DIAGNOSIS OF CHURG-STRAUSS SYNDROME AT 23 WEEKS GESTATION: A CASE REPORT

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ABSTRACT Introduction: Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg Strauss syndrome (CCS) is an extremely rare diagnosis and much less frequently in the childbearing period, particularly in association with pregnancy. This is thought to be due to several considerations, including the paucity of the condition, with the mean age of diagnosis approximately 40s-50s and male gender tendency. In addition, the ambiguity and diversity of clinical manifestations result in delayed diagnosis, aggressive course and a high mortality rate. **Case report:** We report a case of a 28-year-old Palestinian woman primigravida at 23 weeks' gestation who was admitted to the hospital due to acute asthma exacerbation symptoms associated with markedly elevated eosinophilic count and rash. Diagnosis of Churg Strauss syndrome was established as the first reported case of the condition in Palestine, and steroidal medication was initiated with remarkable responsiveness to the regimen. The pregnancy was complicated with intrauterine fetal growth restriction (IUGR) terminated by cesarean delivery of a healthy baby at 32. **Conclusion:** There is no obvious mechanism by which this type of vasculitis affects the pregnancy and vice versa, and it is evident that the risk of obstetric complications, for instance, intrauterine fetal demise, miscarriage, premature rupture of membrane, and intrauterine fetal growth restriction (IUGR) - as in this case-is significantly escalated during the disease. This case also suggests that pregnancy can accelerate the disease process.

KEYWORDS eosinophilic granulomatosis with polyangiitis, Churg-Strauss syndrome, pregnancy, intrauterine fetal growth restriction

Introduction

Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg Strauss syndrome (CSS), is a distinct subtype of the family of diseases marked by systemic necrotizing vasculitis of small-medium sized blood vessels[1]. This category of vasculitis involves eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA), and polyarteritis nodosa (PAN). The fundamental distinction of Churg Strauss syndrome from other conditions in this category is the coexistence of peripheral eosinophilia, asthma and rhinosinusitis[2]. Churg-Strauss syndrome was firstly identified in 1951 by Churg and Strauss[3]. CSS is an uncommon disease with an estimated overall incidence of 1-4 cases per million population and a mean age of roughly 40 years[4]. Clinical features primarily diagnose this syndrome with support of laboratory findings, including allergic rhinitis, asthma, and hyper-eosinophilia. The exact pathogenesis of the disease is still unclear but largely attributed to Anti-Neutrophil Cytoplasmatic Antibodies (ANCA) evolved against breathed pathogens[5].

The Churg-Strauss syndrome is extremely rare in women of childbearing age and much rarer in pregnancy, with a vague correlation between both diagnoses. This is the first reported case in Palestine, and there are only 4 reported cases in which the onset of CSS was during the pregnancy, according to[6]. We introduce a young woman who developed this syndrome associated with pregnancy as the first documented case of the

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condition in Palestine, and prednisolone is being used to control CSS.

Case report

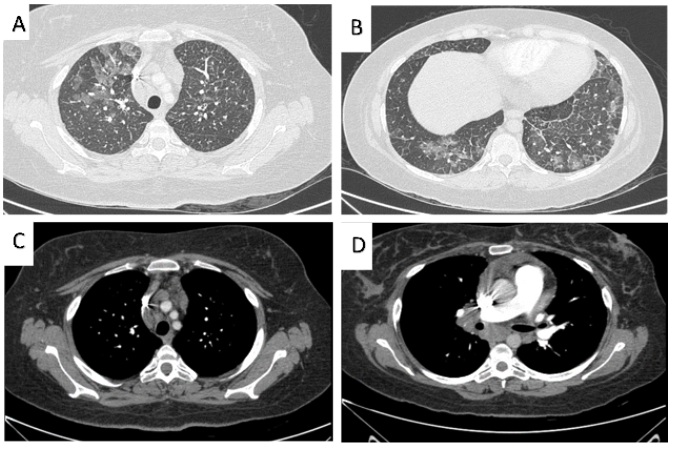
D.J., a 28-year-old primigravida, housewife, Palestinian woman, at 23+5 weeks gestation, was admitted to the hospital on March 22, 2021, complaining of chest pain radiating to the left arm, palpitation, shortness of breath, and dry cough associated with generalized weakness and itchiness mainly on palms and soles without any visible rash. The patient had had bronchial asthma 2 years ago and was treated with a $\beta 2$ agonist. Physical examination on admission showed a severely ill, tachypneic, hypotensive and afebrile patient with bilateral crepitation and lower limb oedema. Gynecologic and obstetric assessment revealed no abdominal pain, vaginal bleeding, leakage of fluid, abnormal discharge, or cramping, and the uterus is nontender. The cervix is closed with an intact membrane. The fundal height is 23 cm. Pelvic ultrasonography revealed a viable single intrauterine fetus measuring 23 weeks gestation, estimated fetal weight of 770 gm, and average amniotic fluid Doppler was normal. Fetal heart rate tracing shows a baseline of 145/min, moderate variability, multiple accelerations, and no decelerations.

Laboratory findings disclosed haemoglobin of 9.2 g/dl, white blood cell count of 14,000/mm 3, eosinophilia of 40%, IgE of 2934 U/ml, C-reactive protein of 16 mg/dL, urinalysis showed asymptomatic bacteriuria. C-ANCA, P-ANCA and ENA antibodies were negative, cardiac enzymes were within normal values, and liver and renal tests were unremarkable (Table 1). Computed tomography of the chest showed diffuse patchy areas of ground glass and faint opacities seen mainly in the right upper lung lobe, marked bilateral interlobular septal thickening in the lower lung lobes, significant enlargement of multiple mediastinal and hilar lymph nodes with the largest one measuring 25*34 mm and mild pericardial effusion (Figure 1). After two days, the patient developed purpuric rash on her back and both feet (Figure 4A, B). Skin biopsy from the affected area illustrated necrotizing vasculitis with extravascular eosinophilic-rich inflammation (Figures 2 and 3); bone marrow biopsy was normal. The stool specimen was positive for occult blood, indicating intestinal bleeding due to vasculitis. The diagnosis of Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg-Strauss syndrome (CSS), has been established based on clinical manifestation and laboratory data, including bronchial asthma, hyper-eosinophilia with biopsy results. The patient was admitted to ICU to initiate her therapy plan with appropriate fetal surveillance. The patient was prescribed prednisolone 60 mg/day with minimal improvement. That is why the cyclophosphamide regimen was discussed with the patient and her family, clarifying all potential adverse effects of the medication though cyclophosphamide was not initiated. Pregnancy was moving straight forward without any significant fetal influence until 31+2 weeks gestation. The fetal movement had been significantly decreased with head circumference (HC) and biparietal diameter (BPD) correlating with 27 weeks gestation. Intrauterine growth restriction (IUGR) was recognized with an estimated fetal weight of 1400 gm. However, the pregnancy was terminated by cesarean section (CS). One day post-operative, the patient returned to the intensive care unit (ICU) and got her first dose of cyclophosphamide (1000 mg IV infusion in 500 ml NS 0.9% over 1 hour), resulting in a significant improvement. On May 21, 2021, she was discharged on scheduled doses of cyclophosphamide, which were once monthly, and the dose of prednisolone was gradually tapered. The patient got six doses of cyclophosphamide, but unfortunately, she died on January 9, 2022.

(Table 1) Laboratory Data

Complete blood count (CBC)		Albumin	3.30 g/dl
▪ Hemoglobin	9.2 g/dl	BUN	5.6 mg/dl
▪ Hematocrit	30.2 %	Creatinine	0.42 mg/dl
▪ Red blood cell	3.68 * 10 µl	hsTnI	3.74 ng/ml
▪ White blood cell	14 * 10^3	Amylase	18 U/L
• Neutrophil	87.9 %	Hb A1c	4.7%
• Lymphocyte	10.2 %	Na^-	134 mg/dl
• Eosinophil	40 %	K^+	3.47 mg/dl
• Monocyte	1.8 %	Cl^-	98.1 mg/dl
• Basophil	0.1%	Mg^{+2}	2 mg/dl
▪ Platelet.	352 * 10^3 µl	Ca^{+2}	8.19 mg/dl
		PO_4	3.2 mg/dl
Erythrocyte sedimentation rate (1 hour) 33 mm		Urinalysis	
C reactive protein	52 mg/dl	Protein	Nill
IgG	1467 mg/dl	Glucose	Nill
IgA	246 mg/dl	RBC	Absent
IgM	123 mg/dl	Cast	Absent
IgE2943 U/ml		Stool occult blood	Negative
RF	Positive		
ANA	Negative	Bronchoalveolar lavage	
Anti-DNA antibody.	Negative	Eosinophils	97%
C-ANCA	Negative	Macrophages	50%
P-ANCA	Negative	Neutrophils	25%
RAST		Lymphocytes	20%
▪ Bacteria (Aspergillus)	+2	Culture	Negative
▪ Yeast (candida)	+2		
Blood chemistry			
▪ Total bilirubin	0.439 mg/dl		
▪ SGOT (AST)	36.6 U/L		
▪ SGPT (ALT)	42.8 U/L		
▪ ALP	80 U/L		
▪ LDH	455 U/L		
▪ GGT	7.4 IU/L		
▪ Total cholesterol	110 mg/dl		

RF: rheumatoid factor, ANA: antinuclear antibody, P-ANCA: perinuclear-antineutrophil cytoplasmic antibody, C-ANCA: cytoplasmic-antineutrophil cytoplasmic antibody, RAST: radioallergosorbent test, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, GGT: gamma-glutamyl transpeptidase, BUN: blood urea nitrogen.



Figures 1(A, B, C, D): figure A: is a CT scan of the chest without contrast showing diffuse patchy areas of ground glass and faint opacities seen mainly in the right upper lung lobe. Figure B: is a CT scan of the chest without contrast showing marked bilateral interlobular septal thickening in the lower lung lobes. Figure C: is a CT scan of the chest with IV contrast showing significant enlargement of multiple mediastinal and hilar lymph nodes, with the largest one measuring 25*34 mm. Figure D: is a CT scan of the chest with IV contrast showing a mild amount of pericardial effusion.

Discussion

Churg-Strauss syndrome (CSS) is a rare multisystem disorder. Worldwide, the estimated prevalence of the disease is 10.7 to 14 per million adults[7, 8]. According to reports, the average age of onset is between 38 and 54 years old, with a median of 40[8]. Since the rarity of this disease, its occurrence during pregnancy considers an exceptional event.

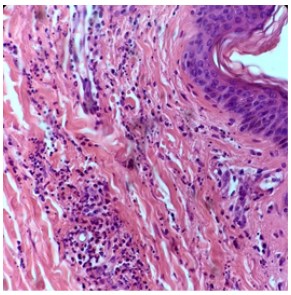


Figure 2: Necrotizing vasculitis with extravascular eosinophil-rich inflammation, fibrinoid necrosis, and fragmented neutrophilic nuclei (leukocytoclasia).

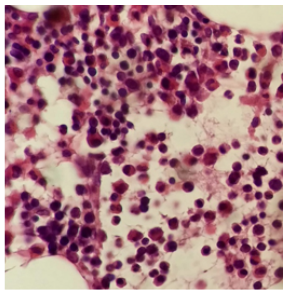
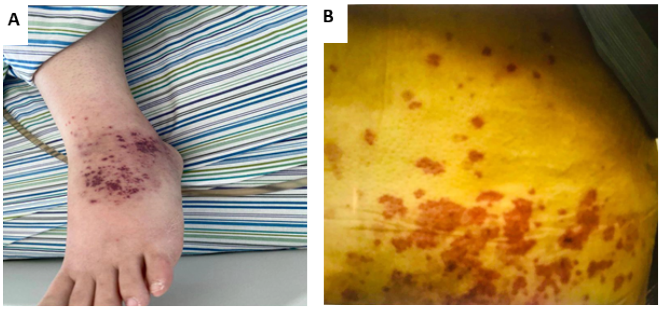


Figure 3: Normocellular bone marrow with left-shifted granulopoiesis and 5% eosinophils.



Figures 4 (A, B): figure A: purpuric skin rash on the left foot. Figure B: purpuric skin rash on the back.

CSS diagnosis is dependent on clinical features rather than histology or lab tests due to the lack of a single diagnostic test. The disorder is categorized into three phases: the prodromal (e.g. consists of asthma preceded by allergic rhinitis), the eosinophilic (e.g., peripheral blood eosinophilia and eosinophilic tissue infiltrate) and the vasculitis phase[8, 9]. These phases may or may not occur in that order. Some people who are affected will not go through all three phases. Other nonspecific laboratory findings, including elevated serum IgE, are detected in 75% of patients. In around 40% of cases, ANCA positivity in CSS, elevated ESR, CRP, and normocytic normochromic anaemia, and extrapulmonary rheumatoid factor in 60% of patients[8, 10].

Our patient suffered from bronchial asthma since the age of 26 and was diagnosed with CSS during her first pregnancy at 23rd weeks of gestation. CSS is diagnosed when 4 of 6 criteria are fulfilled according to ACR classification[9], and this case meets 4 of these 6 criteria, which are asthma, eosinophils >10% (Table 1), nonfixed pulmonary infiltrates as shown in CT(Figure1). Biopsy illustrated necrotizing vasculitis with extravascular eosinophilic-rich inflammation. However, neurological involvement is not found in our patients in contrast to previously reported cases[6, 11].

Although delivery might be one of the triggers of CSS, four cases have been reported with the onset of disease during pregnancy as our case[6, 12]. The fetal outcomes include intrauterine fetal death, spontaneous abortion, intrauterine growth restriction, preterm delivery and prelabor rupture of membranes[6]. In our case, intrauterine growth restriction (IUGR) with the estimated fetal weight of 1400 gm and preterm delivery (at 31+2 weeks via CS) was recognized.

The treatment of severe ANCA-associated vasculitides is divided into two phases: remission induction therapy, which uses a combination of glucocorticoids and another immunosuppressive agent, and once remission is achieved, maintenance therapy is needed. Pregnancy in these patients poses a significant therapeutic challenge[13]. Our patient was prescribed prednisolone 60 mg/day without significantly improving the symptoms, but she ended with the delivery of a healthy baby who is now 8 months old. Moreover, both the mother and the fetus may benefit from steroid medication.

Conclusion

Pregnancy can exacerbate Churg-Strauss syndrome, which can be harmful to both the mother and the fetus. Therefore, it is important to inform patients affected by CSS about the risk of pregnancy. However, a successful outcome can be achieved if well controlled before and during pregnancy, as in our patient.

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Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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