CASE REPORTS
PRIKAZI SLUČAJEVA

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Summary
Introduction. Warm autoimmune hemolytic anemia is the presence of warm autoantibodies against red blood cell with or without complement activation. The presence of warm autoantibodies on the red blood cells is detected by direct antiglobulin test with polyclonal and immunoglobulin G reagents. Antibodies removed from the red blood cells tested by indirect antiglobulin test show panagglutination with a panel of red blood cells. Case Report. We report a rare case of idiopathic warm autoimmune hemolytic anemia in a 26-year-old woman in the early pregnancy. Warm autoimmune hemolytic anemia was mild, so during monitoring the risk to the fetus was assessed as low. The fetal status was assessed every four weeks. The noninvasive Doppler examination of the fetal middle cerebral artery revealed no fetal anemia. The last control before childbirth was done in the 38 week of pregnancy and the fetal direct antiglobulin test was 4+ and indirect antiglobulin test was 2+. The newborn presented with warm autoantibody immunoglobulin G, and positive direct antiglobulin test (3+). The infant was breastfed for nine months after birth. The direct antiglobulin tests were positive (3+) in both mother and child over the following 12 months. Conclusion. In case of warm autoimmune hemolytic anemia, the main purpose is to stop hemolysis and correct anemia in pregnant women, but it is also necessary to monitor the fetal condition in order to detect fetal hemolytic anemia as early as possible.

Key words: Anemia, Hemolytic, Autoimmune; Pregnancy Complications, Hematologic; Autoantibodies; Prenatal Exposure Delayed Effects; Breast Feeding; Pregnancy; Fetal Monitoring

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Autoimmune hemolytic anemia (AIHA) is defined as the increased destruction of circulating red blood cells

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Warm Autoimmune Hemolytic Anemia in Pregnancy

(RBCs) in the presence of anti-RBC autoantibodies with or without complement activation [1]. Warm autoantibodies are typically immunoglobulin G (IgG) antibodies whose optimal reaction temperature is 37°C [2].

The presence of warm autoantibody on the patient’s cells is shown by a positive direct antiglobulin test (DAT) with polyspecific and IgG reagents. The presence of a free warm autoantibody in the patient’s serum is shown by reactivity with all panel cells. Stronger reactivity against some panel cells implies the presence of underlying antibody [3, 4]. The presence of hemolytic anemia is indicated by laboratory evidence of RBCs destruction (low hemoglobin, elevated bilirubin level and lactate dehydrogenase (LDH), RBCs shape changes on the peripheral blood smear etc.) [5]. The main purpose of AIHA treatment is to stop hemolysis and correct anemia.

Warm autoantibodies are detected in 1: 1,000 to 1:50,000 of pregnancies. The pregnant women should be evaluated for RBCs hemolysis. If there is no hemolysis, they may be managed similar to pregnant women without RBCs antibodies. Autoimmune hemolysis in pregnancy from a combination of warm and cold

Abbreviations
AIHA – autoimmune hemolytic anemia
RBCs – red blood cells
IgG – immunoglobulin G
DAT – direct antiglobulin test
WAIHA – warm autoimmune hemolytic anemia
IAT – indirect antiglobulin test
LISS – low ionic strength solution

Table 1. An overview of laboratory test results

| Laboratory tests | Patient’s results | Reference interval |
|------------------|-------------------|-------------------|
| WBC (White Blood Cell) x10⁹/L | 8.8 | Normal | 4–10 |
| RBC x 10¹²/L (Red Blood Cell) | 3.1 | Low | 3.8–6 |
| Hemoglobin g/L | 105 | Low | 120–180 |
| HCT - Hematocrit % | 0.31 | Low | 0.35–0.54 |
| MCV (Mean Corpuscular Volume) fL | 99.4 | High | 80–97 |
| MCH (Mean Corpuscular Hemoglobin) fmol | 30.4 | Normal | 26.5–33.5 |
| MCHC (Mean Corpuscular Hemoglobin Concentration) g/L | 348 | Normal | 315–360 |
| RDW (Red Cell distribution Width) % | 16.6 | High | 10–15 |
| Reticulocyte count % | 4.5 | High | 0.5–2.5 |
| Haptoglobin/Haptoglobin | 0.1 | Low | 0.3–2.0 |
| Platelet count x10⁹/L | 184 | Normal | 120–450 |
| MPV (Mean Platelet Volume) fL | 9.9 | Normal | 6.5–11 |
| PCT (Plateletcrit) % | 0.18 | Normal | 0.5 |
| PDW (Platelet Distribution Width) % | 15.8 | Normal | 10–18 |
| Lymphocytes %/Limfociti % | 37.7 | Normal | 20–40 |
| Monocytes %/Monociti % | 8.5 | Normal | 0.5–10 |
| Neutrophil granulocytes %/Neutrofilni granulociti % | 52.3 | Normal | 50–70 |
| Eosinophilic granulocytes %/Eozinofilni granulociti % | 1.3 | Normal | 0–4 |
| Basophilic granulocytes %/Bazofilni granulociti % | 0.2 | Normal | 0–2 |
| Peripheral blood smear | Macrocytosis and polychromasia |
| Raznaj perferne krvi % | Macrocytosis and polychromasia |
| Bilirubin, total µmol/L/Ukupni bilirubin µmol/L | 5.1 | Normal | 5–21 |
| Bilirubin, conjugated µmol/L/Konjugovani bilirubin µmol/L | 3.6 | High | 0–3.4 |
| AST - Aspartate transaminase U/L/Aspartat transaminaza U/L | 19 | Normal | 0–35 |
| ALT - Alanine transaminase U/L/Alalin transaminaza U/L | 13 | Normal | 0–45 |
| GGT- Gamma glutamyltransferase U/L/Gama glutamittransferaza U/L | 13 | Normal | 0–55 |
| LDH - Lactate dehydrogenase U/L/Laktat dehydrogenaza U/L | 420 | High | 208–378 |
| Fibrinogen g/L/Fibrinogen g/L | 4.38 | High | 1.7–4 |
| Serum iron mmol/L/Serumsko gvožđe mmol/L | 15 | Normal | 14.4–25.1 |
| Ferritin ng/mL/Feritin ng/mL | 35 | Normal | 30–150 |
autoantibodies had been estimated to occur in 1 in 50,000 pregnancies [6]. Since IgG can cross the placenta, the antibody may be detectable in the infant’s serum and/or attached to infant’s cells. Hemolytic disease of the fetus and newborn has been reported [7].

Warm autoimmune hemolytic anemia (WAIHA) caused primarily by pregnancy is rarely reported in the literature [6]. We present a case of idiopathic WAIHA in the early pregnancy of a 26-year-old woman. The WAIHA was mild and did not require active treatment. The risk to the infant was assessed as low during monitoring the fetal condition in order to identify fetal hemolytic anemia as early as possible. The aim of this report was to describe the clinical presentation, diagnostic investigations, and possible outcomes of pregnancy in WAIHA.

Case Report

A 26-year-old woman, who was pregnant for the first time, visited the Blood Transfusion Institute of Vojvodina for routine RBC antibody screening. The woman was twelve weeks pregnant and reported no significant past medical history. She had never had a transfusion before, or abortion of an unintended pregnancy. In her recent medical history, she was not on any medication.

On initial testing, it was determined that the woman had a blood type B, Rh-D-negative, Rh phenotype cede, Kell phenotype Kk. The routine antenatal maternal antibody screening was performed using the indirect antiglobulin test (IAT), gel technique on commercial low ionic strength solution (LISS)/Coombs cards containing anti-IgG and anti-C3d (ID-Card LISS/Coombs, BioRad, Cressier, Switzerland) with commercial test RBC (ID-DiaCell I-II, BioRad, Cressier, Switzerland). Testing was performed using an automated immunoassay analyzer (1H-500, BioRad). The IAT was positive (2+). The antibody specificity was determined by IAT using commercially available 11-cell panel typed for all clinically relevant antigens (ID-DiaPanel, BioRad, Cressier, Switzerland) in LISS/Coombs gel cards. The antibody in the patient’s serum has shown reactivity of the same intensity with all panel cells. The autocontrol has shown reactive activity of the same intensity with all panel cells. The autocontrol was positive (2+-).

The DAT in LISS/Coombs gel card was positive (2+). The aim of performing DAT in LISS/Coombs gel card (DC-Screening I, BioRad, Cressier, Switzerland) was to determine whether IgG, IgA, IgM, C3c, and C3d were bound to RBCs, and DAT was positive only for C3d.

After removal of the antibody from the RBCs using heat elution technique, the eluate was subsequently tested against a commercially available 11-cell panel by IAT. Panagglutination was detected, confirming the presence of a warm autoantibody.

It was determined that the potential father had a blood type O, Rh-D positive, Rh phenotype CcDee, Kell phenotype Kk. The subsequent specimen, taken 4 weeks later, was tested in the same way. Antibody identification cell panel showed strong panagglutination warm autoantibody. Four weeks later, at 20 weeks gestation, the laboratory result was the same, but the pregnant patient presented with fatigue and dizziness so she was referred to a hematologist for further evaluation.

The woman delivered a term male infant at 40 weeks gestation by Caesarean section. The infant presented with Apgar scores of 10 and 10, had no jaundice or anemia and had type O Rh-D-negative with a positive DAT (3+). Elution studies were positive for the maternal warm autoantibody only. Hemoglobin level was 16.2 g/dL (pediatric reference ranges 13.4 – 19.9 g/dL for 0 – 1 month) [8]. The infant was discharged after 3 days in stable condition.

After we assessed that the benefit of breastfeeding would be greater than the risk for the infant, the infant was breastfed for nine months after birth. The DATs were positive (3+) in both mother and child over the following 12 months, but neither needed RBC transfusion. The child’s hemoglobin remained stable for 12 months of follow up. The mother’s anemia went into spontaneous remission several months later.

Discussion

The AIHA may be primary or secondary. No underlying disease or agent can be detected in primary AIHA. The secondary causes of AIHA include lymphomas, Chronic Lymphocytic Leukemia, solid tumors, Systemic Lupus Erythematosus, antiphospholipid syndrome, Sjogren’s syndrome, rheumatoid arthritis, drug abuse [9]. In the present case, the autoantibody was not associated with other autoimmune diseases or malignancies. The warm autoantibody was pregnancy associated. The pregnant woman had a mild autoimmune hemolytic anemia and the basic question during pregnancy monitoring was whether the passage of maternal autoantibodies will pose a risk to the child. Due to the fact that fetal anemia was not detected, we decided only to maintain careful monitoring. As the healthy term infant was without anemia and jaundice, the next question was the risk and potential benefits of breastfeeding for the child. Currently, breastfeeding is accepted as a very effective primary health care strategy for improving infant health, as well as lowering the risk of a significant number of chronic diseases in older children and adults [10]. For these reasons, we recommended breastfeeding and monitoring the baby’s condition during this period.

Pregnancy-induced WAIHA is rarely described in the literature, but in 1982, a group of authors confirmed an association between erythrocyte autosensitization and pregnancy in the largest series of 20 pregnant women with RBC autoantibodies. The clinical manifestation varied from severe to mild hemolytic anemia.
Three infants were mildly affected with hemolytic disease due to the maternal autoantibodies crossing the placenta but no treatment was needed [11]. In case of WAIHA, it is important to detect the presence of an underlying alloantibody when a transfusion is contemplated. The RBC transfusions and corticosteroids (e.g. Prednisone 1 – 1.5 mg/kg/day) can be administered to stabilize hematocrit and to control hemolysis as well as intravenous immunoglobulin or plasma exchange. Other therapy (splenectomy, immunosuppressive, Danazol) is used in the treatment of non-pregnant patients [12].

Conclusion

In warm autoimmune hemolytic anemia, the main purpose is to stop hemolysis and correct anemia in pregnant women. Fetal monitoring in pregnant women with warm autoimmune hemolytic anemia is necessary in order to identify fetal hemolytic anemia as early as possible.

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