

Favorable Pregnancy Outcome in a Granulomatosis With Polyangiitis Patient With Renal Insufficiency

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Abstract

To present a case of successful pregnancy outcome in a granulomatosis with polyangiitis (GPA) patient with renal insufficiency. GPA, formerly known as Wegener's granulomatosis, is a rare necrotizing systemic vasculitis, presenting with classical clinical triad of manifestations involving upper and lower airway and glomerulonephritis. An association of Antineutrophil cytoplasmic antibodies with GPA has been established and the antibodies are present in most patients with active disease. Pregnancy with GPA is burdened with the risk of possible maternal and fetal complications, further leading to higher morbidity and mortality rate. Due to sparsity of studies of GPA in pregnancy, management needs to be individualised. Diagnostic workup should include serological markers, radiological and histopathological examination. Cyclophosphamide combined with prednisolone is the standard induction regimen. A 22-year-old woman, multigravida at 35 weeks of gestation was referred to our department owing to 1-year diagnosis of GPA. During active phase, the disease manifested as pneumonia and acute kidney injury and perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCAs) were positive. She received pulse therapy of injection cyclophosphamide and methylprednisolone as induction regimen, followed by tapering doses of oral prednisolone and azathioprine for maintenance therapy. The disease was in remission at the onset of pregnancy but had flare up at 34 - 35 weeks of gestation and she presented with renal dysfunction. Neither the disease nor the treatment adversely affected the pregnancy and she delivered a healthy baby at 37 weeks. The unpredictable disease course and complications at unexpected gestation appears to be a major variable to take into account when assessing the risk of pregnancy with GPA. Early diagnosis, monitoring and timely intervention resulted in favourable pregnancy outcome in our patient.

Keywords: Granulomatosis with polyangiitis; Wegener's granuloma-

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toxic; Granulomatous vasculitis; Microscopic polyangiitis; Antineutrophil cytoplasmic antibodies

Introduction

Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis (WG) is a rare multisystem autoimmune disorder with wide spectrum of manifestations, characterized by necrotizing granulomatous vasculitis of the upper and lower respiratory tract, pauci-immune segmental necrotizing glomerulonephritis, and small vessel vasculitis [1].

The etiology of GPA remains unidentified, however presence of antineutrophil cytoplasmic antibodies (ANCAs) has been established in most patients with active disease and the antibodies are thought to play a role in disease pathogenesis [2]. Treatment consists of immunosuppressive drugs, essentially cyclophosphamide (CYC) in combination with high-dose corticosteroids.

The peak incidence of the disease is in the fourth and fifth decades, and hence the association of GPA with pregnancy is rare [3]. Owing to this rarity, the management in pregnant women often poses a therapeutic challenge, therefore is individualized and the pregnancy outcome is variable.

We reported a case of successful pregnancy outcome in a patient with known GPA.

Case Report

A 22-year-old woman, Gravida 2 Para 1 Living 1 with 35 weeks of gestation with previous one lower segment cesarean section (LSCS) was referred to our department as a case of 35 weeks pregnancy with GPA with nephritic syndrome in remission. Her past history revealed the disease course, which started 1 year back with painless skin lesions (vesicles and papules) over upper and lower limbs, with recurrent bilateral flank pain and occasional episodes of syncopal attack. Further she developed hemoptysis and breathlessness requiring critical care admission at private hospital in Lucknow, India. On evaluation then, revealed presence of hypertension, perinuclear ANCA (P-ANCA) positive, hemoglobin (5.4 g/dL) suggesting severe anemia, her renal func-

Table 1. Definitions for ANCA-Associated Vasculitis

ANCA-associated vasculitis (AAV)	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels, associated with MPO-ANCA or PR3-ANCA. Not all patients have ANCA. Add a prefix indicating ANCA reactivity, e.g., PR3-ANCA, MPO-ANCA, ANCA-negative.
Granulomatosis with polyangiitis (Wegener's granulomatosis)	Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels. Necrotizing glomerulonephritis is common.
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)	Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present.
Microscopic polyangiitis	Necrotizing vasculitis, with few or no immune deposits, predominantly affecting small vessels. Necrotizing arteritis involving small and medium arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.

ANCA: antineutrophil cytoplasmic antibodies; MPO: myeloperoxidase; PR3: proteinase 3.

tion test (RFT) was impaired, chest X-ray showed bilateral pneumonic consolidation, based on above findings, a diagnosis of ANCA-associated vasculitis (AAV) with pneumonia with severe anemia with acute kidney injury was made. The skin lesion was biopsied too, the histopathology however, had no features of vasculitis. The induction therapy commenced with intravenous pulse administration of CYC and methylprednisolone. In addition, she was also started on antihypertensive therapy with tablet amlodipine and losartan and received four units of packed cell transfusion. She responded well to the treatment and was discharged on tapering doses of oral prednisolone and maintenance therapy with oral azathioprine (AZA) and antihypertensives to continue. Besides this she also gave history of 6 months of antitubercular (ATT) therapy in view of pulmonary tuberculosis few months before conception. She conceived during remission phase and was continued on AZA and amlodipine. At around 30 - 32 weeks, patient herself stopped AZA and Amlodipine. Later at 35 weeks, she was referred to All India Institute of Medical Sciences (AIIMS) nephrology department in view of nephritic syndrome, and AZA was restarted, and she was further referred to our department. She was admitted in view of high-risk pregnancy. All her previous antenatal investigations in the current pregnancy were found to be normal including the anomaly scan. On admission, detailed clinical and laboratory evaluation was done. Her blood pressure was found to be normal. The laboratory evaluation revealed ANCA was negative, RFT values (blood urea nitrogen (BUN) 34 mg/dL, serum creatinine 2.57 mg/dL, urea 52 mg/dL, uric acid 8.3 mg/dL, urine albumin to creatinine ratio (ACR) 1,525.76, urine creatinine 21.19 mg/dL and urine microalbumin 323.52 mg/L. Fundoscopy revealed normal finding, ultrasound was suggestive of fetal growth restriction (FGR) and abnormal umbilical Doppler changes. The pregnancy was terminated at 37 weeks owing to worsening renal function (on serial RFT) with previous LSCS with FGR with delivery of an alive healthy female baby of birth weight 2.05 kg with Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score of 10 in 1 min and 5 min. She remained in remission in her post-partum period and was discharged on maintenance therapy with oral AZA in consultation with

nephrologist. At Present, both the mother and the baby are doing well.

Discussion

The vasculitides are a diverse group of conditions with a wide scale of presentation. The AAV are three separate conditions: GPA, microscopic polyangiitis (MPA), and eosinophilic GPA (EGPA; previously known as Churg-Strauss syndrome) [1].

Definitions for the AAV were described at the Chapel Hill Consensus Conference (CHCC) in 1994 and were revised in 2012 (Table 1) [1]. The Chapel Hill group states that the CHCC is a nomenclature system and not a set of classification or diagnostic criteria [1].

GPA is now a well-recognized clinical entity in India. Prevalence among female population has been seen in the Indian scenario [4].

The diagnosis of GPA is made on the basis of American College of Rheumatology criteria and recently, a modified class which, in addition to the original four criteria (nasal or oral inflammation, an abnormal chest radiograph, urinary sediment and granulomatous inflammation on biopsy) also incorporates a positive serum enzyme immunoassay for antibodies to proteinase-3. Diagnosis can be made if at least two of these five criteria are present [4]. The typical clinical triad described in the literature comprises of upper airway involvement (sinusitis, otitis, nasal mucosa ulcers, bone deformities, and subglottic stenosis), lower respiratory tract involvement (cough, chest pain, hemoptysis), and glomerulonephritis [5].

The vasculitis study group describes the different stages of the disease based on clinical and pathologic criteria (Table 2) [1].

Typically, the course of the disease progresses from localized to generalized, and this progression may take from weeks to years. On the basis of above classification, we can consider our case to be in severe stage with renal involvement.

ANCA are a sensitive and specific marker for ANCA-associated systemic vasculitis. Using indirect immunofluorescence on ethanol-fixed neutrophils, two prime fluorescent

Table 2. Stages of Disease Based on Clinical and Pathologic Criteria

Stage	Features
Limited	Disease localized to the upper airways, no systemic symptoms, no threatened organ function, no renal involvement
Early generalized	Constitutional symptoms, no threatened organ function
Active generalized	Constitutional symptoms with threatened organ function
Severe	Severe renal involvement, life-threatening disease
Refractory	Progressive disease that is unresponsive to therapy

patterns can be identified: a diffuse cytoplasmic staining (C-ANCA), and a perinuclear/nuclear staining (P-ANCA) [6]. Although these patterns are not disease specific but preferential association has been seen between C-ANCA and GPA, whereas P-ANCA was associated more commonly with MPA, idiopathic necrotizing crescentic glomerulonephritis (iNCGN) and EGPA. ANCA levels are useful to monitor disease activity. A significant rise in titers, or the reappearance of ANCA, should warn the clinicians and lead to more intense patient monitoring.

India being a country with highest burden of tuberculosis, GPA used to masquerade as drug-resistant tuberculosis. It has been observed in previous publications that around 40% of patients were initially mistaken for tuberculosis and treated for the same [4]. This diagnostic error is reduced to 20% owing to better understanding about GPA and outspread availability of ANCA test [4]. Histological affirmation of granulomatous vasculitis still being the gold standard for diagnosis, a positive ANCA result often abolishes the need for invasive procedures like lung biopsy [4].

Cutaneous lesions are found in 50% of patients but may be the presenting symptoms in up to 10% of case [7]. Cutaneous vasculitis secondary to GPA can present as palpable purpura, papules, nodules, ulcers mimicking pyoderma gangrenosum, or necrotizing lesions leading to gangrene. There is no single lesion specifically associated with the disease [8]. Skin lesions are usually indicative of an active systemic disease. They can manifest on the face, upper extremities, and the extensor surfaces of the joints, but are typically located on the lower extremities. Oral and nasal ulcerations may also occur. Dermatologic manifestations may be treated with topical steroid. Surgery is only required in cases of severe tissue damage due to fibrosis or necrosis [9]. In our case, the disease started as multiple painless pin head sized skin lesions (vesicles and papules) over upper and lower limbs which later increased in size (approximately 5 × 5 cm), became ulcerated and healed on its own, forming scar.

Pulmonary involvement was seen in 49-84% of cases manifesting as cough, hemoptysis and dyspnea. Pulmonary nodules are the most common chest radiographic manifestation of GPA; occurring in 40-70% of cases. Cavitations occur in approximately 25%. Lung ground-glass attenuation and consolidation often occur in up to 50% of patients with active GPA, these are mostly the consequences of alveolar hemorrhage, although pulmonary edema secondary to renal involvement may also occur [10]. Lung consolidation is often observed in pneumonia, but GPA should be kept in mind in cases of consolidation that are persistent and resistant to treatment

[5]. Other less common pulmonary manifestations include atelectasis and reticular interstitial opacities. Pleural effusion is a rare finding and if present, is exudative in nature. Diffuse alveolar hemorrhage was noticed in a few cases.

In our case, during the active phase of disease, patient had few episodes of hemoptysis and breathing difficulties, chest X-ray showed multiple scattered radio-opaque shadows in bilateral lung fields suggestive of patchy pneumonic consolidation and homogenous opacities in bilateral lung fields suggestive of pulmonary edema. High-resolution computed tomography showed ground glass opacities in bilateral lung fields involving all segments with interlobular septal thickening suggestive of organizing pneumonia. She was admitted under intensive care unit, supportive management was given, received pulse therapy of injection methyl prednisolone 500 mg for 3 days and injection CYC 500 mg for two doses, given 2 weeks apart, to which the patient responded well and was discharged on oral AZA and prednisolone on tapering doses.

Anemia is a common complication of patients with ANCA-associated renal vasculitis. The causes can be multifactorial which include impaired renal function, malnutrition, iron deficiency, alveolar hemorrhage, the use of immunosuppressive drugs and frequent in-hospital phlebotomies [11]. Our patient gives history of multiple blood transfusions in the past and her current blood picture was suggestive of mild anemia (hemoglobin 8.5 g/dL), peripheral examination was suggestive of dimorphic anemia. She received one unit of packed cell transfusion in view of anticipated surgical blood loss.

Glomerulonephritis (GN) occurs in 70-85% of GPA patients during the disease course, but renal insufficiency (serum creatinine > 2.0 mg/dL) occurs in only 11-17% of patients at presentation [12]. On renal biopsy, the characteristic renal lesion seen in cases of GPA is segmental focal GN. Immune complexes are absent or infrequent, consistent with "pauci-immune GN" [12]. Our patient had history of acute kidney injury one year preceding the index pregnancy and received treatment for the same. She had been referred to our department in view of pregnancy with disease flare up, presenting as renal dysfunction. Her RFT was found to be impaired. Further testing showed worsening of renal parameters and the decision for LSCS was made.

Pregnancies occurring in active disease or pregnancies complicated by new-onset disease or recurrent disease have a documented unfavorable maternal and perinatal outcome. However, pregnancies occurring during remission also seem to be associated with increased risk of complications.

Disease activity can be assessed according to Birmingham Vasculitis Activity Score (BVAS), which scores nine organ

systems for new or worse vasculitic findings [13]. Remission is defined as BVAS < 1 for > 6 month on prednisolone \leq 10 mg per day. Remission could be either “on drug” or “drug-free”. Remission in GPA was a rarity until the introduction of regimens combining oral CYC with steroids. Although this combination increased the survival rates, yet the drug toxicity remained a vital challenge in management.

After successful remission induction, guidelines recommend removing the initial immunosuppressive agent and starting a maintenance regimen with either AZA or methotrexate (MTX) [1]. CYC is no longer recommended for maintenance of remission. Early cessation of therapy (< 1 year) is associated with an increased risk of relapse. It is advisable to continue the maintenance therapy for at least 18 - 24 months before being gradually withdrawn.

Rituximab (RTX), a chimeric cluster of differentiation 20 (CD20) monoclonal antibody has also been used for induction of remission in GPA. Other indications for its use include GPA refractory to CYC and unacceptable risk of gonadotoxicity with CYC in reproductive age group. RTX, in fact, has been shown to give excellent results in induction therapy of GPA [14].

GPA is well-known for frequent relapses. British Society of Rheumatology defines relapse as a disease that has been previously well controlled with or without drugs and has become active. Relapse is further classified as “minor” if there is increase of one or more new or worse minor items and no major BVAS items. Major relapse involves increase of one or more major BVAS item [15]. RTX has shown an adequate response in treatment of relapses.

Conclusions

Pregnancy in patients with GPA requires preconceptional planning, careful clinical judgment, and vigorous treatment of active disease. The best time to plan conception is a minimum of six months after entering remission. A multidisciplinary approach is necessary for the diagnosis and therapeutic treatment of GPA. Multiple relapses also occur in some patients. Substantial organ damage due to disease complications and adverse effects of treatment is known to occur, leading to long-term sequelae.

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None to declare.

Conflict of Interest

The authors declare that they have no conflict of interest.

Informed Consent

Informed consent was obtained from the patient.

Author Contributions

All the authors are involved in conceptualizing and designing the study. AV, SR, and SP contributed to the literature search, clinical studies, and manuscript preparation. AV, SR, PT, and SA edited and reviewed the manuscript. AV is the guarantor of the study.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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