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Pregnancy-Induced Leukocytosis: Case report.

Running title: Pregnancy-Induced Leukocytosis

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Abstract

BACKGROUND

Pregnancy is a complex physiological process. Physiological leukocytosis occurs often and is mainly associated with increased neutrophil counts, especially in the third trimester of pregnancy. Non-congenital leukocytosis with white blood cell (WBC) counts above 20×10^9 per L lasting 13 weeks during pregnancy is rare and has been reported occasionally. Herein, we present a case of pregnancy-induced leukocytosis.

CASE SUMMARY

We present the case of a 33-year-old Chinese woman at 27 weeks of gestation who had leukocytosis complication. No abnormalities were detected in the examinations before pregnancy or in the first trimester. From the third trimester of pregnancy, the patient began to suffer from asymptomatic leukocytosis. We administered antibiotics to treat the patient; however, the complication persisted until the patient underwent a cesarean section after 40^{+3} weeks of gestation. One day after the cesarean section, the patient's neutrophil count returned normal. After two years of follow-up, we found that the patient and baby were healthy.

CONCLUSION

Pregnancy-induced leukocytosis seems to be associated with immunoregulation, and the pregnancy termination may be the effective treatment approach for pregnancies complicated with leukocytosis.

Keywords: leukocytosis, pregnancy, in vitro fertilization, case report

Core Tip: Physiological leukocytosis often occurs and is mainly associated with increased neutrophil levels. We present the case of a Chinese woman in her 27th week of gestation who had the complication of leukocytosis with white blood cell count above 20×10^9 per L for13 weeks. One day after a cesarean section, the patient's neutrophil levels returned to normal. After two years of follow-up, the patient and baby were found to be healthy. During

pregnancy, asymptomatic leukocytosis appears to be related to immunoregulation, and the termination of pregnancy may be an effective treatment approach in pregnancies with leukocytosis.

INTRODUCTION

It is a complex physiological process[1]. The normal range of WBC counts changes with age and pregnancy[2, 3]. In pregnant women, local adaptation of the maternal immune system enables the successful coexistence of the mother and fetus/placenta[4]. Physiological leukocytosis (3.5-9.5× 10^9 per L) has a high incidence and is mainly associated with the increased circulation of neutrophils (1.8-6.3× 10^9 per L), especially during the last trimester of pregnancy[5]. It is important for clinicians to distinguish between malignant and non-malignant causes and to identify the most common causes of non-malignant leukocytosis. During pregnancy, the normal WBC count increases gradually (third trimester 95% upper limit = 13.2 × 10^9 per L; 99% upper limit = 15.9 × 10^9 per L)[6]. Leukocytosis is similar in several non-obstetrical cases, such as infections, allergic reactions, malignances, surgery[7], traumas[8], and strenuous physical activities[9]. For pregnant and parturient women, an increased white blood cell count may also be related to gestational and puerperal infections such as endometritis[10] and chorioamnionitis[11]. Other factors that affect WBC count include smoking[12], race[13], and body mass index (BMI)14. Leukocytosis is a common symptom of infections, especially bacterial infections, and physicians should be encouraged to recognize other signs and symptoms of infections. Chorioamnionitis, defined as the inflammation of fetal membranes after 20 weeks of gestation, is one of the main causes of perinatal morbidity and mortality[15]. The traditional diagnostic criteria for clinical chorioamnionitis are fever and at least two of the following: maternal tachycardia, maternal leukocytosis (maternal WBC > 15,000 in the absence of corticosteroids), uterine tenderness, fetal tachycardia (> 160 bpm for 10 minutes or longer), and foul-smelling amniotic fluid[16,17].

Non-congenital leukocytosis with WBC counts above 20 × 10^9 per L for 13 weeks during pregnancy is rare and has been reported occasionally. Herein, we present the case of gestation-induced leukocytosis.

CASE PRESENTATION

Chief complaints

A 33-year-old woman presented to the emergency department with a complaint of high blood pressure for 6 weeks and leukocytosis for 13 weeks.

History of present illness

Patient's leukocytosis had been for 13 weeks, as at the time she presented to the emergency department. For her first implantation failure, she took aspirin enteric-coated tablets 75 mg a day, 5 mg acetate orally once a day, and one vitamin complex tablet a day until 12 weeks of gestation. During her pregnancy, repeated routine blood tests before 20 weeks of gestation showed that the white blood cell and neutrophil counts were within the normal range. Ultrasonography suggested a postplacental hematoma with a diameter of approximately 20-30 mm before 20 weeks of gestation, which disappeared thereafter. At 27 weeks of gestation, the white blood cell rose to 23.73×10^9 per L and the neutrophil count rose to 20.74×10^9 per L (Figure 1).

History of past illness

The patient was diagnosed with polycystic ovarian syndrome (PCOS) and her partner was diagnosed with male factor infertility. The patient had no known allergies to food or medication. In addition, she denied any family history or history of sexually transmitted infections. The patient was an employee of an Internet company, did not smoke, and were not exposed to second-hand smoking during pregnancy.

Physical examination

At the initial inspection, the patient had a blood pressure of 126/87 mmHg and pulse rate of 68 beats per minute. The patient's lungs were clear and she had normal heart sounds with no murmurs on auscultation.

Laboratory examinations

At 27 weeks of gestation, blood analysis revealed leukocytosis of 23.73× 10^9 per L, with predominantly neutrophils (87.4%) with normal hematocrit and platelet count, and the neutrophil count rose to 20.74×10^9 per L (Figure 1). C-reactive protein count was 0.52＜0.8）mg/dl, erythrocyte sedimentation rate was 30（0-20）mm/h, and procalcitonin （PCT） count was ＜0.05 （＜ 0.5 ） ng/ml，which showed no sign of infection.

Methods

The manuscript is a case report and meets the requirements of biostatistics.

FINAL DIAGNOSIS

The final diagnosis of the case is asymptomatic leukocytosis.

TREATMENT

The patient had no fever, and had a normal temperature. In addition, there was no presence of other symptoms, including cough, expectoration, oral ulcers, and shivering. She was administered antibiotic treatment for two weeks, which did not work. Afterward, the patient visited several other hospitals; during this time, routine blood tests showed a sustained high level of white blood cell and neutrophil counts. The patient visited the outpatient department of our institution because of infection. C-reactive protein count was 0.52 mg/dl, the erythrocyte sedimentation rate were 30 mm/h, and PCT count was ＜ 0.05 ng/ml，which showed no sign of infection. Thereafter, the patient visited the outpatient hematology department. The patient refused a bone marrow biopsy. Peripheral blood smear showed that mature neutrophils accounted for 73.2%, and the count of immature granulocytes was 0.95×10^9 per L, accounting for 3.7%. Tests at another hospital showed leukocytosis, but normal levels of red blood cells and megakaryocytes. The patient was hospitalized with elevated blood pressure at 40^{+3} weeks of gestation. At admission, the white blood cell count was 20.09 × 10^9 per L, neutrophil granulocyte count was 15.3 × 10^9 per L, blood platelet count was 343 × 10^9 per

L, and hemoglobin concentration was 140 g/L. The next day, she underwent a cesarean section because of fetal distress. The surgery was successful. The first postoperative day, white blood cell count was 14.71× 10^9 per L, neutrophil granulocyte count was 11.26×10^9 per L, hemoglobin concentration was 124 g/L, and counts of platelet were 304×10^9 per L. Thyroid function tests were within the normal range; free Thyroxine was 16.27 pmol/L and thyrotropin was 1.16 uIU/ml. Ultrasonography of the fetus, abdomen, lower limb arteries, and deep veins showed that all the tested areas were normal. Ultrasonography of the urine showed a right kidney seeper with a renal pelvis approximately 1.1 cm wide. Tests for immunoglobulin M (IgM) against Toxoplasma, IgM against rubella virus, and IgM against cytomegalovirus, herpes simplex type I virus, and herpes simplex type II virus were negative. Tests for hepatitis, human immunodeficiency virus, and Treponema pallidum were negative. By 34 weeks, blood pressure had risen to a range of 138/80 mmHg and 142/90 mmHg , and the patient was diagnosed with pregnancy-induced suspicious hypertension without medication. During 40^{+3} weeks of gestation, she underwent a cesarean section because her blood pressure had increased to 143/90 mmHg. Six weeks postpartum, the patient's blood pressure gradually returned to normal.

OUTCOME AND FOLLOW-UP

Postoperatively, neutrophil granulocytes returned to normal levels. The patient delivered a live, healthy, full-term baby via a cesarean section. After two years of follow-up, the patient and baby were found to be healthy.

DISCUSSION

Hematological diseases in pregnancy should be meticulously managed with multidisciplinary cooperation, including obstetrics and hematology. Distinguishing between reactive and malignant lymphocytosis is challenging and may vary with age and other demographics. Table 1 lists the most common etiologies[18]. The patient did not suffer from allergic reactions, malignancy, surgery, trauma, strenuous physical activity, or smoking; in

addition, the patient had no fever, had normal temperature, experienced no other symptoms such as cough, expectoration, oral ulcers, or shivering. The patient visited the outpatient department for the complaint of an infection. C-reactive protein count was 0.52 mg/dl, erythrocyte sedimentation rate was 30 mm/h, and PCT count was ＜ 0.05 ng/ml，which showed no sign of infection. A peripheral blood smear showed that mature neutrophils accounted for 73.2%, and immature granulocytes count was 0.95×109 per L, accounting for 3.7%. Tests at another hospital showed leukocytosis, but normal levels of red blood cells and megakaryocytes. Six weeks postpartum, the patient's blood pressure gradually returned to normal, which illustrated that it was hardly malignant. Molberg et al. found that the average WBC count in a laboring patient was 12.45× 10^9 per L, with a range of 4.4 × 10^9 per L to 29.1× 10^9 per L. WBC in patients with postpartum complications was similar to that in patients without complications (12.9 × 10^9 per L vs 12.3 × 10^9 per L, p = 0.449)[19]. We describe a case of asymptomatic leukocytosis with WBC counts > 20 × 10^9 per L during pregnancy. The patient did not suffer from leukocytosis until 27 weeks of gestation; after cesarean section, white blood cell and granulocyte counts dropped to normal levels. Levothyroxine sodium is safe for pregnant women, and there is no evidence that its side effects include leukocytosis[20]. At the same time, there was no obvious evidence that hypothyroidism caused leukocytosis, and the patient had no history of using cytotoxic drugs or other medications that explicitly caused leukocytosis. Therefore, we believe that drug-induced leukocytosis was less likely in this case.

There are a few reports on leukocyte counts and differentials related to the severity of pregnancy-induced hypertension. Canzoneri et al.[21] assessed the difference in leukocyte counts between normal pregnancies and pregnancies complicated by preeclampsia (PE). In a retrospective study of 240 women, women with severe PE had a significantly higher white blood cell count than those with mild PE and normal pregnancy controls (10.66 +/- 3.70

versus 9.47 +/- 2.59 and 8.55 +/- 1.93 ($\times 10^9$ per L) [$p < 0.0001$]). The increase in the total white blood cell count was mainly due to an increase in the number of neutrophils (8.05 +/- 4.01 [severe] versus 6.69 +/- 2.23 [mild] and 5.90 +/- 1.79 (controls)($\times 10^9$ per L) [$p < 0.0001$]). Terrone et al.[12] evaluated the total WBC count of 86 patients with severe preeclampsia with and without hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome of 91 patients. The WBC counts in patients with HELLP syndrome (12.5 +/- .442$\times 10^9$ per L) were significantly higher than those in patients with severe preeclampsia (10.3 +/- .288$\times 10^9$ per L). The patient was diagnosed with hypertension during pregnancy, without preeclampsia. Furthermore, the counts of white blood cells were above 20 × 10^9 per L. Leukocytosis may have had nothing to do with hypertension in this case.

There have been few reports on the relationship between leukocytosis and in vitro fertilization and embryo transfer (IVF). Ludwig et al.[22] observed the effects of a luteinizing hormone-releasing hormone antagonist protocol (Cetrorelix) and the administration of recombinant follicle-stimulating hormone (FSH) on the development of leukocytosis compared to the administration of urinary human menopausal gonadotropin. Thirty patients underwent IVF/intracytoplasmic sperm injection treatment after controlled ovarian stimulation using a multiple dose protocol and the luteinizing hormone releasing hormone (LHRH) antagonist Cetrorelix, and no significant leukocytosis was discovered after controlled ovarian stimulation using the LHRH antagonist Cetrorelix and recFSH.

During pregnancy, the integration and balance of these immune factors produce an environment that allows the fetus to escape rejection by the maternal immune system. Multiple mechanisms influence the maternal immune system in accepting semiallogeneic fetal tissues during pregnancy[23]. Female sex hormones affect many immune pathways more often during pregnancy.

Limitations

In summary, the etiology and mechanism of this phenomenon remain largely unknown. In addition, during pregnancy, asymptomatic leukocytosis seems to be related to immunosuppression induced by immunoregulation. The termination of pregnancy may be effective in pregnancies complicated with leukocytosis; however, further studies are needed to confirm this.

CONCLUSION

Thus, we conclude that leukocytosis seems to be associated with the pregnancy itself associated with immunoregulations. Although this study presents a case of leukocytosis without evidence of clinical infection, caution should be exercised when applying these data clinically. We suggest that pregnancy termination may be a therapeutic approach for pregnancies complicated with leukocytosis.

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