3 and the same intercellular pattern with IgG was observed with indirect immunofluorescence. Enzyme-linked immunosorbent assay tests detected high anti-Dsg1 titers (> 200 RU/ml). All these results confirmed the diagnosis of PF.

Therapeutic decisions were challenging and frequent evaluations of both the mother and fetus by the obstetricians were essential. Due to the disease severity (Pemphigus Disease Area Index [PDAI] activity score 55), treatment with oral prednisolone 80 mg/day (1 mg/kg/day; patient weight was 76 kg) was initiated and the disease activity was controlled after 8 days (PDAI score 31). The initial dose was maintained for 1 month and progressively tapered off

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^{*} Corresponding author.

E-mail address: mltkokolios@yahoo.gr (M. Kokolios).



Fig. 1. Crusted lesions on the abdomen.

at this timepoint (i.e., end of the consolidation phase [Murrell et al., 2008]; PDAI activity score 0, PDAI damage score 9). The patient followed a tapering schedule of 5 mg every 3 days and maintained on 30 mg/day for a month. The corticosteroid dose was then tapered to 5 mg every week and the patient managed to reach the minimal therapeutic dose (5 mg/day of oral prednisone) during week 29 of the pregnancy.

The minimal dose was increased to 10 mg/day on the day before the delivery. The patient did not develop gestational diabetes or glucose intolerance. She delivered a premature (at 33 weeks) but otherwise healthy baby girl who weighed 1870 gr at the time of birth and had no skin lesions. Premature rupture of the membranes seemed to occur after a cervical cerclage was performed by the patient's obstetrician (Drassinower et al., 2011). The indications for this procedure during week 33 of gestation seemed controversial because the cerclage does not appear to improve the preterm delivery rate of < 35 weeks in low-risk women (Daskalakis, 2009).

The patient tapered the treatment with oral prednisone to 5 mg/day on day 5 after the delivery and remained on minimal therapy postpartum. Ten months after the delivery, she was free of lesions and the anti-Dsg1 titers were negative.

Discussion

Although the immunological and hormonal status of a woman changes rapidly during conception and early pregnancy, PF may occur for the first time or aggravate during pregnancy (Fainaru et al., 2000). The patient in this case study had no history of skin lesions before the pregnancy and the initial lesion on her nose must have erupted at the time of conception. Lin et al. (2015) reviewed

47 cases of pemphigus that were reported between 1966 and 2014 with a diagnosis before or after pregnancy and found only two cases of new onset PF during pregnancy. Daneshpazhooh et al. (2011) reviewed the files of 1851 Iranian patients who were diagnosed with pemphigus between 1984 and 2006 and only one case of PF during pregnancy was found.

Transient neonatal lesions that are due to the transplacental transmission of IgG antibodies from mother to fetus is not a rare phenomenon in PV (Goldberg et al., 1993). Although severe maternal PV seemed to be strongly associated with neonatal PV, neonatal lesions have also been reported in some cases with mild disease in the mother. Rocha-Alvarez et al. (1992) studied 19 mother/newborn pairs (diagnosis of Fogo Selvagem was established in all mothers before pregnancy) and found negative or very low titers of FS autoantibodies in the neonates' cord sera even though positive titers (1:40-1:320) were found in the mothers' sera on the day of the delivery.

PF in pregnant women rarely leads to neonatal skin lesions, which may be due to the low transfer of IgG4 autoantibodies through the placenta and the immunosorbent effect of the placenta that contains desmosomes and desmogleins (Aplin et al., 2009; Harris et al., 2009; Malek, 2003; Malek et al., 1995). Wu et al. (2000) found that the distribution of Dsg1 and Dsg3 in neonatal epidermis is different than in adult epidermis and demonstrated that Dsg3 expression in the superficial epidermis of neonates provides protection against anti-Dsg1 antibodies. This report could explain why infants rarely develop neonatal PF despite the high titers of maternal anti-Dsg1 antibodies (Ranella Hirsch et al., 2003). Accordingly in the current case, despite the fact that the patient had extended disease (PDAI score 55) and high anti-Dsg1 titers, the neonate was born free of skin lesions.



Fig. 2. Lower extremities. Superficial erosions surrounded by an erythematous collarette.



Fig. 3. Erythematous lesions and superficial erosions on the upper and lower back.

The management of pemphigus during pregnancy is intriguing. Topical steroid medications can be very useful and a safe therapeutic option to treat mild disease. Therapy aims to control the acute phase while simultaneously being safe for the fetus and should be accompanied by close obstetric monitoring. Braunstein and Werth (2013) recommended the prolonged use of no more than 7.5 mg of prednisone per day and efforts should be made to avoid doses > 20 mg daily. On the other hand, some argue that withholding therapy may yield a child to be severely affected by the transplacentally acquired maternal antibodies (Ranella Hirsch et al., 2003; Avalos-Díaz et al., 2000).

In the current case, therapy initiation after the first trimester and disease severity were the two main reasons for the aggressive therapeutic scheme (1 mg/kg/day until disease control and then tapering). The disease was controlled in approximately one week and there was a rather satisfactory clinical response during the first month. Although studies have shown that prenatal exposure to prednisone may result in intrauterine growth retardation, premature rupture of the membranes, or preterm delivery (Braunstein and Werth, 2013; Makol et al., 2011), the steroid therapy did not seem to be the main cause of the premature rupture of the membranes and preterm delivery in the current case. Treatment with oral prednisone is thought to be relatively safe during pregnancy (U.S. Food and Drug Administration [FDA] class C) and considered one of the firstline treatments (Saltzberg et al., 2014). However, some cases of fetal adrenal suppression have been reported when high daily doses of steroid medications (> 100 mg/day) were used (Makol et al., 2011; Kurtoglu et al., 2011). In the current case, the patient delivered a healthy baby girl.

Adjuvant therapy with steroid-sparing, immunosuppressant medication could be useful to disease control. Methotrexate, mycophenolate mofetil, and cyclophosphamide are contraindicated during

pregnancy and azathioprine (FDA class D) is not recommended but when used as necessary, the dose should be kept low to prevent fetal harm (Braunstein and Werth, 2013). Other alternatives to steroid therapy as plasma exchange could be effective (Piontek et al., 2000) but there is always the need to give the patient immunosuppressive therapy (Lehman et al., 2008). Intravenous immunoglobulin (IVIg) still remains an expensive therapy; however, Ahmed and Gurcan (2011) argue that the use of 10 to 13 cycles of IVIg is safe and effective as a monotherapy to treat pemphigus during pregnancy. Hence, more studies on larger series of patients would provide new evidence on whether IVIg should be considered as a credible alternative therapeutic option. Although intravenous rituximab (FDA class C) at one or two courses of 375 mg/m² proved useful (Faurshou and Gniadecki, 2008; Marzano et al., 2007) and was initially considered a safe therapeutic option (Braunstein and Werth, 2013), some studies argue that its use during pregnancy may lead to newborn immunosuppression and pregnancy should be recommended to be delayed for 1 year after rituximab treatment (Chakravarty et al., 2011).

Conclusions

This report detailed a case of PF that was initially diagnosed during pregnancy. Only three cases of PF with onset during pregnancy have been reported as part of a retrospective case review in the English-language bibliography. Pemphigus during pregnancy is a rare disease and treatment guidelines have not yet been elucidated; therefore, management of these cases is individually evaluated. In all cases, the primary goal should be control of the maternal disease along with the safety of the fetus.

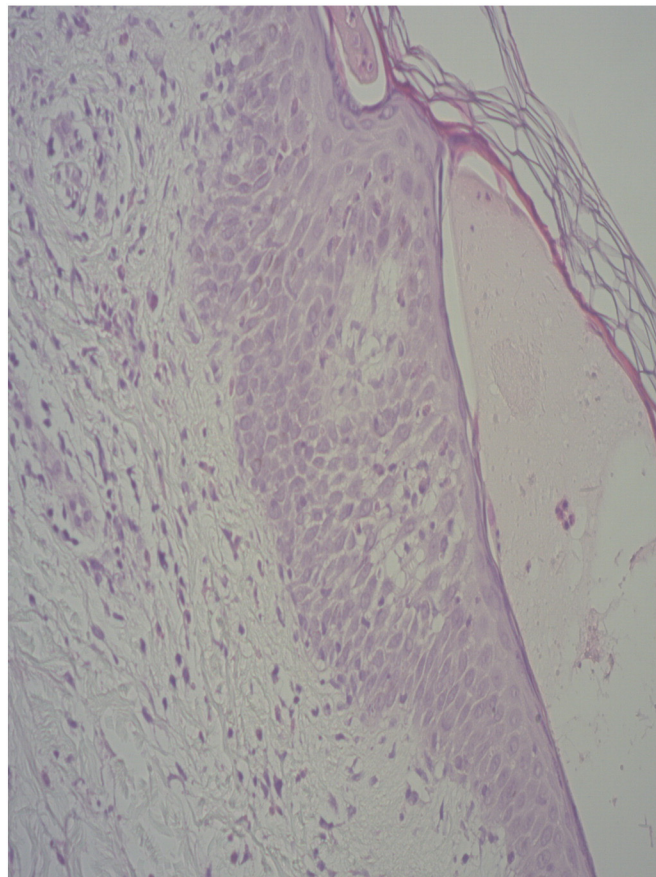


Fig. 4. Subcorneal serum collection, eosinophilic spongiosis in the epidermis, inflammatory infiltrate in the dermis.

References

- Ahmed AR, Gurcan HM. Use of intravenous immunoglobulin therapy during pregnancy in patients with pemphigus vulgaris. *J Eur Acad Dermatol Venereol* 2011;25:1073–9.
- Aplin JD, Jones CJ, Harris LK. Adhesion molecules in human trophoblast—a review. I. Villous trophoblast. *Placenta* 2009;30:293–8.
- Avalos-Díaz E, Olague-Marchan M, López-Swidorski A, Herrera-Esparza R, Díaz L. Transplacental passage of maternal pemphigus foliaceus autoantibodies induces neonatal pemphigus. *J Am Acad Dermatol* 2000;43:1130–4.
- Braunstein I, Werth V. Treatment of dermatologic connective tissue disease and autoimmune blistering disorders in pregnancy. *Dermatol Ther* 2013;26:354–63.
- Chakravarty EF, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. *Blood* 2011;117:1499–506.
- Daneshpazhooh M, Chams-Davatchi C, Valikhani M, Aghabagheri A, Mortazavizadeh SM, Barzegari M, et al. Pemphigus and pregnancy: A 23-year experience. *Indian J Dermatol Venereol Leprol* 2011;77:534.
- Daskalakis G. Prematurity prevention: The role of cerclage. *Curr Opin Obstet Gynecol* 2009;21:148–52.
- Drassinower D, Poggi S, Landy HJ, Gilo N, Benson JE, Ghidini A. Perioperative complications of history-indicated and ultrasound-indicated cervical cerclage. *Am J Obstet Gynecol* 2011;205:53.e1–5.
- Fainaru O, Mashiach R, Kupfermine M, Shenhav M, Pauzner D, Lessing J. Pemphigus vulgaris in pregnancy: A case report and review of literature. *Human Reprod* 2000;15:1195–7.
- Faurouchou A, Gniadecki R. Two courses of rituximab (anti-CD20 monoclonal antibody) for recalcitrant pemphigus vulgaris. *Int J Dermatol* 2008;47:292–4.
- Goldberg N, DeFeo C, Kirshenbaum N. Pemphigus vulgaris and pregnancy: Risk factors and recommendations. *J Am Acad Dermatol* 1993;28:877–9.
- Harris LK, Jones CJ, Aplin JD. Adhesion molecules in human trophoblast—a review. II. Extravillous trophoblast. *Placenta* 2009;30:299–304.
- Kurtoglu S, Sancı D, Akin MA, Daar G, Korkmaz L, Memur S. Fetal adrenal suppression due to maternal corticosteroid use: Case report. *J Clin Res Pediatr Endocrinol* 2011;3:160–2.
- Lehman JS, Mueller KK, Schraith DF. Do safe and effective treatment options exist for patients with active pemphigus vulgaris who plan conception and pregnancy? *Arch Dermatol* 2008;144:783–5.
- Lin L, Zeng X, Chen Q. Pemphigus and pregnancy. Analysis and summary of case reports over 49 years. *Saudi Med J* 2015;36:1033–8.
- Makol A, Wright K, Amin S. Rheumatoid arthritis and pregnancy: Safety considerations in pharmacological management. *Drugs* 2011;71:1973–87.
- Malek A. Ex vivo human placenta models: Transport of immunoglobulin G and its subclasses. *Vaccine* 2003;21:3362–4.
- Malek A, Sager R, Zakher A, Schneider H. Transport of immunoglobulin G and its subclasses across the in vitro-perfused human placenta. *Am J Obstet Gynecol* 1995;173:760–7.
- Marzano AV, Fanoni D, Venegoni L, Berti E, Caputo R. Treatment of refractory pemphigus with the anti-CD20 monoclonal antibody (rituximab). *Dermatology* 2007;214:310–8.
- Murrell DF, Dick S, Ahmed AR, Amagai M, Barnadas MA, Borradori L, et al. Consensus statement on definitions of disease, end points and therapeutic response for pemphigus. *J Am Acad Dermatol* 2008;58:1043–6.
- Piontek JO, Borberg H, Sollberg S, Krieg T, Hunzelmann N. Severe exacerbation of pemphigus vulgaris in pregnancy: successful treatment with plasma exchange. *Br J Dermatol* 2000;143:455–6.
- Ranella Hirsch R, Anderson J, Weinberg J, Burnstein P, Echt A, Fermin J, et al. Neonatal pemphigus foliaceus. *J Am Acad Dermatol* 2003;49:S187–9.
- Rocha-Alvarez R, Friedman H, Campbell IT, Souza-Aguiar L, Martins-Castro R, Diaz LA. Pregnant women with endemic Pemphigus foliaceus (Fogo Selvagem) give birth to disease-free babies. *J Invest Dermatol* 1992;99:78–82.
- Saltzberg KW, Gero MJ, Ragsdale BD. Pemphigus vulgaris in pregnancy. *Cutis* 2014;94:206–9.
- Wu H, Wang ZH, Yan A, Lyle S, Fakhrazadeh S, Wahl JK, et al. Protection against pemphigus foliaceus by desmoglein 3 in neonates. *N Engl J Med* 2000;343:31–5.