CASE REPORT

Extreme hyperleucocytosis of the premature

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SUMMARY

Physiological leucocytosis is common in neonates. Leukemoid reaction is defined as a variable degree of leucocytosis with immature precursors, similar to that occurring in leukaemia but because of other causes. Leukemoid reactions are well-recognised in the neonatal intensive care unit population and are associated with antenatal corticosteroids, Down's syndrome, chorioamnionitis, funisitis and perinatal infections. However, extreme hyperleucocytosis, exceeding a white blood cell count of $100 \times 10^9/l$ is rare. In the 7-year period from 2005 to 2012 three premature infants in our hospital presented with extreme hyperleucocytosis. Since there were no signs of neonatal leukaemia, transient myeloid disorder or leucocyte adhesion defect, a leukemoid reaction owing to antenatal corticosteroids, chorioamnionitis and funisitis was diagnosed. No obvious complications of hyperleucocytosis were observed. Therapy was not necessary and the leucocytes normalised spontaneously. In our small case series, extreme hyperleucocytosis in prematures occurred in the absence of leukaemia and had a mild course.

BACKGROUND

Occurrence of hyperleucocytosis in non-malignant disease in infants was first described in 1963 in a group of 14 children, including one premature neonate.¹ Thereafter, many other articles were published, focusing on prematures.^{2–7} A leukemoid reaction is defined as the presence of hyperleucocytosis with $>2\%$ of immature precursor cells (myeloblasts, promyelocytes and myelocytes) in the differential of the white blood cell count, similar to that occurring in leukaemia but because of other causes.⁸ Various cut-off values for the number of leucocytes are used, ranging from $>30 \times 10^9$ to $>50 \times 10^9/l$. The incidence of leukemoid reaction in premature infants ranges from 1.3% to 15%,^{2–4} and is associated with many different conditions. Initially, administering of antenatal corticosteroids^{5–7} and presence of a trisomy 21^{9–11} were described as possible causes. We now know that chorioamnionitis and funisitis^{4 12} or perinatal infection^{13–15} are also causes of leukemoid reaction. The average length of this reaction is 1.5–32 days.^{2 6 9 15}

Hyperleucocytosis in children and adults usually occurs in acute leukaemia or myeloproliferative disorders. However both diseases are extremely rare in neonates.¹⁶ Hyperleucocytosis owing to one of the aforementioned diseases can result in leukostasis with respiratory and neurological complications.¹⁷ Hyperhydration or invasive treatments such as leukopheresis or exchange transfusion may be necessary.^{17–19} On the other hand, in prematures

presenting with a hyperleucocytosis owing to a leukemoid reaction, watchful waiting is justified according to the literature.^{2 15}

Extreme hyperleucocytosis in premature infants have not often been described. In this report we describe three prematures with leucocyte counts exceeding $>100 \times 10^9/l$. Based on the patients' histories, physical examinations and the aspects of the differentials of the white blood cell counts, a leukemoid reaction was diagnosed and a wait-and-see policy was chosen. None of the patients developed obvious complications of the hyperleucocytosis.

CASE PRESENTATION

Three infants, born between January 2005 and July 2012 in the Maxima Medical Centre in Veldhoven, the Netherlands, presented with a leucocyte count of $>100 \times 10^9/l$ in 2 days postpartum. For patient characteristics see table 1.

All three infants were prematures, born at a gestational age between 25+4 and 26+4 weeks. Because of signs of imminent preterm births, tocolytic therapy and antenatal corticosteroids had been given to the mothers. In all three cases a perinatal infection was suspected because of prolonged rupture of membranes, maternal fever and elevated infection parameters or an odorous child. None of the patients had hepatosplenomegaly or dysmorphic features suspicious for trisomy 21. Karyotyping was not performed. Owing to the premature birth and the suspicion of a perinatal infection, treatment with antibiotics in the form of amoxicillin–clavulanic acid and gentamicin was started after collection of cultures.

INVESTIGATIONS

Laboratory testing showed a significant increase in C reactive peptide in one patient. In all three patients there was a significant hyperleucocytosis with a maximum leucocyte count between 102 and $173 \times 10^9/l$ (for comprehensive course and differentiation, see table 2 and figures 1 and 2).

The differential of the white blood cell count showed an increase of immature neutrophil precursors and toxic granulation. An occasional blast cell was seen. There was no anaemia, thrombocytopenia or renal impairment. Serum lactate dehydrogenase in electrolytes were within reference values. Stomach culture of patient 2 showed a β -haemolytic group B *Streptococcus*, which was also found in the vaginal culture of the mother. Other cultures remained sterile. Pathological-anatomical examinations of the placentae and umbilical cords of all three prematures were suggestive of a (serious) chorioamnionitis and funisitis.

To cite: Jansen E, Emmen J, Mohns T, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2012-008385

Table 1 Patient characteristics of 3 premature infants with extreme hyperleucocytosis

	Patient 1	Patient 2	Patient 3
Gender	Female	Female	Male
Gestational age (weeks)	26+4	26+1	25+4
Birth weight (g)	1050	800	845
Apgar score	3/6/9	1/5/9	1/6/9
Corticosteroids antenatal	Yes	Yes	Yes
Respiratory distress syndrome	Grade 1	Yes, grade unclear	Grade 3
Blood pressure support	No	Yes	No
Persistent ductus arteriosus	Yes	Yes	Yes
Cultures	No vegetation	Blood in sputum, no vegetation, stomach P-haemolytic group B <i>Streptococcus</i>	No vegetation
Pathology placenta	Severe chorio amnionitis and funisitis	Chorioamnionitis and funisitis	Severe chorioamnionitis and funisitis
Intraventricular haemorrhage	Grade 1 left and 2 right	Grade 3 and posthaemorrhagic ventricle dilation	No
Bronchopulmonary dysplasia	No	Yes	Unclear

DIFFERENTIAL DIAGNOSIS

Apart from a transient leukemoid reaction, a neonatal leukaemia, a transient myeloid disorder (TMD) of Down's syndrome or a leucocyte adhesion defect were considered. However, because of the absence of both skin disorders (leukaemia cutis; specific leukemic cutaneous infiltrates), anaemia, thrombocytopenia and only an occasional blast in the differential count, leukaemia and TMD of Down's syndrome were considered unlikely. Because of the presence of particularly immature neutrophils and no delay in umbilical cord sloughing, the possibility of a leucocyte adhesion defect was also rejected (see also figure 3).

TREATMENT

In all infants, antibiotic therapy was given for 7–14 days because infection was considered as the underlying cause of the hyperleucocytosis. No hyperhydration, exchange transfusion or leukapheresis was performed. The leucocyte count decreased and fell below the limit of $30 \times 10^9/l$ in 9–11 days postpartum.

OUTCOME AND FOLLOW-UP

All three prematures had respiratory distress syndrome (RDS), requiring artificial ventilation. Patients 2 and 3 received

surfactant. Despite hyperleucocytosis, there were no signs of organ dysfunction such as renal impairment or electrolyte disturbances. According to our protocol, cerebral ultrasound was performed, which showed signs of intraventricular haemorrhage (IVH) in patients 1 and 2. Patient 2 developed a posthaemorrhagic ventricular dilation and received a ventricular–peritoneal drain. Patient 2 also developed a bronchopulmonary dysplasia requiring oxygen supplementation and diuretics. Both patients 1 and 2 have a normal neurological and physical development at the age of 1 year. Patient 3 was lost for follow-up after discharge.

DISCUSSION

Hyperleucocytosis in prematures is commonly encountered. On the other hand, extreme hyperleucocytosis of $>100 \times 10^9/l$ is rare. In this case series we describe three patients born at a gestational age of 25–26 weeks, presenting with a leucocyte count of $102\text{--}173 \times 10^9/l$. Acute leukaemia was considered. However, congenital leukaemia is a very rare condition with an incidence of 1–5 per 1 million newborn, being 0.8% of all children with leukaemia. The diagnosis of neonatal leukaemia is made by physical examination and laboratory diagnostics. In neonatal

Table 2 Laboratory parameters of 3 premature infants with extreme hyperleucocytosis

	Patient 1		Patient 2		Patient 3	
Hours postpartum	27	77	20	56	64	34
Leucocytes ($\times 10^9/l$)	160	137	114	173	97	78
Blasts (%)	2	1	1		1	1
Neutrophils	48	50	48		82	63
Lymphocytes	9	11	4		6	6
Monocytes	6	4	8		0	7
Eosinophils	3	0	0		0	0
Metamyelocytes	8	5	9		2	4
Myelocytes	10	17	14		7	4
Neutrophil Granulocytes	13	11	10		2	11
Promyelocytes	1	0	6		0	3
Toxic granulation	++	+++	++		–	+++

Figure 1 Toxic granulation of patient 1.

leukaemia 80% of cases have hepatosplenomegaly, 25% enlarged lymph nodes and 60% signs of leukaemia cutis. The latter condition is the presenting sign in 50% of the neonates.¹⁹ Hyperleukocytosis is present in 85% of acute lymphoid leukaemia and in 49% of acute myeloid leukaemia patients.^{19 20} In addition, most neonates have anaemia and thrombocytopenia.¹⁹ Despite improved treatment options, the death rate of neonatal leukaemia is high.²⁰

These patients had no signs of haematopoietic cell infiltration into non-haematopoietic tissue like hepatosplenomegaly or leukaemia cutis, suggestive of congenital leukaemia. Peripheral blood analysis showed massively increased and left-shifted granulopoiesis without anaemia or thrombocytopenia. Only occasional blasts were seen without signs of tumour lysis syndrome. Because of the aforementioned signs and because of the rarity of this disease, congenital leukaemia was considered unlikely and bone marrow puncture was not performed. None of the children had dysmorphic features suspicious of Down's syndrome. We realise that neonates, especially extremely premature babies, may not present initially with these typical physical signs.²¹ However TMD of Down's syndrome is typically associated with thrombocytopenia, which was not present in these patients.²²

Furthermore, we considered a leucocyte adhesion defect (LAD). LAD is also a very rare condition, during which recurrent infections occur. The first symptom of LAD type 1, even before an infection has occurred, is a delay in umbilical cord sloughing (usually within 5, 8 and 10 days). In addition, infections such as omphalitis, perirectal or labial cellulitis can occur

in combination with an extreme neutrophilia.¹⁶ None of the mentioned symptoms was applicable to our patients.

A β -haemolytic group B *Streptococcus* was isolated from the culture of the stomach of patient 1. In the other two children the cultures remained sterile. Interestingly, the pathological-anatomical examination of the placentae of all three patients demonstrated chorioamnionitis and funisitis. All three mothers had been given antenatal corticosteroids. Since there were no signs of neonatal leukaemia, Down's syndrome or leucocyte adhesion defect, a leukemoid reaction owing to antenatal corticosteroids, chorioamnionitis and funisitis was diagnosed in our three patients.

Hyperleukocytosis may result in leukostasis resulting in occlusion of the microcirculation by accumulation of leucocytes. Appearance of hypoperfusion in case of more than $100 \times 10^9/l$ leucocytes is possible. Especially respiratory and neurological complications, such as dyspnoea, pulmonary haemorrhage, cerebral and visual problems, can occur. Less common manifestations include myocardial ischaemia, priapism and renal failure. These various clinical presentations have been described in neonates with congenital leukaemia.¹⁹ In contrast, no short-term organ dysfunction has been observed in neonates with leukemoid reaction.^{2 15} However, several studies have shown that prematures with leukemoid reaction, compared with peers without leukemoid reaction, have an increased risk of developing a bronchopulmonary dysplasia. The risk of IVH in case of a leukemoid reaction is controversial, ranging from 0% to 37.9%.^{4 23} At the time the hyperleukocytosis was present, the three preterm infants at our hospital showed no signs of organ dysfunction. Respiratory support was needed because of the prematurity and previous RDS, and no signs of dyspnoea were observed. One of these three cases clearly showed bronchopulmonary dysplasia (BPD) with prolonged oxygen requirement. However, this infant was extremely premature, which is a known risk factor for the development of BPD.²⁴ Two of the three patients had IVH for which patient 2 needed drain placement. Prematurity is a major risk factor for the development of an IVH. Approximately 20–25% of premature infants weighing less than 1500 g will have an IVH²⁵ whereby this risk increases in case of persistent ductus arteriosus, need of pressure support, surfactant therapy, inotrope drug administration, neonatal resuscitation and antenatal corticosteroids.²⁶ Whether the development of the IVH can also be (partially) attributed to the observed hyperleukocytosis is unclear.

In the presence of a hyperleukocytosis in the context of acute leukaemia, hyperhydration and potential invasive treatment such as an exchange transfusion or leukapheresis may be necessary in order to avoid the aforementioned complications of leukostasis.^{17 19} Our patients did not receive any of these treatments. Antibiotics were administered immediately postpartum because of prematurity in all three patients. Duration was determined according to the biochemical indicators and cultures.

A leukemoid response is transient and is resolved when the leucocyte count falls below $30 \times 10^9/l$. This was also seen in our patients; leucocyte count decreased gradually to normal values in 9–11 days.

In conclusion, extreme leukemoid reactions in premature infants have not often been reported. In this report we describe three prematures with hyperleukocytosis of $>100 \times 10^9/l$. Based on history, physical examination, absence of anaemia and thrombocytopenia and differential of the white blood cell count we diagnosed a leukemoid reaction and chose a wait-and-see policy. None of the patients developed obvious complications of the hyperleukocytosis.

Figure 2 Course of leucocytes.

Figure 3 Decision tree in case of hyperleukocytosis.

Learning points

- ▶ Extreme hyperleukocytosis can be present in a premature infant without leukaemia or myeloproliferative disease.
- ▶ Causes are antenatal corticosteroids, transient myeloid disorder (TMD) in Down's syndrome, chorioamnionitis and funisitis or a response to a perinatal infection.
- ▶ If history, physical examination and differential of the white blood cell count are not indicative of leukaemia, TMD or a leukocyte adhesion defect, a leukemoid reaction is likely and a wait-and-see policy is justified.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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