TITLE: Leukoerythroblastosis in a young child with severe malaria and superimposed Gram negative infection

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ABSTRACT

Background

Leukoerythroblastosis, a non-specific and often short-lasting response of the bone marrow to different diseases such as malignancies or infections, is characterized by the presence in the peripheral blood of immature red and white cells.

Methods

We present a case of leukoerythoblastosis occurring in a 24 months-old Mozambican girl, in the context of a severe malaria episode and an associated urinary tract infection. Peripheral blood smear was used for diagnosis of malaria and leukoerythroblastosis. *Enterobacter Cloacae* isolation and antibiotic susceptibility testing were performed by conventional microbiology.

Results

Peripheral blood smear was positive for *Plasmodium falciparum* and showed a leukoerythroblastosis with red cell aniso-poiquilocytosis and left shifted neutrophils. Urine culture confirmed the presence of a multi-resistant *Enterobacter Cloacae*. Treatment of underlying conditions resolved the leukoerythoblastic reaction.

Conclusions

Leucoerythroblastosis may be related to different infectious diseases and may also appear in the context of severe malaria. Bacterial superinfection needs to be investigated.

INTRODUCTION

Malaria patients can present with different haematological alterations affecting all cell lines. White blood cell count (WBCC) is often affected and changes in every white blood cell line have been described. If WBCC left shift is accompanied by red blood cells (RBCs) leukoerythroblastosis should be contemplated. Leukoerythroblastosis is defined as the presence of immature cells of the myeloid series and nucleated red blood cells (nRBCs) in the circulating blood, with or without anaemia [1]. Leukoerythroblastosis can be associated with different pathologies, including infectious diseases [2]. Leukoerythroblastic reactions have been mainly described affecting adults [3] and only a few cases have been reported in children [4-7]. Some of those cases were attributed to infections. We present a leukoerythroblastic reaction in a Mozambican child, occurring in the context of a severe malaria episode with an associated bacterial sepsis from urinary origin.

CASE REPORT

The patient, a 24 months-old Mozambican girl was admitted with a three-day history of fever and general malaise and after starting treatment for uncomplicated malaria on a local facility two days before admission. On the day of admission, she developed four episodes of generalized tonic-clonic seizures, and was transferred to Manhiça District Hospital with suspicion of severe malaria. The patient had no relevant past clinical history. On examination, the child was fully conscious but in a general poor condition, presenting fever, tachypnoea, tachycardia, prostration and pallor. There were no other relevant findings on examination. Peripheral blood smear was positive for *Plasmodium falciparum (Pf)* with a parasitaemia of 47065 parasites/μL. Human immunodeficiency virus test on admission was negative. Initial laboratory tests showed a haemoglobin of 5.5g/dL, red blood cells of 2.03 x10^3/μL, haematocrit of 16.6% and a WBCC of 33.73 x 10^3 leukocytes/μL with a differential count of neutrophils 37.4 %, lymphocytes 54 %, monocytes 8.3 %, eosinophils 0.1% and basophils 0.1%. No others important laboratory results were reported. Treatment including parenteral artesunate, empirical ceftriaxone and blood transfusion was initiated. The patient showed a good clinical evolution and fever disappeared after 32 hours. Parasite clearance was demonstrated at 42 hours. After three doses of artesunate, a complementary full course of oral artemeter-lumefantrine was administered, according to Mozambican National guidelines for treatment of malaria. Forty-eight hours after admission, the patient's clinical status worsened, developing fever again and showing an escalating WBCC peaking at 138,5x10^3 leucocytes/μL at day 5 post admission. A peripheral blood smear obtained on day 6 confirmed an elevated WBCC (manually calculated at around 28x10^3 leucocytes/uL), although of a much lesser magnitude than the 78,13 x10^3

leukocytes/ μL reported at the same time by the automated coulter haemogram counter. The haemopathologist report described a leukoerythroblastosis with red cell aniso-poiquilocytosis and left shifted neutrophils (Figure 1). Although bone narrow examination is essential for making a definitive diagnosis no bone marrow sample could be obtained due to lack of site resources. Malignancies and erythrocyte abnormalities were ruled out considering the information provided by the blood smear and the clinical evolution. New samples of blood and urine were taken for cultures and antibiotic was switched empirically from ceftriaxone to ciprofloxacin with temperature normalization 24 hours later. Subsequently, the urine culture obtained on day 6 grew a multi-resistant *Enterobacter cloacae* resistant to ceftriaxone and sensible to ciprofloxacin. No microorganism was isolated in the first and second blood culture. The patient also presented a drop of haemoglobin at 98 and 174 hours to 4.8 and 4.3 g/dL respectively, requiring two additional blood transfusions. After those interventions, the patient improved swiftly, with temperature and WBCC normalization, and was discharged on day 10 with a haemoglobin of 7.9g/dL and WBCC of $17.27x10^3/\mu$L. On day 14 after admission, an outpatient clinical and laboratory control was made. The patient remained asymptomatic and its haemogram showed a haemoglobin of 7.7g/dL, RBCs of 2,33 $x10^3$ / μL, haematocrit of 26% and WBCC of 12.17 $x10^3$ leukocytes/μL with a normal WBCC.

DISCUSION

Different leukocyte alteration patterns have been reported in relation to malaria infections including normal WBCC, leukopenia and leukocytosis [8-13]. Differential diagnosis of WBCC alterations is challenging, particularly in poor settings where diagnostic resources and specialized staff are scarce. Those alterations, are normally detected by automated haematology analysers and in certain circumstances, it is recommended to obtain a peripheral blood smear, and whenever possible, conduct a bone marrow examination [14]. The microscopic observation of the peripheral blood smear may not only quantify the real magnitude of the WBBC elevation but can also detect qualitative abnormalities in all haematological series, including leukocytes, erythrocytes and platelets [14]. If WBCC left shift is accompanied by RBCs leukoerythroblastosis should be considered. Leukoerythroblastosis is characterized by the appearance of immature cells of the myeloid series and nRBCs in the circulating blood, with or without anaemia [1]. Leukoerythroblastosis has been better defined in adults [3] and can appear as a result of a wide range of diseases including leukaemia or malignancies, infections, haemorrhages or drug reactions [14, 15]. In children only a handful of cases have been reported, associated with malignancy [4], parvovirus B19 infections [5, 6] or inguinal abscess [7].When the underlying condition is treated, WBCC normalizes rapidly, leading to the resolution of the leukoerythroblastic reaction, as occurred in this case. Although the relative weight of malaria

infection and its relationship with leukoerythroblastosis cannot be ruled out, the timeline of events suggests that in this case it was mainly caused by a bacterial sepsis of urinary origin. The co-existence of malaria and superimposed bacterial infections is relatively frequent and entails a poorer prognosis [16]. This case report is illustrative of such an association, with the initial severe *Pf* infection being complicated by an UTI due to a multi-resistant *Enterobacter cloacae*, with the previously unreported particularity of being expressed as a leukoerythoblastosis.

CONCLUSIONS

Leukoerythroblastosis in childhood may be related to different diseases including infections of a transient and acute nature. Differential diagnosis is challenging in poor settings with lack of laboratory facilities and specialized staff. In the context of a severe malaria episode it may reflect a coexisting infection that needs to be further investigated.

LIST OF ABBREVIATIONS

nRBCs: nucleated red blood cells

Pf: Plasmodium falciparum

RBCs: red blood cells (RBCs)

WBCC: White blood cell count

COMPETING INTERESTS

The authors declare that they have no competing interests

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