Dupilumab as a novel steroid-sparing treatment for pemphigoid gestationis: A new case report and review of literature

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Key words: dupilumab; dupixent; gestational pemphigoid; herpes gestationis; pemphigoid gestationis.

INTRODUCTION

Pemphigoid gestationis (PG) is a vesiculobullous disorder that has significant overlap with bullous pemphigoid clinically and histopathologically and classically develops in late pregnancy or in the postpartum period. The disease is believed to result from autoantibodies against bullous pemphigoid antigen 180 (BP180) located within the hemidesmosome of the basement membrane zone. It is associated with risks of prematurity and small-for-gestational age neonates and may cause mild transient lesions in up to 10% of newborns. Treatment involves potent topical and/or systemic corticosteroids, tapering the dose as blister formation is suppressed and often temporarily increasing the dosing with the expected flare during delivery. However, there are risks of systemic corticosteroid use in pregnant women, which include a slight increased risk of cleft lip or palate in the first trimester, or with long-term use, fetal growth restriction or adrenal insufficiency. Other treatments reported include dapsone, doxycycline or minocycline with nicotinamide, pyridoxine, cyclosporine, and intravenous immunoglobulin. Dupilumab is a drug that is United States Food and Drug Administration-approved to treat multiple conditions including atopic dermatitis and prurigo nodularis with a favorable safety profile. Only 4 cases thus far have reported improvement of PG with dupilumab. Here we present a new case of PG successfully treated with dupilumab and discuss its potential mechanism of action.

Abbreviations used:

BP180:	bullous pemphigoid antigen 180
PG:	pemphigoid gestationis
Th2:	T helper 2

CASE PRESENTATION

A 38-year-old woman presented to our clinic for a pruritic eruption of the trunk and extremities that had first presented at 19 weeks gestation. It started as a red annular plaque around and involving the umbilicus, and within weeks developed annular, coalescing dusky red papules and plaques with slight central clearing and vesicles on the border (Fig 1, *A, B*). Her medical history was significant for Graves' disease. Her obstetric history was Gravida: 5, Para: 2 Term, 0 Preterm deliveries, 2 Spontaneous abortions, and 2 Living children. A punch biopsy from her mid back showed spongiotic dermatitis with eosinophils and early subepidermal blister formation (Fig 2, *A*). An immunohistochemical stain for C3d demonstrated deposition of the latter along the basal layer of the epidermis (Fig 2, *B*), a finding that has been shown to have similar sensitivity and specificity to direct immunofluorescence studies in diagnosing pemphigoid.[1] BP180 IgG antibody level was elevated to 64 U/mL and BP230 IgG, desmoglein 1, and 3 IgG antibody levels were normal. These results were consistent with PG. She had no history of PG in prior pregnancies, which were all with the

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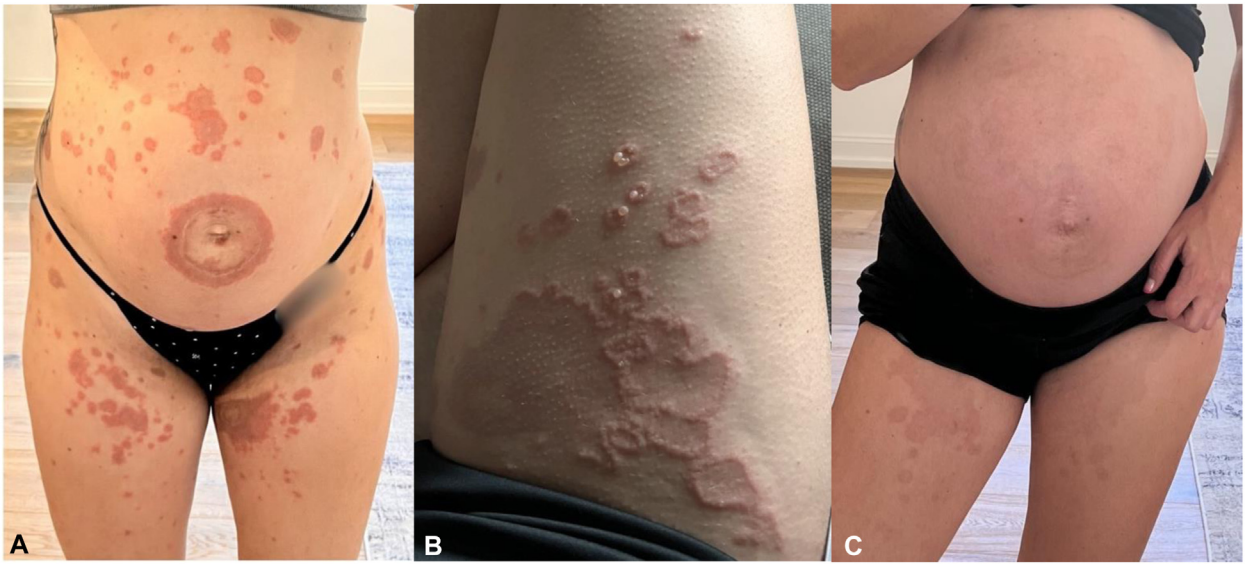

Fig 1. A, Before treatment with prednisone or dupilumab. Annular, coalescing dusky red papules and plaques with slight central clearing on the trunk and extremities. Patient at 23 weeks gestation. **B,** Two weeks into treatment with oral prednisone. Vesicles developing on the borders of annular plaques on the anterior aspect of the right thigh. Patient at 25 weeks gestation. **C,** A few days after the second dose of dupilumab. Thin annular coalescing hyperpigmented plaques in areas of prior rash and no active blisters. Patient at 31 weeks gestation.

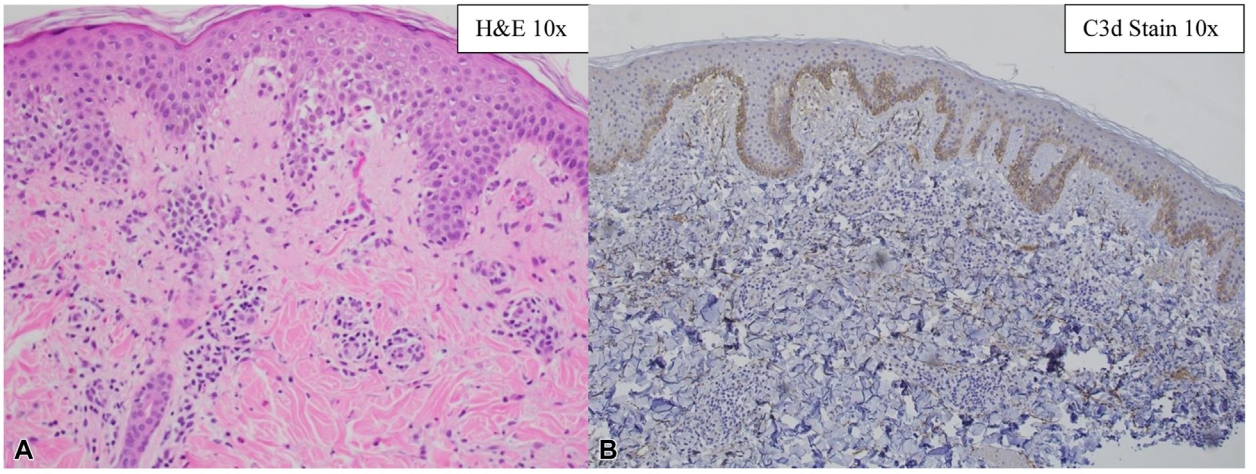

Fig 2. A, Histopathology of a papular lesion on the back showing spongiotic dermatitis with eosinophils and early subepidermal blister formation. **B,** Immunohistochemical stains showing C3d deposition along the basement membrane. (**A,** Hematoxylin-eosin stain; **B,** C3d stain; original magnifications: **A** and **B,** ×10.)

same partner. The clinical differential diagnosis includes polymorphic eruption of pregnancy, which presents similarly with urticarial papules and plaques and with disease progression, vesicles, erythema, and target lesions. Polymorphic eruption of pregnancy, however, is usually seen in primiparous women during late third trimester or immediately postpartum and tends to start within the abdominal striae and spare the umbilicus. Histology is nonspecific, and direct immunofluorescence and enzyme-linked immunosorbent assay for BP180 IgG autoantibody studies are negative.

At 23 weeks gestation, the patient started treatment with oral prednisone 40 mg daily (0.5 mg/kg) with improvement, however, upon tapering, she had reflaring of the disease. At 29 weeks gestation, she

Table I. Previously published cases of pemphigoid gestationis treated with dupilumab

Authors, country	Patient age, gestational age during onset of PG	Medications tried	Gestational age when initiating dupilumab	Dupilumab dosage and length of treatment	Discontinued prednisone?	Gestational age at delivery, baby healthy?
Riquelme-Mc Loughlin C and Mascaró,[5] Spain	37 yo, 20 wk	Topical betamethasone diproprionate, oral prednisone 0.5 mg/kg	30 wk	600 mg loading dose, then one 300 mg dose 2 wk later	No, continued 10 mg/d, unspecified until when	34.4 wk, yes
Alvarez et al,[3] Spain	28 yo, 27 wk	Topical clobetasol propionate, oral prednisone 0.5 mg/kg, one dose omalizumab 300 mg subcutaneously	Not specified	600 mg loading dose, then 300 mg every 2 wk until 6 wk postpartum—8 total injections	Yes, unspecified when	Not specified, yes
Liu et al,[4] China	28 yo, 22 wk	Topical steroids, oral prednisone 1 mg/kg	25 wk	600 mg loading dose, then 300 mg every 2 wk, unspecified stop date	No, continued 10 mg/d until delivery	36.2 wk, yes
Chen et al,[2] United States	36 yo, 18 wk	Topical diphenhydramine, topical steroids, oral cetirizine, oral prednisone 0.5 mg/kg	22 wk	600 mg loading dose, then 300 mg every 2 wk until 4 wk postpartum	Yes, 10 wk after starting dupilumab	39 wk, yes

PG, Pemphigoid gestationis; *yo*, years old.

was started on dupilumab (loading dose of 600 mg subcutaneously, then 300 mg every 14 days), which improved the rash significantly and allowed her to taper the prednisone by 5 mg each week without flaring. At 32 weeks gestation, while on 20 mg prednisone daily, she had no active blisters but residual hyperpigmentation in areas that were -previously involved (Fig 1, *C*). BP180 had decreased to 58 U/mL. She completely tapered off prednisone while on dupilumab by 35 weeks gestation, with her skin eruption completely resolved. She delivered a healthy baby with a normal-appearing skin examination at 39 weeks gestation and continued dupilumab until 6 weeks postpartum. She reported episodes of moderate pruritus of the thighs in areas of prior skin involvement but no new lesions. At 3 months postpartum, BP180 remained elevated at 52 U/mL however the patient's skin remained clear, and the pruritus had resolved.

DISCUSSION

Only 1 case of PG treated with dupilumab in the United States,[2] and 3 cases worldwide[3-5] have been reported (Table I). In 2 cases,[4,5] dupilumab was used in conjunction with oral prednisone tapered down to 10 mg/d until delivery, and in the other 2 cases[2] oral prednisone was discontinued before delivery as in our case.[4,5] Two babies were born prematurely,[4,5] but all were healthy and without skin lesions. Dupilumab is a monoclonal antibody that targets interleukin 4 and interleukin 13 signaling in T helper 2 (Th2) inflammation and IgE production. Pregnancy causes a relative shift from Th1 to Th2 immunity to tolerate fetal cells expressing both maternal and paternal proteins while also maintaining ability to fight infections.[6] This causes an increase in production of cytokines, which promote antibody class switching, including to IgE. Although IgG autoantibodies against the basement membrane zone are well known to play a role in the pathogenesis of PG, both IgG and IgE-class autoantibodies against BP180 have been found in patients with PG.[7] In a study comparing the sera of healthy pregnant women with nonpregnant controls, a small proportion of pregnant women were found to produce IgE autoantibodies against BP180.[6] Furthermore, omalizumab, a recombinant antibody that targets circulating IgE and prevents it binding to mast cells and basophils, has also been reported to successfully treat 2 cases of recalcitrant PG.[8] Thus, dupilumab may reduce disease activity in PG as it targets this Th2 inflammation and elevated IgE production.

PG has significant clinical and histopathologic overlap with bullous pemphigoid, and retrospective studies have shown that dupilumab treatment was associated with improved clinical symptoms in patients with bullous pemphigoid.[9] A clinical trial investigating dupilumab as a treatment for bullous pemphigoid is currently underway (LIBERTY-BP, ID: NCT04206553). Dupilumab also has a favorable side effect profile, primarily injection site reactions and conjunctivitis in 5% to 10% of patients. It is associated with minimal risk of adverse effects for both pregnant patients using it to treat atopic dermatitis and their fetuses.[10]

Our case is another example that showed that dupilumab allowed for successful tapering off prednisone while maintaining complete resolution of rash in patients with PG. Future studies are needed to further investigate its mechanism of therapeutic action in PG.

Conflicts of interest

None disclosed.

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