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CASE REPORT

Successful treatment of new onset Wegener's granulomatosis with IVIG (intravenous immunoglobulin) during pregnancy: a case report

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Abstract We describe a patient with limited Wegener's granulomatosis (WG) presenting during pregnancy with aggressive cutaneous involvement. She was treated with a combination of high-dose corticosteroids and intravenous immunoglobulin (IVIG) during her third trimester. The patient had otherwise uneventful pregnancy and a satisfactory outcome for both herself and her newborn. In the English literature, prior to this report, there have been de novo cases of WG in pregnant women that were diagnosed and treated during pregnancy and three cases of WG treated successfully with IVIG during pregnancy.

Keywords Wegener's granulomatosis · Pregnancy · Intravenous immunoglobulin

Introduction

Wegener's granulomatosis (WG) is a necrotizing systematic vasculitis that can cause sino-nasal, pulmonary, renal, ocular, and cutaneous manifestations. The standard treatment of WG with corticosteroids and cytotoxic drugs such as cyclophosphamide improves survival, but the potential effects of these cytotoxic drugs on the developing fetus have not been formally investigated. Intravenous immunoglobulin (IVIG) has recently been used as a potential therapy for WG, even during pregnancy. We report a patient with onset of WG during pregnancy whose disease most strikingly affected the skin and who was treated successfully with high-dose corticosteroid and IVIG.

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Case report

A 24-year-old Caucasian woman in the 29th week of pregnancy presented to the Hospital of the University of Pennsylvania in August 2006 with multiple deep ulcers and surrounding induration for several months. Prior to her pregnancy, she had been well including one uncomplicated normal pregnancy a few years ago. At approximately 5–6 weeks' gestation, the patient developed a painful and pruritic subcutaneous nodule in her left arm. The lesion became enlarged and ulcerated over the next 3 months. She also noticed similar lesions on her thighs, buttocks, shoulders, and the right breast.

Initially, she was treated with oral antibiotics for possible cellulitis by dermatology. However, multiple wound cultures never revealed any infectious organisms and the lesions got bigger, deeper, and more painful over the time. The patient also complained of sinus congestion, postnasal drip, frequent headaches, and cough during this pregnancy. She had a biopsy of a left thigh nodule in June 2006 that revealed acute inflammatory infiltrates with a granulomatous response. In July 2006, a skin biopsy of the lesion on her left arm revealed superficial and deep dermal and subcutaneous mixed inflammatory infiltrates with neutrophils, mononuclear cells, numerous eosinophils and plasma cells. She was initially admitted to the Psychiatry service to exclude the possibility of self-inflicted injuries. Psychiatric evaluation did not reveal any sign of depression or any other psychiatric illnesses.

Physical examinations were notable for an erythematous and crusty nasal mucosa, sinus tenderness and several deep

ulcerated skin lesions without surrounding erythema. She also had a few painful well-circumscribed subcutaneous nodules. The biggest lesion was on her right breast measuring 7 × 12 cm^2 (Fig. 1).

Initial laboratory studies showed a hemoglobin level of 9.7 g/dl and a leukocyte count of 14,200/μl with 75.8% neutrophils. Electrolytes, blood urea nitrogen level, creatinine level and liver function tests were within normal ranges. Urinalysis was notable for a small amount of blood and protein of 30 mg/dl without active sediment. Further workup included negative antinuclear antibody, rapid plasma reagin, angiotensin-converting enzyme, anti-SSA/SSB, cryoglobulin, hepatitis B and C antibodies. However, her cytoplasmic antineutrophilic cytoplasmic antibody (c-ANCA) was detected with a positive serine protease-3 (PR-3) antibody of 23 U (normal: 0–20). An erythrocyte sedimentation rate and C-reactive protein level were 134 mm/h and 8.9 mg/dl, respectively. Complement levels were normal. A spot urine protein to creatinine ratio was 0.12. A chest radiograph revealed a nodular opacity in the right costophrenic angle and underneath the left anterior second rib. Subsequently, the patient underwent sinonasal biopsies that showed acute and chronic sinusitis with moderate eosinophilia and squamous metaplasia. To minimize any radiation exposure to the fetus, no further imaging studies were obtained at that time.

The diagnosis of Wegener's granulomatosis was undertaken, and the patient was treated with oral prednisone 1 mg/kg daily and 400 mg/kg of IVIG daily for 5 consecutive days in her 29th week of pregnancy, as the patient and her physicians wanted to avoid cyclophosphamide due to potential side effects. Given the patient's clinical deterioration and desire to avoid cyclophosphamide, both IVIG and steroids were used at the same time to maximize the chance of rapid induction. The dosage of IVIG was chosen as per the previous case report by Bellisai et al. [1]. During her hospitalization, the high-risk obstetric team monitored her fetus carefully. Soon after starting the treatment, her skin lesions improved significantly. She did not develop any more new skin lesions either. During her 34th week of pregnancy, a second course of IVIG (400 mg/kg) for 3 consecutive days was given to achieve the remission. Bellisai et al. also used a monthly IVIG of 400 mg/kg to maintain the remission of WG in their case. Prednisone was gradually tapered down to 0.7 mg/kg a day. Her skin ulcers continued to improve. At 37 weeks' gestation, she gave birth to a healthy baby girl weighing 2.99 kg after an induced vaginal delivery due to decreased amniotic fluid. Within 2 months of initiating treatment with high-dose steroid and IVIG, all her deep ulcerated skin lesions were healed with some scarring (Fig. 2), and the c-ANCA became negative. The pulmonary nodules seen in the initial chest X-ray also disappeared on the follow-up chest radiograph obtained after delivery.

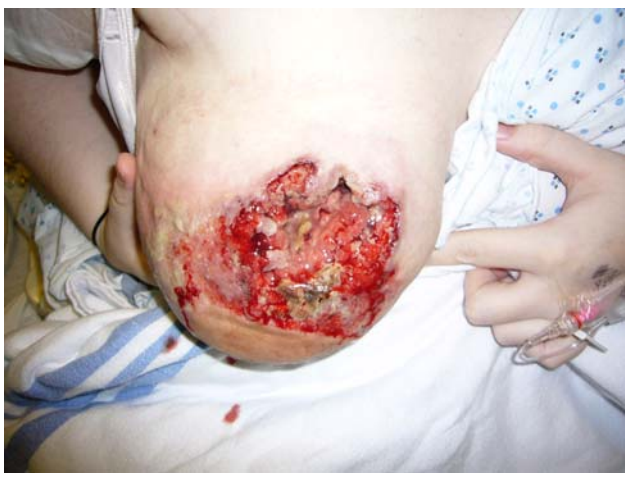

Fig. 1 At 29 weeks of gestation

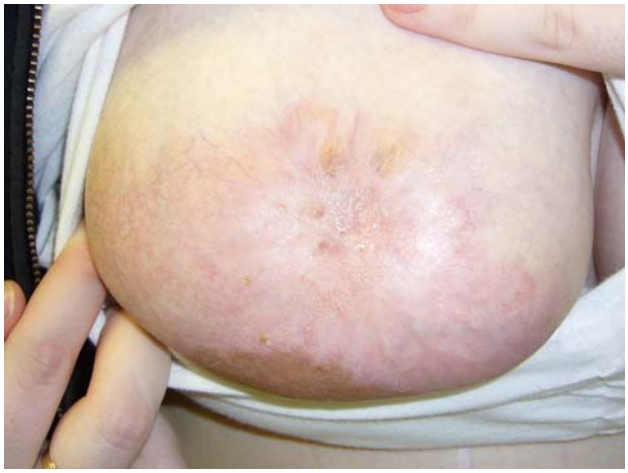

Fig. 2 At 2 weeks after delivery

Discussion

In the existing literature, there are six reported de novo cases of symptoms of WG that were diagnosed and subsequently treated during pregnancy [2–7] (see Table 1). In four of the cases, patients were successfully treated with a combination of corticosteroids and cyclophosphamide during pregnancy (and, in one case, also with hemodialysis), with the delivery of three healthy preterm babies [2, 6] and one full-term baby [7]. However, in cases where corticosteroids were used alone or with only TMP-SMX, the outcomes were not successful. In the fifth case [3], the patient, who presented at 7 weeks' gestation, was treated with prenisolone alone, but she progressed and ultimately had an elective therapeutic abortion in order to initiate cytotoxic treatment with cyclophosphamide. In the

Table 1 De novo cases of Wegener's granulomatosis with pregnancy

Patient	Reference	Age	Sx onset (estimated GA) (weeks)	Organ syst involved	ANCA	Biopsy	Rx	Pregnancy outcome	Outcome for mother
1	Talbot [2]	28	22	UR, LR, skin, renal	NA	Nasal: vasculitis, giant cells	Pred + CYC	26-week GA by LMP, 28 weeks by Dubowitz, mild respiratory distress but otherwise healthy	Progressive improvement
2	Palit [3]	24	7	LR	Strong +	NA	Pred + CYC	Therapeutic termination with the addition of CYC, CYC changed to AZA 2 years later	Clinical improvement and remission 3 years later
3	Fields [4]	23	17	UR, LR, skin, renal	NA	Nasal: intense vasculitis, granulomas, giant cells	Pred + CYC	33-week GA, healthy	ESRD but resolution of other symptoms
4	Habib [5]	21	18	UR, LR	+	Nasal: multinucleated giant cells, necrotizing angiitis, necrosis	Pred + TMP/SMX Pred + CYC	Therapeutic abortion	Progression of symptoms Clinical and radiographic improvement
5	Luisiri [6]	21	18	UR, LR	Strong +	Nasal: inflammation and necrosis	Pred + CYC	31-week GA, healthy	Clinical improvement
6	Dayoan [7]	20	18	UR, LR	Strong +	Lung: necrotizing and supporative granuloma and granulomatous pneumonitis	Pred + CYC	36-week GA, healthy	Clinical remission

Sx symptoms, *GA* gestational age, *Rx* treatment, *pp* postpartum, *UR* upper respiratory tract, *LR* lower respiratory tract, *NA* not applicable, *Pred* prednisone, *CYC* cyclophosphamide, *AZA* azathioprine, *TMP/SMX* trimethoprim/sulfamethoxazole, *ESRD* end-stage renal disease

sixth case [5], the patient was treated with prednisone and TMP-SMX, but progressed significantly and required therapeutic abortion and treatment with prednisone and cyclophosphamide.

In two cases where corticosteroids were used alone in de novo presentation of WG, therapeutic abortion was ultimately employed with the intention of initiating treatment with cyclophosphamide. Although several of the above cases described successful treatment of WG with combination of corticosteroid and cyclophosphamide, the safety of these drugs is still very worrisome, particularly in pregnancy. Three of the four cases above were associated with premature delivery. In addition, the infertility rate from treatment with cyclophosphamide is up to 50% in women of childbearing age [8].

In the early 1990s, Rossi et al. suggested that IVIG could alter the activity of systemic vasculitis and in vivo by interfering with binding of ANCA to their antigens through idiotypic mechanisms and by inhibiting ANCA-induced neutrophilic activation [9]. In addition, several studies [10–16] on ANCA-associated systemic vasculitis with IVIG therapy supported that IVIG may have some therapeutic benefit in systemic vasculitis including WG. Although IVIG therapy has been safely used to treat a number of other diseases during pregnancy [17], prior to our case there were only three reported cases in the English literature using IVIG to treat pregnant women with WG. The first case [18] described a 32-year-old woman with a twin gestation and a known diagnosis of WG who relapsed during pregnancy. She was treated with high-dose corticosteroid, an increased dose of azathioprine, a 5-day course of plasma exchange followed by 5 days of IVIG. She subsequently achieved remission and had healthy twins via Caesarean section at 31 weeks of gestation. The second case study [1] reported on a 26-year-old woman with corticosteroid- and cyclophosphamide-refractory WG who became pregnant while getting treatment with IVIG. This patient achieved remission of her disease and had a healthy, nearly full-term baby. In the third case [19], a 30-year-old woman was diagnosed with de novo WG during the first trimester of pregnancy. After treatment with IVIG and corticosteroids, she was in remission of WG and delivered a healthy baby girl at 34 weeks. In our case, treatment with IVIG and corticosteroids was associated with significant clinical improvement and the delivery of a healthy, nearly full-term baby girl.

In conclusion, on the basis of this report and a review of the literature, we believe that IVIG therapy can be used as an effective and a safe alternative to cytotoxic therapy for a patient with WG during pregnancy.

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