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CASE REPORT

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Two cases of Leukemoid reaction in premature infants caused by fetal inflammatory response syndrome

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Abstract

Background Fetal inflammatory response syndrome (FIRS) is a systemic inflammatory response caused by the activation of the fetal immune system. The serological diagnostic criterion for fetal inflammatory response syndrome is a cord blood interleukin-6 concentration that exceeds 11 pg/mL, while pathologic evidence indicates the presence of funisitis or chorionic vasculitis. It can affect all systems of the fetus. Alterations in patients' hematopoietic system are primarily reflected by changes in peripheral blood leukocyte and neutrophil counts.

Case presentation We performed placental pathology to identify FIRS and showed two cases of neonatal leukemoid reaction caused by FIRS. These two babies' alterations in hematopoietic system resolves spontaneously with the inflammation relief, without specific interventions. During the 16-month and14- month follow-up period, their motor and intellectual development was normal.

Conclusions . Neonatal leukemoid reaction is a reactive disease characterized by abnormal blood parameters similar to those of leukemia, but not leukemia. It is an aberrant hematopoietic response that typically resolves spontaneously with cause relief without requiring specific interventions.

Keywords Fetal inflammatory response syndrome, Neonatal leukemoid reaction, Premature infants, Hematopoietic system

Background

Fetal inflammatory response syndrome (FIRS) refers to a systemic inflammatory response caused by the activation of fetal immune system and the release of a large number of proinflammatory cytokines. 1 FIRS is characterized by an increase in pro-inflammatory cytokines and multisystemic involvement in utero or in the immediate neonatal period [1-2]. Some studies have demonstrated that FIRS might increase the risk of perinatal multisystemic disorders such as intraventricular hemorrhage, hydrocephalus, periventricular leukoencephalopathy, early-onset sepsis and neonatal respiratory distress syndrome, bronchopulmonary dysplasia, and neonatal death. However, few studies on the hematopoietic system have been reported. Neonatal leukemoid reaction refers to a peripheral blood WBC count exceeding 50×10^9/L, a neutrophil count $>30\times10^9$/L, or a neutrophil count that is greater than two standard deviations from the mean for the corresponding gestational age and the presence of immature cells. We present two cases of neonatal leukemoid reaction caused by FIRS affecting the hematopoietic system in premature infants admitted to our hospital, aimed at

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improving clinicians' understanding of abnormal hematopoietic reactions induced by FIRS and providing a reference for diagnosis and treatment.

Case presentation

Case 1

The female infant was born at 28+6 weeks of gestation by spontaneous vaginal delivery (gravida 5 para 2), weighing 1370 g (50–75th percentile). No anomalies were detected in the umbilical cord, amniotic fluid or placenta. Apgar scores of six at 1 and 5 min. The mother received four doses of antenatal dexamethasone, 6 mg, q12h, im. The fetal heart rate increased one day before delivery, and the mother's temperature peak reached 37.5 ˚C. The mother's laboratory tests revealed leukocytosis: white blood cell (WBC) count 16.17×10^9/L, neutrophilic granulocyte percentage (NE%) 75%, and an increase in highly sensitive c-reaction protein (hs-CRP) 46.42 mg/L (normal range: 0-1 mg/L) 16 h before delivery. Physical examination on admission revealed no rash on the whole body, the liver was 2.0 cm under the rib, and the spleen was not palpated. The infant was administered cefepime and ampicillin intravenously, and symptomatic support, such as alveolar surfactant supplementation and mechanical ventilation, was provided. The infant's postnatal complete blood count (CBC) was as follows: WBC 64.31×10^9/L, NE% 72%, NE 46.09×10^9/L, lymphocyte percentage (LY%) 22%, and monocyte percentage (MO%) 6%. At 11 h, the baby's temperature peak reached 39.1 ˚C. The blood cell morphology examination on day 2 revealed that precursor neutrophils accounted for 31% of the total WBC count and six nucleated red blood cells per 100 classified WBCs. Procalcitonin (PCT) was 25 ng/ml (normal range: 0.00-0.01ng/ml); hs-CRP was 12.41 mg/L. Cranial ultrasound revealed a Grade II intraventricular hemorrhage. On day 3, the infant's CBC was as follows: WBC 88.10×10^9/L, NE% 85%, NE 74.87×10^9/L, LY% 11%, and MO%, 4%. Blood cell morphology examination revealed that precursor neutrophils constitute 26% of the total WBC count. The infant had a fever again at the age of three days, with a peak temperature of 38.3 ˚C. We discontinued antibiotics after the blood culture and metagenomic next-generation sequencing results were negative at five days postnatal age. The infant's blood cell morphology examination at the postnatal day six revealed that precursor neutrophils constitute 14% of the total WBC count. The WBC count gradually decreased (Table 1). No immature blood cells were observed under a microscope on day 20. Maternal placental pathology revealed necrotizing histological chorioamnionitis (stage 3, grade 2; Fig 1) with abscess formation, chorionic vasculitis, and umbilical vasculitis (stage 2, grade 1; Fig 1). On day 29, the baby was still inseparable from respiratory support therapy and was diagnosed with bronchopulmonary dysplasia. On day 33, the baby was diagnosed with retinopathy of prematurity. The patient improved and was discharged from the hospital on day 65. At the corrected gestational age of 16 months, her body length was 81 cm (P80), her weight was 12 kg (P80), and her motor and intellectual development was normal.

Case 2

The female neonate was delivered via cesarean section (gravida 1 para 1) at 30+3 weeks of gestation with a birth weight of 1380 g (50th percentile) due to a premature rupture of membranes lasting 45 h and fetal tachycardia with no uterine contraction. No anomalies were detected in the umbilical cord, amniotic fluid or placenta. The Apgar score were seven at 1 min and eight at 5 min. The mother received four doses of antenatal dexamethasone, 6 mg, q12h, im. The mother's laboratory tests revealed leukocytosis (WBC: 17.10×10^9/L and NE% 88%) and hs-CRP elevation (52.8 mg/L) 6 h before delivery. At the 10 h after delivery, the mother presented with a postpartum fever of 39.0 ˚C. Physical examination on admission revealed no rash on the whole body, the liver was 2.0 cm under the rib, and the spleen was not palpated. The infant was administered cefepime and ampicillin intravenously and received symptomatic support such as alveolar surfactant supplement and respiratory support. The baby's postnatal CBC was as follows: WBC 50.84×10^9/L, NE% 77%, NE 39.17×10^9/L, LY% 13%, MO% 4%. Blood cell morphology examination on the second day revealed that precursor neutrophils constitute 21% of the total WBCs. PCT was 25 ng/mL, and hs-CRP 12.41 was mg/L. On day three, the infant's CBC was as follows: WBC 80.35×10^9/L, NE% 82%, NE 66.23×10^9/L, LY% 11%, and MO% 11%. Cranial ultrasound revealed a grade II

Table 1 CBC of the infant in case 1

Day-age	WBC ($\times10^9$/L)	NE ($\times10^9$/L)	NE (%)	LY (%)	MO (%)	RBC ($\times10^{12}$/L)	HGB (g/dl)	PLT ($\times10^9$/L)
D1	64.31	46.09	72	22	6	4.47	16.8	300
D3	88.10	74.87	85	11	4	4.42	15.3	357
D7	65.97	52.81	80	13	5	4.89	16.6	307
D14	20.61	9.13	44	35	12	4.79	15.9	271
D19	16.43	8.21	50	36	11	4.24	13.8	259
D25	14.39	2.70	19	69	9	3.88	12.3	378

Table 2 CBC of the infant in case 2

Day-age	WBC ($\times 10^9$/L)	NE ($\times 10^9$/L)	NE (%)	LY (%)	MO (%)	RBC ($\times 10^{12}$/L)	HGB (g/dl)	PLT ($\times 10^9$/L)
D1	50.84	39.17	77	11	11	3.58	13.1	229
D3	80.35	66.23	82	13	4	3.65	13.7	282
D8	52.29	40.75	78	17	5	3.25	11.8	257
D10	38.53	38.53	68	24	6	3.26	11.5	378
D14	18.80	8.12	43	42	7	3.09	10.6	418
D20	12.82	4.12	32	53	11	2.83	9.7	401

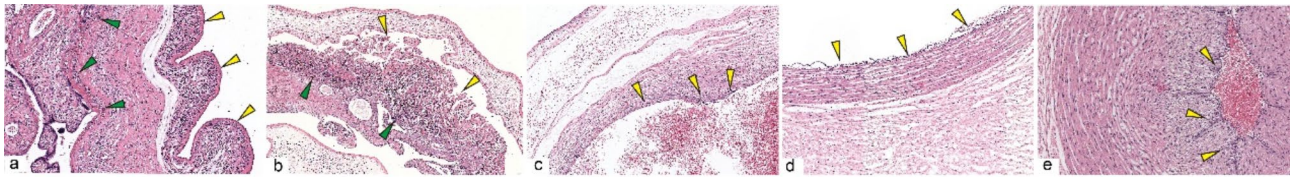

Fig. 1 The maternal placental pathology of the infant in case 1. **a**. Chorioamnionitis (yellow arrow), subchorionitis (green arrow). **b**. Microabscess formation (green arrow) and necrosis (yellow arrow) within the chorionic plate. **c**. Chorionic vasculitis (yellow arrow). **d**. Umbilical phlebitis (yellow arrow). **e**. Umbilical arteritis (yellow arrow)

intraventricular hemorrhage. The infant presented with a postpartum fever three days after delivery, with a temperature of 38.2 ˚C. We stopped antibiotics after the blood culture and metagenomic next-generation sequencing were negative on day 6. The infant had a fever on day 10 with a temperature of 38.1 ˚C. The WBC count gradually decreased (Table 2). On day 13, the infant's CBC was as follows: WBC 18.18×10^9/L, NE% 43%, NE 8.12×10^9/L, and no immature blood cells were observed during blood cell morphology examination. Maternal placental pathology revealed necrotizing histological chorioamnionitis (stage 3, grade 2) with abscess formation, chorionic vasculitis, and umbilical vasculitis (stage 2, grade 2). On day 23, the baby did not need respiratory support therapy, improved and was discharged from hospital on day 38. At the corrected gestational age of 14 months, her body length was 78 cm (P75), weight was 9kg (P10), and her motor and intellectual development is normal.

Discussion and conclusions

FIRS is characterized by the elevation of fetal proinflammatory cytokines. The serological diagnostic criteria for FIRS is a cord blood interleukin-6 (IL-6) concentration that exceed 11 pg/mL, while pathologic evidence indicates the presence of funisitis or chorionic vasculitis [3]. FIRS is primarily caused by intrauterine infection with microorganisms such as bacteria, viruses, and protozoa. It is a special type of systemic inflammatory response syndrome occurs during the fetal period. Cord blood IL-6 levels were not detected in either patient. Similarly, no amniotic fluid microbiological examination and cytokine detection was performed in either patient. On placental pathology examination, both patients exhibited funisitis and chorionic vasculitis, leading to the diagnosis of FIRS.

The impact of FIRS on the hematopoietic system is primarily characterized by an increase in peripheral blood leukocyte and neutrophil counts [4]. Neonatal leukemoid reaction is a reactive disease characterized by abnormal blood parameters similar to those of leukemia, but not leukemia. It is an aberrant hematopoietic response that typically resolves spontaneously with cause relief without requiring specific interventions. It is associated with various clinical conditions, such as premature birth, infection, chromosomal anomalies, histologic chorioamnionitis, and exposure to antenatal corticosteroids [5]. The incidence of neonatal leukemoid reactions in term and preterm infants ranges from 1.3 to 15%, and approximately one-quarter of patients are diagnosed with culture-proven infections [6]. Both cases in the report were premature infants, had necrotizing histological chorioamnionitis, were exposed to antenatal corticosteroids, and the mothers had signs of systemic infection, all these may impact the occurrence of neonatal leukemoid reactions to some extent. Because the blood culture and metagenomic next-generation sequencing were negative, neither patient had sepsis.

One study revealed that neonatal leukemoid reaction were significantly associated with sepsis, intraventricular hemorrhage, bronchopulmonary dysplasia and higher mortality rates in low birth weight neonates [7]. For example, case 1 was diagnosed with bronchopulmonary dysplasia. Therefore, neonatal leukemoid reaction may be a potential predictor of severe complications in certain pediatric FIRS patients.

The predominant cell types observed in the bone marrow with neonatal leukemoid reactions were metaphase and late-stage immature granulocytes, with rare promyelocytes. Toxic granular and vacuolar degeneration of neutrophils is common, but anemia and

thrombocytopenia are usually absent. There was no evidence of extramedullary hematopoiesis or organ infiltration, distinguishing neonatal leukemoid reaction from leukemia. The hyperactivity of granulocyte proliferation was accompanied by a conspicuous leftward shift in nuclear morphology, whereas erythrocytes and megakaryocytes remained unchanged. The primary purpose of a bone marrow examination is to rule out the possibility of leukemia. Routine blood examination is crucial for diagnosing neonatal leukemoid reaction. Peripheral blood cell morphology is the primary diagnostic basis for identifying the underlying disease.

There has been little research on the effects of FIRS on the fetal and neonatal hematopoietic systems. The available literature suggests that alterations in this system are primarily reflected by changes in peripheral blood leukocyte and neutrophil counts. Romero [4] demonstrated that leukocytosis was present in approximately two-thirds of preterm infants with FIRS while the nucleated red blood cell count increased. However, there was no significant association between FIRS and hemoglobin concentration, platelet count, lymphocyte count, monocyte count, basophil count or eosinophil count. It has been reported that preterm infants with funisitis have an increase in total monocyte count [8]. Although the mechanism of FIRS-induced neonatal leukemoid reaction is unknown, some researchers believe that an increase in leukocytes and neutrophils may be related to increased serum IL-6 and serum granulocyte colony-stimulating factor in FIRS [9, 10]. Studies have demonstrated an increase in the expression of CD14, CD64, and CD66b on granulocytes and monocytes in the cord blood of children with FIRS and an increase in WBC metabolic activity [11], which may contribute to neonatal leukemoid reaction.

Abbreviations

FIRS	Fetal inflammatory response syndrome
WBC	White blood cell
NE	Neutrophilic granulocyte
hs-CRP	Highly sensitive c-reaction protein
CBC	Complete blood count
LY	Lymphocyte percentage
MO	Monocyte percentage
PCT	Procalcitonin

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the ethical committee of The First Hospital of Jilin University. The committee's reference number was: 2024-070. Informed Consent from patients' parents was obtained

Consent for publication
The patient's guardian provided written informed consent for the publication of the data. Informed consent for the publication of identifiable information/images in open-access journals was obtained from parents.

Competing interests
The authors declare no competing interests.

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