A Case of Alloimmune Thrombocytopenia, Hemorrhagic Anemia-Induced Fetal Hydrops, Maternal Mirror Syndrome, and Human Chorionic Gonadotropin–Induced Thyrotoxicosis

Venu Jain, MD, PhD[1] Gwen Clarke, MD[2] Laurie Russell, MD[2] Angela McBrien, MD[3] Lisa Hornberger, MD[3] Carmen Young, MD[1] Sujata Chandra, MD[1]

[1] Division of Maternal-Fetal Medicine Royal Alexandra Hospital, University of Alberta, Edmonton, Alberta, Canada
[2] Department of Pathology and Laboratory Medicine, Royal Alexandra Hospital, University of Alberta, Edmonton, Alberta, Canada
[3] Division of Pediatric Cardiology/Fetal and Neonatal Cardiology Program, Royal Alexandra Hospital, University of Alberta, Edmonton, Alberta, Canada

Address for correspondence Venu Jain, MD, PhD, Assistant Professor, 5S131 Lois Hole Hospital, Royal Alexandra Hospital, 10240 Kingsway Avenue, Edmonton, Alberta T5H 3V9, Canada (e-mail: venu.jain@albertahealthservices.ca).

Am J Perinatol Rep 2013;3:41–44.

Abstract

Fetal/neonatal alloimmune thrombocytopenia (FNAIT) can be a cause of severe fetal thrombocytopenia, with the common presentation being intracranial hemorrhage in the fetus, usually in the third trimester. A very unusual case of fetal anemia progressed to hydrops. This was further complicated by maternal Mirror syndrome and human chorionic gonadotropin–induced thyrotoxicosis. Without knowledge of etiology, and possibly due to associated cardiac dysfunction, fetal transfusion resulted in fetal demise. Subsequent testing revealed FNAIT as the cause of severe hemorrhagic anemia. In cases with fetal anemia without presence of red blood cell antibodies, FNAIT must be ruled out as a cause prior to performing fetal transfusion. Fetal heart may adapt differently to acute hemorrhagic anemia compared with a more subacute hemolytic anemia.

Keywords

- FNAIT
- NAIT
- antiplatelet antibodies
- HPA 1a
- intrauterine transfusion
- intraperitoneal transfusion

Fetal anemia, if untreated, can progress to hydrops fetalis and fetal demise, and a high output cardiac failure is thought to be the mechanism involved.[1,2] Despite advent of rhesus D immune globulin, red blood cell isoimmunization remains a common cause of fetal hydrops.[1,3] In addition to immune hydrops fetalis, fetal anemia is also the cause of 10 to 27% of cases of nonimmune fetal hydrops.[2] Etiologic mechanisms include fetomaternal hemorrhage, hemoglobinopathies, and parvovirus infection. Currently, middle cerebral artery (MCA) Doppler has replaced amniocentesis as a noninvasive screen for fetal anemia.[3,4] Invasive approaches (i.e., cordocentesis and intrauterine transfusion) are needed for confirmation and treatment of fetal anemia.[5]

Case Report

A 36-year-old Caucasian gravida 2, para 0 at 25 weeks 6 days gestation with limited prenatal care was referred for maternal hypertension, elevated liver transaminases, and worsening maternal edema. On arrival, she gave a history of palpitations and shortness of breath. Her weight gain in this pregnancy was 30 pounds. She was noted to be mildly tachycardic, with labile blood pressure (BP), and nondependent edema. Serial investigations showed low/downtrending hemoglobin (107 to 90 g/L), low normal/downtrending platelet counts (192 to 146), increasing aspartate aminotransferase/alanine

received
August 8, 2012
accepted after revision
August 11, 2012
published online
January 25, 2013

DOI http://dx.doi.org/10.1055/s-0032-1331379.
ISSN 2157-6998.

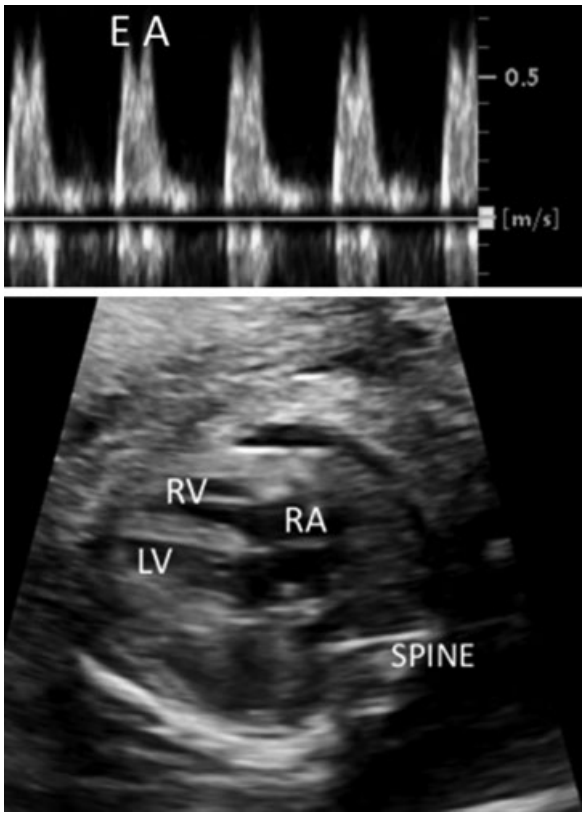

Fig. 1 (Upper panel) Biventricular inflow Dopplers were abnormal with greater flow in early diastole (E) compared with late diastole atrial systole (A), potentially in keeping with abnormal myocardial diastolic function. (Lower panel) Four-chamber view of the heart demonstrating mild cardiomegaly associated with increased biventricular wall thickness or hypertrophy and no chamber dilation. The calculated combined cardiac output was normal for gestational age. LV, left ventricle; RA, right atrium; RV, right ventricle.

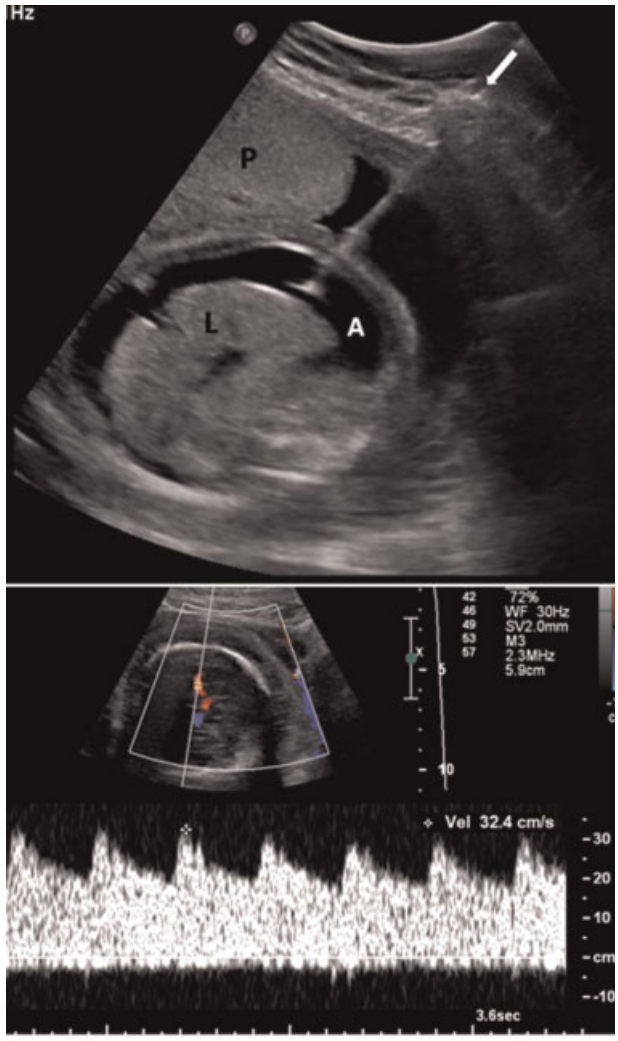

Fig. 2 (Upper panel) Peritoneal aspiration and transfusion. The white arrow delineates the needle inserted into fetal abdomen for drainage of ascites and intraperitoneal transfusion. (Lower panel) Posttransfusion middle cerebral artery Dopplers. The peak systolic velocity is within normal range for this gestation; however, very high diastolic flow is seen. A, hemorrhagic ascites; L, fetal liver; P, hydropic placenta.

aminotransferase (62 to 152/70 to 174 U/L), high normal urate (287 µmol/L), and no significant proteinuria. Obstetric ultrasound showed a low normal amniotic fluid volume, a thick placenta, and fetal hydrops (skin edema, moderate ascites, and mild pleural effusion). MCA Doppler showed elevated peak systolic velocity (PSV; 60 cm/s, $>$ 1.55 multiple of median [MoM]), suggesting fetal anemia. Furthermore, reduced flow in atrial systole in the ductus venosus suggested cardiac dysfunction. Serological testing was negative for red blood cell antibodies. Other routine laboratory investigations for fetal hydrops including a screen for parvovirus and a Kleihauer-Betke test were also performed. Fetal echocardiography showed moderate cardiomegaly and biventricular hypertrophy with normal end diastolic ventricular dimensions and normal systolic function (►**Fig. 1**). Pulsed Doppler findings were consistent with mild diastolic dysfunction with increased ventricular inflow velocities during early diastole (►**Fig. 1**), abnormal tissue velocities, and increased a-wave reversal in the hepatic veins.

Given the diagnosis of nonimmune fetal anemia with hydrops, a fetal transfusion was planned for the next day. With an anterior placenta, cordocentesis was performed at the placental root. Bedside testing showed that fetal hemoglobin was 39 g/L. To avoid fetal cardiac overload, exchange transfusion was performed without complication with a low target hemoglobin of approximately 90 g/L and net transfusion of 22 mL. No streaming of blood was noted from the cord root site after completion of transfusion. Furthermore, to allow a slower additional transfusion, decision was made to proceed with an intraperitoneal transfusion.[6] Upon entry into the peritoneal cavity, the aspirated fluid was noted to be bloody rather than serous as expected in fetal hydrops (►**Fig. 2**). Peritoneal fluid (40 mL) was removed and 20 mL of blood was transfused. Immediately posttransfusion, MCA PSV declined appropriately to 32 cm/s. An unusual MCA finding was the presence of very high diastolic flow velocities suggesting cerebral redistribution (►**Fig. 2**). Unfortunately, an hour later, the fetus was noted to have died. The mother subsequently underwent induction of labor. During induction, because of her respiratory symptoms, a maternal echocardiogram, ventilation perfusion scan, and lower-extremity

ultrasound were performed and were normal. However, the chest X-ray showed interstitial edema suggesting mild pulmonary edema, further supporting a diagnosis of Mirror syndrome.[7] Maternal thyroid-stimulating hormone (TSH) was severely depressed (< 0.03 mU/L) with elevated free T3/T4 (11.5/36.9 pmol/L) and markedly elevated human chorionic gonadotropin (hCG; 440,000 U/L). With a diagnosis of chorionic gonadotropin-induced thyrotoxicosis, she was started on a β-blocker.

The pretransfusion fetal blood sample subsequently analyzed by the laboratory confirmed severe fetal anemia (hemoglobin 21 g/L) and identified the unexpected finding of severe thrombocytopenia (platelet count 9×10^9/L). In addition, antiplatelet antibodies with anti-human platelet antigen (HPA)-1a specificity were present in maternal blood. The fetus was confirmed, on the basis of DNA obtained from fetal postmortem tissue, to have an HPA 1a/1b genotype, and maternal genotyping for the HPA gene indicated HPA 1b/1b. Maternal antibodies to parvovirus were absent and Kleihauer-Betke test was negative. Pathological examination of the fetus showed extensive petechial hemorrhages into the skin (►**Fig. 3**), with bloody fluid in the pleural and peritoneal cavities. Evaluation of the cord root did not identify any significant hematoma. Evaluation of peritoneal fluid obtained prior to peritoneal transfusion showed presence of fetal blood (hemoglobin F–positive) with no maternal (hemoglobin A–containing) blood cells. In addition, the fetal pleural cavity was not entered during fetal therapy, ruling out procedural trauma as cause of hemorrhage. Examination of fetal bone marrow confirmed the presence of adequate numbers of erythroid precursors (with subacute hemorrhage, presumed secondary to thrombocytopenia) and megakaryocytes (supporting a consumptive cause of thrombocytopenia).

Discussion

Fetal/neonatal alloimmune thrombocytopenia (FNAIT) is caused by the transplacental passage of maternal immunoglobulin G immune globulins, which subsequently cause destruction of fetal platelets.[8] It is most commonly caused by maternal–fetal incompatibility in the HPA-1a platelet antigen, with up to 25% of babies with this HPA mismatch affected.[8] The usual presentation is intracranial hemorrhage in the fetus or the neonate.[8] FNAIT has been reported as the likely cause of fetal anemia (61 g/L) with hydrops in one case at 28 weeks of gestation.[9] However, in this case, no major hemorrhage was noted anywhere in the fetus, and chronic microhemorrhagic anemia was presumed. In another reported case, intracranial and perirenal hemorrhages were noted in a nonhydropic fetus at 22 weeks, and FNAIT was suspected, though neither anemia nor thrombocytopenia could be confirmed.[10] The case described here is the first case to our knowledge where FNAIT was the cause of very early onset and severe hemorrhagic anemia causing hydrops. This is supported by presence of severe thrombocytopenia in the fetus with hemorrhage into multiple sites, severe anemia, anti-HPA-1a antibodies in the mother and HPA-1a antigen in the fetus, and lack of any other identifiable cause of anemia. As reported by Stanworth et al[9] and in the current case, fetal red blood cell transfusion resulted in fetal demise. In neither of the cases was concurrent platelet transfusion undertaken as the diagnosis was not suspected. This resulted from the fact that platelet antibody testing is not part of the usual investigation for fetal anemia ± hydrops.[11] Based on this case, in the setting of suspected fetal anemia ± hydrops and the absence of red blood cell antibodies, we propose screening for FNAIT prior to initiating fetal red blood cell transfusion, as this may allow concurrent platelet transfusion if needed and thereby reduce the risk of fetal loss. The screen results are usually available within 24 hours, making this testing feasible. Another option is to have platelets ready for transfusion whenever the procedure is performed in hydropic fetuses. Hydropic fetuses have a high risk of thrombocytopenia even without platelet issues.[12,13] This may be a result of blood cell precursors being diverted into red blood cell production.[12] Platelets can be readied and a platelet count performed before the needle is removed from the cord. Platelets can then be transfused if needed. Future pregnancies in mothers with a previous child affected by FNAIT are at a high risk for reoccurrence, usually with more severe features and at an earlier gestation. Intravenous immunoglobulin and/or prednisone are the mainstays of therapy, with cordocentesis/platelet transfusion reserved for cases refractory to these therapies.[8]

Fetuses with the gradual anemia resulting from red blood cell isoimmunization-induced hemolysis usually show elevated cardiac outputs, with hydrops resulting from high-output cardiac failure.[14] However, the likely acute nature of this hemorrhagic anemia may explain the absence of ventricular dilation and compensatory elevation in cardiac output. The biventricular hypertrophy and diastolic dysfunction may have played an additional role. The contribution of maternal thyrotoxicosis to fetal myocardial dysfunction is unclear, though less likely. Although a relatively small exchange transfusion was given to the fetus to avoid cardiac overload, the fetus did not survive, possibly because of a lower cardiac reserve in this situation. The other possibility is that the baby had further hemorrhage from the site of cordocentesis or the abdominal puncture site, although no spuming was noted from the placental cord insertion site or from the abdominal entry site. Usually, a low posttransfusion hemoglobin target is used when fetal transfusion is performed in the setting of

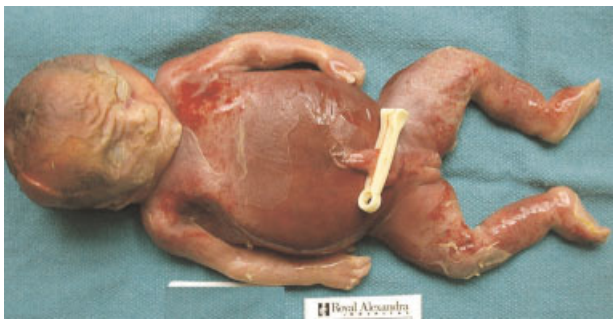

Fig. 3 The stillborn fetus shows hydrops and extensive petechial hemorrhages on skin.

hydrops. However, when normal cardiac output is noted in the presence of severe fetal anemia and hydrops, even lower hemoglobin targets may need to be considered.

Mirror syndrome is known to occur in cases of fetal hydrops.[7] Also known as Ballantyne syndrome or triple edema, fetal and placental hydrops leads to symptoms resembling preeclampsia in the mother. The predominant feature is generalized maternal edema, often with pulmonary involvement. Other features include weight gain, elevated BP, proteinuria, elevated uric acid, elevated liver transaminases, and low platelets. The hydropic placenta is believed to be the cause of this syndrome, and excessive shedding of placental trophoblast and/or angiogenic factors derived from the placenta have been implicated in the pathogenesis.[7] A feature that can differentiate Mirror syndrome from preeclampsia is hemodilution (versus hemoconcentration usually seen in the latter) as was also present in this case.[15] In addition to Mirror syndrome, this patient also developed features of thyrotoxicosis. The levels of hCG (produced by placental trophoblast) are often increased in Mirror syndrome and can cause thyrotoxicosis.[13] Because of structural homology with TSH, hCG has weak thyroid-stimulating activity, which can cause increased levels of thyroxine in addition to suppressing TSH production, especially with levels greater than 400,000 U/L.[16] Assessment of maternal hCG should be considered as part of the evaluation of fetal hydrops with Mirror syndrome in the mother.

In summary, we describe a case of hemorrhagic fetal anemia caused by severe alloimmune thrombocytopenia that progressed to fetal hydrops, with maternal Mirror syndrome and thyrotoxicosis further complicating the clinical picture. Possibly due to a lower cardiac reserve/compensatory capacity, in addition to the lack of knowledge that the fetus was severely thrombocytopenic, the disease process was lethal despite fetal therapy. Screening for FNAIT prior to therapeutic intervention in such cases with readiness for platelet transfusion may reduce the lethality of this rare condition.

Note

Presented at the 11th World Congress in Fetal Medicine, Kos, Greece, June 24 to 28, 2012.

References

1 Nordvall M, Dziegiel M, Hegaard HK, et al. Red blood cell antibodies in pregnancy and their clinical consequences: synergistic effects of multiple specificities. Transfusion 2009;49:2070–2075
2 Forouzan I. Hydrops fetalis: recent advances. Obstet Gynecol Surv 1997;52:130–138
3 Illanes S, Soothill P. Management of red cell alloimmunisation in pregnancy: the non-invasive monitoring of the disease. Prenat Diagn 2010;30:668–673
4 Mari G, Deter RL, Carpenter RL, et al; Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal red-cell alloimmunization. N Engl J Med 2000; 342:9–14
5 Weiner CP, Williamson RA, Wenstrom KD, et al. Management of fetal hemolytic disease by cordocentesis. II. Outcome of treatment. Am J Obstet Gynecol 1991;165(5 Pt 1):1302–1307
6 Nicolini U, Kochenour NK, Greco P, Letsky E, Rodeck CH. When to perform the next intra-uterine transfusion in patients with Rh allo-immunization: combined intravascular and intraperitoneal transfusion allows longer intervals. Fetal Ther 1989;4:14–20
7 Gedikbasi A, Oztarhan K, Gunenc Z, et al. Preeclampsia due to fetal non-immune hydrops: mirror syndrome and review of literature. Hypertens Pregnancy 2011;30:322–330
8 Bussel JB, Berkowitz RL, Hung C, et al. Intracranial hemorrhage in alloimmune thrombocytopenia: stratified management to prevent recurrence in the subsequent affected fetus. Am J Obstet Gynecol 2010;203:135, e1–e14
9 Stanworth SJ, Hackett GA, Williamson LM. Fetomaternal alloimmune thrombocytopenia presenting antenatally as hydrops fetalis. Prenat Diagn 2001;21:423–424
10 Paladini D, Maruotti GM, Sglavo G, Fratellanza G, Quarantelli M, Martinelli P. Massive fetal hemorrhage and fetomaternal alloimmune thrombocytopenia from human platelet antigen 5b incompatibility: an unusual association. Ultrasound Obstet Gynecol 2007;29:471–474
11 Anandakumar C, Biswas A, Wong YC, et al. Management of non-immune hydrops: 8 years' experience. Ultrasound Obstet Gynecol 1996;8:196–200
12 Saade GR, Moise KJ Jr, Copel JA, Belfort MA, Carpenter RJ Jr. Fetal platelet counts correlate with the severity of the anemia in red-cell alloimmunization. Obstet Gynecol 1993;82:987–991
13 van den Akker ES, de Haan TR, Lopriore E, Brand A, Kanhai HH, Oepkes D. Severe fetal thrombocytopenia in Rhesus D alloimmunized pregnancies. Am J Obstet Gynecol 2008;199:387, e1–e4
14 Copel JA, Grannum PA, Green JJ, et al. Fetal cardiac output in the isoimmunized pregnancy: a pulsed Doppler-echocardiographic study of patients undergoing intravascular intrauterine transfusion. Am J Obstet Gynecol 1989;161:361–365
15 McCann SM, Emery SP, Vallejo MC. Anesthetic management of a parturient with fetal sacrococcygeal teratoma and mirror syndrome complicated by elevated hCG and subsequent hyperthyroidism. J Clin Anesth 2009;21:521–524
16 Lockwood CM, Grenache DG, Gronowski AM. Serum human chorionic gonadotropin concentrations greater than 400,000 IU/L are invariably associated with suppressed serum thyrotropin concentrations. Thyroid 2009;19:863–868