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CASE REPORT

Leukoerythroblastosis in sickle cell disease: think about parvovirus B19 infection!

António Figueiredo[1]*, *Teresa Ferreira*[2], *Sónia Mota Faria*[1], *Filipa Salazar*[1], *Lucinda Silva*[1], *and Alexandra Santos*[1]

[1]*Serviço de Patologia Clínica;* [2]*Serviço de Pediatria. Hospital Prof. Doutor Fernando Fonseca E.P.E., Amadora, Portugal*

Abstract

Introduction: Leukoerythroblastosis is a rare condition characterized by leukocytosis and myeloid and erythroid precursors in the peripheral blood. Only a few cases of parvovirus B19 associated leukoerythroblastosis in a context of SCD have been reported. **Case report:** A 27-month-old girl with HbSS presented with fever and non-specific symptoms; a WBC of 92,300 × 109/L, hemoglobin 3.3 g/dL, platelets 607 × 109/L, and 113 NRBCs/100 WBCs; her reticulocyte count (RC) was 11,000/uL. A marked leukoerythroblastosis and thrombocytosis were evident on the blood smear. After appropriate treatment and within 48 hours her RC rose to 391,000/uL, her WBC had fallen to 19,500 and her platelets to 419,000. The PB19 IgM was positive. **Discussion:** This case describes the unusual association between leukoerythroblastosis and thrombocytosis, in conjunction with a transient aplastic crisis secondary to PB19 infection. It also illustrates the clinical utility of the IRF parameter in documenting marrow recovery. PB19 should be considered in the laboratory examinations of children with leukoerythroblastosis.

Keywords: Leukoerythroblastic. Thrombocytosis. Sickle cell disease. Parvovirus B19. Aplastic anemia.

Leucoeritroblastose na doença falciforme: pense em infecção por parvovírus B19!

Resumo

Introdução: A reação leucoeritroblástica é uma condição rara caracterizada por leucocitose e percursores mielóides e eritróides no sangue periférico. Estão descritos poucos casos de leucoeritroblastose associada ao parvovirus B19, no contexto de Drepanocitose. **Relato do caso:** Menina de 27 meses com hemoglobinopatia SS procura cuidados médicos por febre e sintomas inespecíficos. Tinha 92,300 × 109/L leucócitos, hemoglobina de 3,3 g/dL, plaquetas de 607 × 109/L, e 113 eritroblastos/100 leucócitos; reticulocitopenia de 11,000/ul; na morfologia do sangue periférico observava-se leucoeritroblastose e trombocitose. Após tratamento a contagem reticulocitária subiu em 48h para 391,000/ul, com descida dos leucócitos e plaquetas. A IgM para PB19 foi positiva. **Discussão:** O caso descreve a associação invulgar entre leucoeritroblastose e trombocitose, no contexto de crise aplástica secundária a PB19. É ilustrativo da utilidade do parâmetro IRF (immature reticulocyte fraction) na documentação da recuperação medular. A infeção a PB19 deve ser considerada no estudo de crianças com leucoeritroblastose.

Palavras-chave: Reação leucoeritroblástica. Trombocitose. Drepanocitose. Parvovirus B19. Anemia aplástica.

***Correspondence:**
António Figueiredo
E-mail: antonio.e.figueiredo@ulsasi.min-saude.pt

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Keypoints

What is known

- A leukoerythroblastic reaction is always an abnormal finding and may indicate a myeloproliferative neoplasia among other non-malignant causes.
- PB19 infection causes an aplastic crisis in SCD patients
- Immature reticulocyte fraction (IRF) is used to document bone marrow response in different scenarios, mainly following transplant.

What is added

- Additional evidence of parvovirus B19 as an etiologic agent of leucoerythroblastic reaction in SCD (third case described in the literature).
- Association of leucoerythroblastic reaction and thrombocytosis
- *Wait and see* approach in the described scenario, before conducting invasive exams to exclude malignancy.
- Clinical utility of immature reticulocyte fraction (IRF) to document marrow recovery following an aplastic crisis.

Introduction

Leukoerythroblastosis (LEB) is a rare condition, particularly in pediatric ages. It is characterized by leukocytosis and the presence of myeloid and erythroid precursors in the peripheral blood.[1] Leukoerythroblastic reaction (LER) has been poorly described in various clinical scenarios, mostly in association with malignancies.[2] The association of parvovirus B19 (PB19) with LEB has rarely been reported.[3-7]

In a setting of sickle cell disease (SCD), PB19 infection can cause a transient aplastic crisis, which can be life threatening. However, there are only two reported cases of an association between leukoerythroblastic reaction and PB19 in SCD patients.[8-9]

We report the case of a 27-month-old girl with SCD, hemoglobin SS disease (HbSS), who presented with severe anemia, LEB and thrombocytosis, secondary to a parvovirus B19 infection.

Case-report

A 27-month-old girl with HbSS was seen at the emergency department due to intermittent fever over the previous week. She also had a cough, vomiting and felt progressively unwell. Her SCD was diagnosed at 11 months of age in a context of dactylitis. Her medical history showed a vaso-occlusive crisis at 19 months of age and a fever with no localizing signs when she was 24 months old; she was on amoxicillin prophylaxis and she was receiving the recommended standard of care. On examination, she was prostrated, pale, mildly dehydrated with a grade 3/6 systolic ejection murmur. No splenomegaly was observed.

Her full blood count (FBC) showed a white blood count (WBC) of 92,300 × 10^9/L (36% neutrophils, 42% lymphocytes), hemoglobin (Hb) 3.3 g/dL (baseline 7.5 – 8 g/dL), platelets (PLT) 607 × 10^9/L, and 113 nucleated red blood cells (NRBCs)/100 WBCs; her reticulocyte count (RC) was 11,000/uL which raised the suspicion of PB19 infection. Morphologic examination

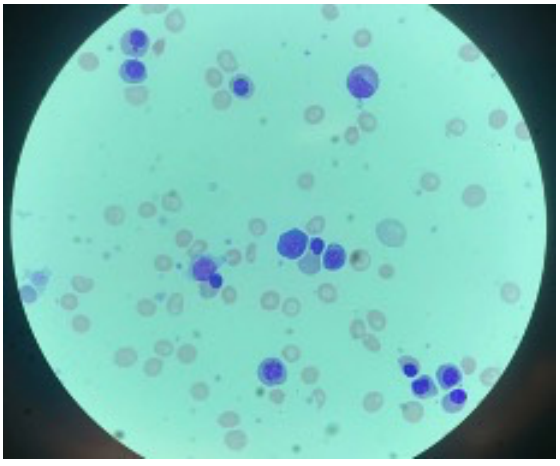

Figure 1. Peripheral blood showing marked leukoerythroblastosis.

of the peripheral blood showed marked leukoerythroblastosis, low myeloblasts (< 2%), high NRBCs, and thrombocytosis (Fig. 1); C-reactive protein was 1.49 mg/dL and lactate dehydrogenase (LDH) was 1870 U/L. The patient was transfused with packed red blood cells, and received intravenous hydration and ceftriaxone. Within 48 hours, the RC rose to 391,000/uL (652,000/uL at 72 hours) and 325 NRBCs/100 WBC; the WBC had fallen to 19,500/uL and the platelets to 419,000. Two weeks later her FBC showed baseline values (Table 1). Seroconversion to PB19 was documented: IgM positive (index > 48, rf > = 1.1), as well as IgG (24); IgG and IgM one month before were both negative and four months after the episode, her IgM was 1.4 and IgG was > 46. The search for other infectious agents, namely EBV, was negative. From a clinical point of view, the outcome was excellent with a full recovery.

Discussion

The child described presented with blood counts suggesting a myeloproliferative neoplasia, but was

Table 1. Red cell parameters, WBC and platelet count, upon admission and at follow-up

	Days of admission				Days after discharge	
	1	2	3	4	10	16
GV (x10^{12}/L)	1.12	2.20	2.27	2.40	3.31	3.00
HGB (g/dL)	3.3	6.2	6.5	6.7	8.9	8.2
HTC (%)	9.4	18.6	20.4	21.7	27.8	23.6
RET (%)	1	2.9	17.2	27.2	9.1	10.3
RET (x10/L)	11,000	62,000	391,000	652,000	301,000	319,000
RPI	0.5	2.4	15.4	26.2	14	10.8
IRF (%)	36.8	57.1	63.8	44.9	18	23.1
HFR (%)	14	22	38.8	23	5.8	8.8
MFR (%)	22.8	35.1	25	21.9	12.2	14.3
LFR (%)	63.2	42.9	36.2	55.1	82	76.9
EB/100 L	113	272	325	183.8	3.8	1.2
WBC (x 10^9/L)	92,300 (36.8%N 42.7%L 17%M)	37,300 (41.8%N 47.2%L 9.7%M)	19,500 (21.2%N 72.4%L 5.1%M)	14,400 (20.5%N 70.2%L 7.2%M)	14,900 (25.5%N 64.4%L 8.4%M)	24,400 (19.1%N 71.7%L 7.1%M)
Plat (x 10^9/L)	607,000	494,000	419,000	334,000	547,000	306,000

ultimately diagnosed with transient leukoerythroblastosis. This scenario overlaps with the one with two children with SCD, parvovirus B19 infection and a leucoerythroblastic reaction, described in the literature.[8-9] These children were three and 12 years old, both splenectomized, with the following laboratory values at presentation: WBC 62.3 × 10^9/L, Hb 5 g/dL, PLT 586 × 10^9/L, 111 NRBCs per 100 WBCs and WBC 72.2 × 10^9/L, Hb 3.9 g/dL, PLT 1533 × 10^9/L, and 15.3 NRBCs per 100 WBCs, respectively. They also demonstrated signs of laboratory recovery at 24-48 hours after treatment, and baseline values within one week. As the leukoerythroblastic peripheral blood findings seen in this patient were transient, there was less concern about a primary bone marrow disease or bone marrow necrosis, and therefore a bone marrow biopsy was not performed. It is also important to highlight that focal bone marrow necrosis can be a complication of a vaso-occlusive crisis in SCD patients, paradoxically more frequent in patients affected by less severe heterozygote genotypes,[10] and they can present with a leukoerythroblastic blood picture.

A recent systematic review of the causes of LEB showed two principal groups of diseases, corresponding to solid and hematological malignancies.[2] Although it is typically associated with marrow infiltrative processes, it may also represent marrow response to stressors such as hypoxia, peripheral destruction/sequestration, or sepsis. Other etiologies, in order of frequency, were hemolytic diseases and infection. The authors concluded that its presence in malignant disease is an indicator of adverse prognosis. On the other hand, in cases where LER had neither underlying hematological or solid neoplasms, its manifestation, prognosis, and impact on daily clinical practice was undetermined due to insufficient data. The child described had a favorable outcome in the setting of a transient viral infection, as previously reported.

The most common causes of LER in children and young adults are viral infections and juvenile myelomonocytic leukemia (JMML); less frequently observed, but also important are osteopetrosis, myelofibrosis, and neuroblastoma.[11-14] Leukoerythroblastosis that mimics juvenile myelomonocytic leukemia has been reported in children with viral diseases, such as Epstein-Barr virus,[15-16] cytomegalovirus,[17] and parvovirus B19, as mentioned before.[3-7] Several groups have recently shown a leukoerythroblastic peripheral smear in COVID-19 adult patients without any history of an underlying hematological malignancy,[18-20] with this being more rare in children.[21] Other conditions rarely described in association with a leucoerythroblastic reaction include Kawasaki disease and severe malaria.[22-23]

Specifically regarding parvovirus B19, it shows tropism to bone marrow, particularly erythroid progenitor cells, and

is responsible for erythema infectiosum (fifth disease) in immunocompetent children and for transient red cell aplasia (aplastic crisis) in those who have an underlying hemolytic disease, such as SCD. Infection suppresses erythropoietic activity and infected cells fail to proliferate and mature, thereby compromising the production of new red blood cells. Reticulocytopenia is a cardinal sign, but also the quantity of RNA found in reticulocytes quantified by flow cytometry (IRF, immature reticulocyte fraction) is a measurable change within the cell that can define the maturity of the various subpopulations in circulation. Bone marrow 'stress or shift' reticulocytes are primarily defined by high RNA within the cell. It has been shown that sequential IRF measurements entail a practical significance in their ability to assess the status of engraftment during the post-transplant period because IRF increases three to five days prior to the increase seen in reticulocyte counts and therefore can assess marrow erythropoietic activity earlier than the reticulocyte count.[24,25] This earlier increase was also seen in our patient (Table 1), although less strikingly, providing further evidence of the transient nature of the clinical condition. IRF behaved as an early and sensitive indicator of erythropoiesis and a useful parameter for monitoring the regenerative bone marrow response, following an aplastic crisis.

In conclusion, a leukoerythroblastic reaction is always an abnormal finding. This case is unique as it describes the unusual association between leukoerythroblastosis and thrombocytosis, in conjunction with a transient aplastic crisis secondary to parvovirus B19 infection. Moreover, it perfectly documents the reticulocyte/erythroblastosis response in the timeline of a PB19 infection, specifically in the setting of SCD. Our patient's presentation suggests that PB19 serology should be considered in the laboratory examinations of children who present with leukoerythroblastosis and that watchful waiting might be a wise initial approach. The IRF is a useful tool in documenting marrow recovery and can potentially provide additional information in the diagnostic work-up.

Author contributions

A. Figueiredo: data collection, critical reviewing; S. Mota Faria: data collection, bibliographical search, critical reviewing; F. Salazar: bibliographical search, critical reviewing; A. Santos: bibliographical search, analysis and interpretation, critical reviewing.

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Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The authors have followed their institution's confidentiality protocols, obtained informed consent from all patients, and secured approval from the Ethics Committee. SAGER guidelines have been followed as applicable to the nature of the study.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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