Massive fetomaternal hemorrhage and late-onset neutropenia: description of two cases

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SUMMARY: Zuppa AA, Scorrano A, Cota F, D'Andrea V, Fracchiolla A, Romagnoli C. Massive fetomaternal hemorrhage and late-onset neutropenia: description of two cases. Turk J Pediatr 2008; 50: 400-404.

Massive fetomaternal hemorrhage (FMH) occurs in approximately 1:1,000 deliveries. In most cases, the cause is not identified. The clinical manifestations and the prognosis of a FMH depend on the volume of the hemorrhage and the rapidity with which it has occurred.

We describe two cases of chronic massive fetomaternal hemorrhage with favorable outcome. During the follow-up, both infants showed late-onset neutropenia, which was not previously reported in healthy, growing infants with history of massive FMH.

Key words: massive fetomaternal hemorrhage, late-onset neutropenia.

Massive fetomaternal hemorrhage (FMH), though uncommon, is not rare, occurring in approximately 1:1,000 deliveries. FMH is caused by bleeding of the fetus into the maternal circulation with a blood loss of 80 ml or greater. It is more common after traumatic diagnostic amniocentesis or external cephalic version and is rarely the result of placental abruption and maternal trauma. In most cases, the cause is unexplained[1,2].

We report two cases of chronic massive FMH in women with low-risk pregnancies. Both neonates had good outcome and showed late-onset neutropenia during the follow-up, defined as an absolute neutrophil count (ANC) of less than 1,500/mm^3 at a postnatal age of more than three weeks[3,4]. Late-onset neutropenia in stable, growing infants with history of massive FMH has not been reported previously.

Case Reports

Case 1

A 30-year-old woman, gravida 1 para 0, presented to the delivery room at Gemelli's Hospital at 39 weeks of gestation with history of decreased fetal movements for 24 h before admission. She had been regularly attending the antenatal clinic with no risk factors. On admission, the cardiotocograph showed a sinusoidal pattern. She delivered a female newborn weighing 3360 g by an emergency cesarean section under spinal anesthesia.

At birth, the newborn was pale and hypotonic and was resuscitated and intubated for 3 minutes, with an Apgar score of 3 at 1 minute and 8 at 5 minutes.

Thirty minutes after the birth, the newborn was still pale, hypotonic and had the following vital parameters: heart rate 130/min, respiratory rate 50/min, central venous pressure (CVP) 4 cmH_20, and blood pressure 67/40 mmHg (mean arterial pressure 47 mmHg). The pH was 7.26 with a base deficit of 9.1 mEq/L. A complete blood count showed a hemoglobin level of 4.49 g/dl with a hematocrit of 13.4%. On the peripheral smear, reticulocytes were 30% and the erythroblasts 54%.

The newborn needed oxygen therapy for 24 hours, fluid therapy with sodium bicarbonate administration and one packed red cells transfusion of 20 ml/kg that raised the hemoglobin level to 10.8 g/dl with a hematocrit of 32%.

During the first three days of life she developed a mild, transient hypertonia. She had a good outcome and was discharged on the 15th

day when a complete blood count showed: hemoglobin 11.4 g/dl, hematocrit 33%, reticulocytes 1.2%, white blood cells (WBCs) 9510/mm^3, ANC 5690/mm^3, and platelets 513000/mm^3.

Hemolytic diseases and causes of hemorrhage, such as obstetric accidents, malformations of placenta and cord, and internal hemorrhage, were excluded. The Kleihauer-Braun-Betke test was performed, resulting in 5% of fetal red cells in maternal circulation equivalent to 175 ml.

During the follow-up, a complete blood count was performed every 2-4 weeks. In the 7th week of life, complete blood count showed an ANC of 267/mm^3. WBCs were 3900/mm^3, hemoglobin 9.0 g/dl, hematocrit 28%, reticulocytes 2.5% and platelets 211000/mm^3. It was an incidentally discovered condition, which occurred in a healthy growing infant. There was no clinical or laboratory evidence of infections and no specific causes were found. Lymphopoiesis was assessed and no abnormalities were found.

The neutropenia continued for two more months and the ANC slowly increased as shown in Table Ia. The research of anti-neutrophil antibodies was negative, and bone marrow examination excluded bone marrow failure syndromes and myelodysplasia. The neutropenia spontaneously resolved at 4 months of life as shown in Table Ia.

Case 2

A 34-year-old woman, gravida 2 para 0, presented to the delivery room at Gemelli's Hospital at 38 weeks of gestation with a history of decreased fetal movements since the previous day. Six days before a routine physical and ultrasound scan examination were normal.

On admission, the ultrasound scan confirmed the decreased fetal movements and the cardiotocograph showed a sinusoidal pattern. A female newborn weighing 2430 g was delivered by an emergency cesarean section under epidural anesthesia.

The newborn was pale at birth and her Apgar score was 7 at 1 minute and 8 at 5 minutes.

Thirty minutes after the birth, the newborn was still pale with a mild hypotonia and had the following vital parameters: heart rate 200/min, respiratory rate 60/min, CVP 6 cmH_20, and blood pressure 58/28 mmHg (mean arterial pressure 32 mmHg). The pH was 7.30 with a base deficit of 5.9 mEq/L. The hemoglobin was 4.04 g/dl with a hematocrit of 12.7%. On the peripheral smear, reticulocytes were 12.3% and erythroblasts 28%.

The newborn needed fluid therapy and one packed red cells transfusion of 20 ml/kg, which raised the hemoglobin level to 9.29 g/dl with a hematocrit of 28%. Hemolytic diseases and other causes of perinatal hemorrhage were excluded. The Kleihauer-Braun-Betke test resulted in 6% of fetal red cells in maternal circulation equivalent to 210 ml.

The newborn improved with the fluid therapy and blood transfusion and was discharged on the 16th day, when a complete blood count showed: hemoglobin 9.2 g/dl, hematocrit 27.5%, reticulocytes 1.5%, WBCs 6820/mm^3, ANC 2620/mm^3, and platelets 221000/mm^3.

In the 8th week of life, a complete blood count showed an ANC of 570/mm^3; WBCs were 4710/mm^3, hemoglobin 9.1 g/dl, hematocrit 29%, reticulocytes 3.0% and blood platelets 260000/mm^3. The infant had no signs or

Table Ia. Hematological Parameters of Case 1

	Day 1	Day 15	Week 7	Week 8	Week 9	Week 10	Week 12	Week 14	Week 16
RBC (10^6/mm^3)	1.15	3.29	2.42	2.60	2.89	2.90	2.99	3.15	3.01
Hb (g/dl)	4.49	11.4	9.0	9.3	9.7	9.7	10.0	10.4	10.5
Ht (%)	13.4	33.3	28.0	28.3	28.7	28.8	29.2	30.0	29.0
Plt (10^3/mm^3)	162	513	211	205	213	201	245	237	237
WBC (mm^3)	9280	9510	3900	4270	5011	5020	5589	5949	6050
ANC (mm^3)	4060	5690	267	484	679	690	987	1239	1707
Reticulocytes (%)	30	1.2	2.5	2.7	2.6	2.2	1.5	1.1	0.9

RBC: Red blood cells. Hb: Hemoglobin. Ht: Hematocrit. Plt: Platelets. WBC: White blood cells.
ANC: Absolute neutrophil count.

symptoms of infections; viral and common bacterial infections were excluded. Immunodeficiency syndromes were also ruled out.

The neutropenia lasted for two months and resolved spontaneously in the 4th month, as shown in Table Ib. Investigations to exclude autoimmune neutropenia and bone marrow failure syndromes were carried out.

The diagnosis of a FMH great enough to result in anemia at birth can be made with certainty only by the demonstration of fetal cells in the maternal circulation. The Kleihauer-Braun-Betke test is the simplest and most ordinary method for the detection of fetal cells. This test is based on the property of hemoglobin F to resist elution from the cell in an acid medium.

Table Ib. Hematological Parameters of Case 2

	Day 1	Day 16	Week 8	Week 9	Week 10	Week 11	Week 13	Week 15	Week 17
RBC (10^6/mm^3)	1.05	2.30	2.09	2.08	2.23	2.34	2.87	3.02	3.25
Hb (g/dl)	4.04	9.2	9.1	9.2	9.4	9.7	10.0	10.5	10.8
Ht (%)	12.7	27.5	29.0	28.4	29.1	29.8	30.1	30.8	30.0
Plt (10^3/mm^3)	120	221	260	234	256	283	298	304	310
WBC (mm^3)	9230	6820	4710	4543	4789	4958	5349	5745	5890
ANC (mm^3)	4020	2620	570	525	602	649	893	1397	1670
Reticulocytes (%)	12.3	1.5	3.0	2.9	2.7	2.2	1.9	1.5	1.2

RBC: Red blood cells. Hb: Hemoglobin. Ht: Hematocrit. Plt: Platelets. WBC: White blood cells.
ANC: Absolute neutrophil count.

Discussion

The clinical manifestations and prognosis of FMH depend on the volume of the hemorrhage and the rapidity with which it has occurred.

In a published review, the outcome ranged from one asymptomatic newborn who lost 435 ml, representing more than his total fetoplacental blood volume, to a severely ill newborn with poor outcome who lost 80 ml, representing 20% of his blood volume[1].

As shown by our cases, if the hemorrhage has been prolonged or repeated during the course of the pregnancy, anemia develops slowly, giving the fetus an opportunity to develop hemodynamic compensation with increased hemopoietic activity (increased reticulocytes and erythroblasts in the peripheral smear). The diagnosis is often postnatal and these infants may manifest only pallor at birth.

In acute FMH, rapid blood loss is followed by perinatal hypoxia and intrauterine death or severe anemia and hypoxia at birth[5]. A decrease in fetal movements associated with abnormal cardiotocographic findings, such as a sinusoidal pattern of the fetal heart rate, may be a warning sign of a massive FMH, especially in a low-risk pregnancy[2,5].

A maternal blood smear is stained with eosin: fetal red blood cells (RBCs) stain darkly; adult RBCs do not stain and appear as "ghost cells". The formula (fetal red cell volume = [maternal blood volume maternal hematocrit % fetal red cells] / newborn hematocrit) calculates the FMH whole blood volume by assuming a maternal blood volume of 5,000 ml at term, a maternal hematocrit of 35%, and a newborn hematocrit of 50%.

In cases of FMH, the prognosis is poor but may be improved by prompt delivery by cesarean section and a neonatal transfusion, or if the fetus is premature, by cord sampling and an intrauterine transfusion[6,7].

The new element pointed out from these cases is the late-onset neutropenia in asymptomatic, growing infants with a history of massive FMH. Causes of neutropenia in infants include decreased production of neutrophils, increased destruction, or a combination of both mechanisms (Table II). During infancy, neutropenia is usually transient and often following viral or common bacterial infections, does not present serious complications, and in most cases resolves spontaneously[8]. The unexpected finding of neutropenia in an infant

Table II. Causes of Late-Onset Neutropenia

Decreased production of neutrophils
Cyclic neutropenia
Kostmann syndrome
Shwachman-Diamond syndrome
Chédiak-Higashi syndrome
Barth syndrome
Cartilago-hair hypoplasia
Reticular dysgenesia
Glycogen storage disease type 1b
Neutropenia associated with bone marrow failure
Neutropenia associated with immunodeficiency syndromes
Increased destruction of neutrophils
Neonatal autoimmune neutropenia
Drug-induced neutropenia
Decreased production and increased destruction of neutrophils
Infections
Viral: rubella, measles, CMV, EBV, HIV, HAV, HBV, VZV, parvovirus, influenza, RSV
Bacterial: bacterial sepsis, mycobacteria tuberculosis, typhoid, brucella
Drug-induced neutropenia

CMV: Cytomegalovirus. EBV: Epstein-Barr virus. HIV: Human immunodeficiency virus. HAV: Hepatitis A virus. HBV: Hepatitis B virus. VZV: Varicella-zoster virus. RSV: Respiratory syncytial virus.

should prompt consideration of infection, which may cause decreased production and increased destruction of neutrophils.

The infection investigations in both infants showed absence of the indices of infection (such as C-reactive protein), negative cultures of body fluids (blood, urine and stool cultures) and negative serological tests (antibody detection of the most frequent infectious agents connected to neutropenia, i.e. viruses: influenza A and B, coxsackie A and B, cytomegalovirus, Epstein-Barr virus, parvovirus B19).

If the neutropenia does not resolve within 1-2 months, other causes of destruction or underproduction of neutrophils, such as autoimmune neutropenia, immunodeficiencies, myelodysplasia and inherited marrow failure syndromes, must be considered in the differential diagnosis.

A search of anti-neutrophil antibodies in a serum sample was made in both infants. Other tests performed included the granulocyte agglutination test, the granulocyte immunofluorescence test and the monoclonal antibody immobilization of granulocyte antigens. These tests were negative for autoimmune neutropenia.

Since neutropenia may occur in association with immunodeficiency syndromes, lymphopoiesis was assessed and did not show any typical immune alterations.

Bone marrow examination was performed to exclude neutropenia associated with bone marrow failure syndromes. Small lymphocytes were the predominant cell type accounting for more than 50%, while myeloid cells accounted for 20% and erythroid precursors for 20-25%.

In both cases, there was no evidence of any congenital or acquired neutropenia as listed in Table II.

In the literature, late-onset neutropenia has been reported in well, very low birth weight infants with anemia and reticulocytosis[3,9]. It has been speculated that a requirement of progenitor cells for enhanced erythropoiesis associated with the physiological anemia of prematurity limits their availability for granulopoiesis leading to a decrease in neutrophil production.

A normal regulation of hematopoiesis is accompanied by a balance between colony-stimulating factors, such as erythropoietin and granulocyte colony-stimulating factor, which regulate erythropoiesis and granulopoiesis.

Our hypothesis is that the progenitor cells available for hematopoiesis may be consumed during the enhanced erythropoiesis caused by anemia secondary to FMH, and may limit their availability for granulopoiesis. Further investigation will be needed to clarify the exact mechanism responsible for the development of late-onset neutropenia in asymptomatic infants with history of FMH.

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