Pregnancy Induced Autoimmune Warm Antibodies Hemolytic Anemia: A Case Report

Schwangerschaftsinduzierte autoimmunhämolytische Anämie vom Wärmetyper: ein Fallbericht

Abstract

Background: Autoimmune haemolytic anaemia (AIHA), caused primarily by pregnancy, is poorly described in the literature. There is especially little information on coping with cases that are not responsive to glucocorticoid treatment, monitoring a fetal condition, and identifying fetal haemolytic anaemia as early as possible.

Case: A case of pregnancy-induced autoimmune haemolytic anaemia is reported with major problems in differential diagnosis, treatment and the risks posed to both the mother and the fetus. The anaemia went into spontaneous remission of the disease several weeks after delivery.

Conclusion: Autoimmune haemolytic anaemia is rarely reported in literature, but can be dangerous for both fetus and mother. It therefore should be described and discussed among obstetricians and gynaecologists, and the etiopathogenesis should be further studied.

Zusammenfassung

Hintergrund: Es gibt nur wenige Berichte zur schwangerschaftsinduzierten autoimmunhämolytischen Anämie (AIHA). Noch weniger Informationen gibt es über die adäquate Vorgehensweise bei Patientinnen, die nicht auf eine Behandlung mit Glukokortikoiden ansprechen, sowie zur Bedeutung einer Überwachung des fetalen Zustands und einer frühestmöglichen Ermittlung einer fetalen hämolytischen Anämie.


Schlussfolgerung: In der Literatur gibt es nur wenige Berichte zur autoimmunehaemolytischen Anämie, die aber ein erhebliches Risiko für Mutter und Fetus darstellt. Sie sollte daher eingehend beschrieben und unter Gynäkologen sowie Geburts­helfern diskutiert werden. Es sind weitere Studien zur Klärungen der Ätiopathogene gefordert.

Abbreviations

AFLP acute fatty liver of pregnancy
AIHA autoimmune haemolytic anaemia
ALT alanine aminotransferase
APS antiphospholipid syndrome
AFTT activated partial thromboplastin time
AST aspartate aminotransferase
DAT direct antiglobulin test
EB Epstein-Barr virus
Hb haemoglobin
HUS haemolytic uremic syndrome

IgG, IgM immunoglobulin G, immunoglobulin M
LDH lactate dehydrogenase
MAHA microangiopathic haemolytic anaemia
MCA middle cerebral artery
MCH mean cell haemoglobin
MCHC mean corpuscular haemoglobin concentration
MCV mean cell volume
NST nonstress test
PSV peak systolic velocity
RHD Rh(D) factor

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Key words

- pregnancy
- haemolytic anaemia
- steroids

Schlüsselwörter

- Schwangerschaft
- hämolytische Anämie
- Steroide

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SLE  systemic lupus erythematosus  
SPA  Stago protrombin assay  
TTP  thrombotic thrombocytopenic purpura

Introduction

Autoimmune haemolytic anaemia (AIHA), caused primarily by pregnancy, is poorly described in the literature [1–4]. AIHA is characterized by the development of antibodies directed against one’s own red cell antigens. When such an autoantibody belongs to the IgG class, the condition is potentially dangerous to both the mother and the fetus, since IgG crosses the placenta readily [4]. In most reported cases, idiopathic AIHA occurred late in the pregnancy and responded well to steroid therapy and/or transfusions, with slight or no haemolytic process in the newborn. We therefore encountered a lack of information about how to cope with a case of AIHA that does not respond to glucocorticoid treatment and how to monitor a fetal condition and suspect possible fetal haemolytic anaemia as early as possible. And which is better: to treat the mother and fetus in utero until the term or to treat them separately post partum? These questions merit the depiction of this rare case for reporting and further discussions.

A case of pregnancy-induced autoimmune haemolytic anaemia is reported herein along with the major problems in differential diagnosis, treatment and the risks posed to both the mother and the fetus.

Case Report

A 34-year-old pregnant patient in the 29th week of gestation presented to the emergency room with severe weakness and headache. She had a history of six medical abortions and one normal pregnancy and delivery at term. Until three days previously, she had felt fine throughout this pregnancy and had not had any complaints. At age 12 she had had a thrombotic thrombocytopenic purpura episode that was treated by steroids for 3 years. Since then, she did not have any symptoms of that or any other severe disease.

Physical examination revealed marked pallor and icteric discoloration of her skin and conjunctiva, tachycardia and tachypnea. The fetal status was normal. The nonstress tests (NST) were reactive. Ultrasound did not show any fetal abnormalities, the amount of amniotic fluid was normal, and dopplerometry of umbilical, uterine and middle cerebral arteries were within normal range. An automated cell counter of peripheral blood showed a normal total leukocyte count with normal differentiation and a normal platelet count. Evaluation of blood parameters revealed features of severe anaemia (haemoglobin [Hb] = 38 g/l) with normocytosis (MCV = 86.4 fl) and normal MCH (30.4 pg) and MCHC (352 g/l) as well as reticulocytopenia 0.38%. The haematocrit level was decreased to 0.108 l/l. Biochemical analysis showed indirect hyperbilirubinemia (28.4 mmol/l) with normal AST (36 U/l) and ALT (29 U/l) and increased LDH (552 U/l). Increased fibrinogen (4.38 g/l) and D-dimer test (1835 mg/kg) and normal APTT (29.4 s) and SPA (112%) and SPA (0.95 INR) were found. Urine analysis was normal. Serum iron (70.4 mmol/l), ferritin (418.9 mg/kg) and haptoglobin (< 0.08 g/L) were detected in normal ranges. Erythropoietin concentration was 104 U/l. Molecular tests for acute Parvo B19 virus were negative. EB virus IgM was negative and IgG positive. An abdominal ultrasound showed slight hepatosplenomegaly. Bone marrow aspiration showed expanded erythropoiesis and there were no abnormal cells. The patient’s blood group was A (II), RHD positive. Direct (IgG) and indirect Coomb’s tests were positive. Rhesus phenotype ccEe. The anti-RHD antibodies titre was 1 : 2000.

Six units of group A (II), RHD-negative packed red cells were transfused and treatment with corticosteroids was initiated (two days of dexamethasone 6 mg intramuscularly at 12-hour intervals. Oral prednisolone was started at 1 mg/kg, for a total 60 mg po bid from the third day) with co-administration of fraxiparine, proton pump inhibitors and folic acid.

The fetal status was observed daily and maternal blood tests were checked regularly. Despite corticosteroid treatment, haemolysis was present and ongoing with persistent reticulocytopenia. Fetal anaemia was detected with non-invasive fetal middle cerebral artery dopplerometry at day 9 of treatment (a. cerebi media PS velocity increased up to 0.67). Due to an inadequate response to medical conservative treatment and worsening fetal wellbeing, it was decided to terminate the pregnancy. A Caesarean section was performed at gestation of 30 weeks and four days. The patient was asked whether she wanted to undergo a splenectomy during the surgery, but she refused this option. During the operation, 5 units of group A (II), RHD-negative packed red cells were transfused. A female newborn was delivered with severe indirect hyperbilirubinemia (150 mmol/l) and mild anaemia (haemoglobin 136 g/l). Blood group A (II), RHD positive and positive indirect Coombs test led to diagnosis of severe rhesus alloimmunization of a newborn. The treatment of the newborn was initiated with an exchange transfusion of blood, followed by fototerapy. On the second day the infant experienced mild seizures, which were treated by liuminal. After her status was stabilized, at 6 days old the newborn was transferred to a paediatric hospital’s newborn intensive care unit for further treatment and investigation. The infant was followed up by neonatologists. Despite prematurity, alloimmune haemolytic anaemia with reticulocytopenia was observed. Severe haemolytic anaemia was initially corrected after delivery with an exchange hemotransfusion followed by two hemotransfusions during the first month. On follow-up three months later, normal haemoglobin and reticulocyte counts were observed.

The mother was followed up after the delivery and medical treatment was continued. After several weeks, her blood haemoglobin levels reached 124 g/l and reticulocytosis of 3.68 % was present (Table 1). Prednisolone dosage was decreased to 0.5 mg/kg per day.

Comment

We have presented a case of autoimmune haemolytic anaemia that was detected accidently and presented as severe anaemia, with a wide range of differential diagnosis. Clinical presentation and laboratory parameters were consistent with haemolysis and a working diagnosis of warm antibodies autoimmune haemolytic anaemia (AIHA) was made.

Haemolysis occurs in other pregnancy conditions. HELLP syndrome occurs in approximately one out of 500 pregnancies, AFLP in one out of 10000 pregnancies, and TTP/HUS in one out of...
usually is called pregnancy-induced haemolytic anaemia [7] with negative direct and indirect Coombs tests. This pathology describes clinically severe haemolytic anaemias (37°C) [6].

Warm haemolysis refers to IgG autoantibodies which maximally bind red blood cells at body temperature or other factors [7]. Warm haemolysis can be primary (idiopathic) or secondary due to underlying diseases and no transfusion was needed. Healthy babies were delivered naturally with no evidence of haemolysis.

Despite reported cases, there is no case report in which autoimmune haemolytic anaemia appeared quite early (around the 30th week) in pregnancy and was resistant to steroidal treatment. However, this treatment should be considered teratogenic and contraindicated during pregnancy unless absolutely required to treat maternal life-threatening con-
In the literature no recommendations were found about how to served with the need of exchange hemotransfusion occasionally. In some reported cases with AIHA during pregnancy [1, 15,22], a wide range of haemolytic diseases in newborns was ob-

duced a condition equivalent to rhesus alloimmunization for the fetus. Mycophenolate mofetil can be a cause of ear malformations. Long-term effects in humans from exposure to cytostatics during pregnancy are unknown [16, 17].

Monoclonal antibodies anti-CD20 (rituximab) has produced pro-

longed remissions in a proportion of cases and anti-CD52 (Cam-

path-IH) has been tried successfully in a few cases. Klink and El-

burg with co-authors demonstrated that rituximab passes the placenta and inhibits neonatal B-lymphocyte development. However, after 6 months, B-lymphocyte levels normalized and vaccination titres after 10 months were adequate. No infection-

related complications occurred. Rituximab administration during pregnancy appears to be safe for the child [18]. Another study presented rituximab therapy as a viable option for deferring cyto-
toxic therapy early during pregnancy; it might help reduce the risk of fetal malformation or abortion [19]. Rituximab is reported to be effective in about 80–90% of cases of warm AIHA [20].

In a recent guideline, high-dose immunoglobulin was not recom-

mended for use in AIHA, except under certain life-threatening circumstances [21]. High-dose immunoglobulin has been used but with less success than in idiopathic thrombocytopenic pur-
pura [17].

The first problem encountered in management of the present case was when the patient refused steroid treatment because she feared the treatment could be dangerous for her baby. After long negotiations she accepted the treatment. Although manage-

ment with corticosteroids was started, it was found insufficient, because of persistent haemolysis. Nevertheless, while the litera-
ture describes the therapeutic utility of corticosteroids, it is not confirmed to be universally successful. The effect in some cases was achieved only with top-up blood transfusions [8]. Other medical options for treating AIHA are not well described in the literature for use during pregnancy or are too inconsistent to be applied in a gravid state.

Blood transfusion therapy in AIHA is challenging, and the most compatible red blood cells (i.e., those with the least cross-react-
ing antibodies) should be given [6]. The grouping and cross-
matching packed red cells for transfusion was complicated due to excessive agglutination of erythrocytes. The patient’s blood group was A (II), RHD-positive and group A (II), RHD-negative packed red cells were transfused.

Despite the problems in management of the disease, the main challenge in the present case was establishing criteria for fetal condition and prognosis. Since the main pathogenetic factor in this case was IgG auto-antibodies against RHD factor, it was sus-
ppected that these antibodies could cross the placental barrier and, if the fetal blood group proved RHD positive, they could in-

duce a condition equivalent to rhesus alloimmunization for the fetus.

In some reported cases with AIHA during pregnancy [1,15,22,23], a wide range of haemolytic diseases in newborns was ob-
served with the need of exchange hemotransfusion occasionally. In the literature no recommendations were found about how to monitor fetal conditions in AIHA, so standard investigations for assessment of the severity of fetal anaemia in RHD alloimmunization therapy were used. Pretlove et al. [24] in their systematic review pro-
vided compelling evidence that a Doppler assessment of the fetal middle cerebral artery (MCA) peak systolic velocity (PSV) is the best non-invasive tool for predicting fetal anaemia in at-risk pregnancies. Invasive techniques such as amniocentesis or cordocen-
tesis are more hazardous to the mother and fetus and should be reserved for patients with increased MCA-PSV [25].

Fetal status was observed with an NST several times a day and Dopplerometry of fetal middle cerebral artery peak systolic velocity was taken once a day. MCA-PSV was in normal range until the ninth day of the treatment and at the same moment it was clear that medical treatment of AIHA fails. Because of inadequate response to conservative medical treatment and signs of severe fetal anaemia, it was decided to terminate the pregnancy. Due to the urgent need to help the mother and fetus, a C-section was done.

The post partum newborn demonstrated severe haemolytic anaemia and underwent an exchange transfusion which is pre-
ferred over a simple transfusion because it not only corrects anaemia but also reduces haemolysis by replacing antibody-
coated neonatal RBCs with donor RBCs. Donor RBCs do not have the sensitizing antigen, and remove a portion of the unbound maternal antibody [26].

The maternal patient was followed up by haematologists post partum and, surprisingly, haemolysis stopped. Such a scenario is consistent with available data in literature. The disease could be referred to as pregnancy-induced autoimmune warm antibodies haemolytic anaemia.

Unfortunately, this condition has rarely been reported in litera-
ture, and not enough data are available for management of such cases, especially when steroidal treatment fails and there are challenges in determining criteria for fetal prognosis. Patho-
genesis must be further studied, keeping in mind the feto-
placental immunological, hormonal and biochemical factors that could be responsible for this condition occurring during pregnancy and disappearing post partum.

Teaching points:
1. AIHA should be considered in cases of severe anaemia during pregnancy.
2. The main purpose of the treatment of AIHA is to stop haemolysis and correct anaemia.
3. The nature of the AIHA is still not completely understood and needs further investigation.

Conflict of Interest

None.

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