

TEACHING FILES (GRAND ROUNDS)

LEUKOERYTHROBLASTOSIS IN A CHILD WITH SICKLE CELL DISEASE - WHAT'S THE DIAGNOSIS?

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Clinical Problem:

A 7-year-old girl with SCD, attending a routine consultation at her referral center, performed a laboratory evaluation that revealed hemoglobin (Hgb) 4.3 g/dL (baseline Hgb 8-9 g/dL), hematocrit 12.1%, reticulocyte count $11.90 \times 10^9/L$ (0.64%), white blood cell (WBC) count of $68.74 \times 10^9/L$, neutrophils $46.19 \times 10^9/L$ (67.2%), lymphocytes $16.02 \times 10^9/L$ (23.3%), monocytes $5.50 \times 10^9/L$ (8%), eosinophils $0.76 \times 10^9/L$ (1.1%), basophils $0.27 \times 10^9/L$ (0.4%), platelets $737 \times 10^9/L$. Peripheral blood smear showed marked anisopoikilocytosis, some drepanocytes, blister cells, many erythroblasts, and myeloid left shift, without abnormal hematolymphoid cell populations. The remaining blood test results were unremarkable (normal renal function and electrolytes, total bilirubin 1.08 mg/dL, aspartate aminotransferase 84 U/L, alanine aminotransferase 19 U/L, lactate dehydrogenase 1604 U/L, C-reactive protein 7.5mg/L, ferritin 703 ng/mL, normal folic acid and vitamin B12 levels). The only notable symptoms were mild intermittent low back pain with a 3-day duration and acute fatigue during major physical activities. She presented a good general condition, pale but hydrated mucous membranes, fever 38°C (first febrile peak), tachycardia (150 bpm), systolic murmur and no organomegalies. Given these findings, the child was admitted to the hospital. Etiologic evaluation revealed positive parvovirus B19 IgG and IgM antibodies and, subsequently, detection of parvovirus B19 in her blood by polymerase chain reaction (PCR). The remaining serologies showed cytomegalovirus (CMV) IgG positive and IgM negative antibodies; Epstein-Barr virus (EBV) IgG positive and IgM negative antibodies; Epstein-Barr virus nuclear antigen (EBNA) positive and Mycoplasma pneumoniae IgG and IgM negative. CMV and EBV PCR were also negative, as well as PCR for influenza A and B and SARS-CoV-2. The child received a red blood cell (RBC) transfusion and

intravenous fluid therapy. Within 12 hours, laboratory results showed improvement with Hgb 7.4 g/dL, WBC $38.65 \times 10^9/L$, platelets $677 \times 10^9/L$. After an additional 48 hours, Hgb increased to 8.3 g/dL without further transfusions, WBC decreased to $13.55 \times 10^9/L$, platelets to $574 \times 10^9/L$, and reticulocytes rose to 20.56%, indicating a return of Hgb to baseline levels, reticulocytosis, and resolution of leukocytosis. The patient was discharged on the third day from admission.

Is the association with leukoerythroblastosis a red flag regarding malignancy?

Discussion:

Severe hypoproliferative anemia is common in children with sickle cell disease affected by acute parvovirus B19 infection.^{1,2}

Some viral infections can affect the normal production of erythroid precursors, causing a temporary drop in Hgb levels that is usually mild in healthy children. However, in patients with SCD, the bone marrow fails to respond normally, leading to a transient aplastic crisis, most frequently caused by parvovirus B19.^{3,4}

Patients with SCD affected by parvovirus B19 usually present with severe hypoproliferative anemia and may also have pancytopenia.^{3,4,5} However, other causes of severe anemia must be checked in these patients, such as infection/sepsis, splenic sequestration, acute chest syndrome and hyperhemolysis syndrome.^{6,7} The diagnosis of acute parvovirus B19 infection can be made using serology or by detecting viral DNA through PCR. Viremia occurs in the first week of infection, while specific IgM and IgG antibodies usually appear only after 10-12 days and two weeks, respectively. IgM can persist for months after viremia has cleared and IgG presumably persists for life. DNA PCR has higher sensitivity and specificity in early stages of infection.² In our case, because both IgM and IgG serologies were positive, PCR testing was performed, yielding a positive result, consistent with an acute infection. The patient had severe anemia and reticulocytopenia, supporting the diagnostic hypothesis of an aplastic crisis in the context of parvovirus B19 infection. However, the presence of thrombocytosis and leukocytosis is uncommon in this situation. Although it may be a normal

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body response in some cases, leukocytosis $>50 \times 10^9/L$ raises concerns for a possible hematologic malignancy, such as leukemia.⁸ Observation of the peripheral blood smear is important for differential diagnosis. Leukoerythroblastosis is characterized by leukocytosis and the presence of immature erythroid cells and myeloid precursors (left shift) in peripheral blood. Although this rare condition is usually associated with neoplastic diseases, it can also be seen in a variety of acute and transient conditions, such as infections or hemolytic anemia.^{5,9,10,11,12,13,14,15,16} There are a few reported cases of leukoerythroblastosis associated with parvovirus B19 infection. Most of the patients were younger than ours, and only two were SCD patients who also presented with thrombocytosis.^{9,10,11,12,13,14,15,16} In these two cases, improvement was observed within the first 24 hours after RBC transfusion, and full recovery within one week, consistent with our patient's course.^{9,15} The thrombocytosis in this context can be attributed to a hyperactive bone marrow response to severe anemia, which is further exacerbated by functional asplenia in SCD patients.¹⁷ As described in the literature, acute viral infections, such as parvovirus, CMV and EBV, can mimic myeloproliferative neoplasm and myelodysplastic syndromes, which appears to be the case.^{5,8,9,10,11,12,13,14,15,16,18} The rapid resolution with only supportive treatment supports a benign etiology. In conclusion, we describe the case of a young girl with SCD who developed a transient aplastic crisis with thrombocytosis and leukoerythroblastosis in the context of an acute parvovirus B19 infection. In the presence of a sudden and severe hypoproliferative anemia with an increase of other myeloid lines, infectious agents, namely parvovirus B19, should be considered and thoroughly investigated, before carrying out other invasive tests.

Compliance with ethical standards

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Conflict of Interest: None

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