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Aplastic crisis caused by parvovirus B19 in an adult patient with sickle-cell disease

Crise aplástica por parvovírus B19 em um paciente adulto com doença falciforme

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Abstract *We describe a case of aplastic crisis caused by parvovirus B19 in an adult sickle-cell patient presenting with paleness, tiredness, fainting and dyspnea. The absence of reticulocytes lead to the diagnosis. Anti-B19 IgM and IgG were detected. Reticulocytopenia in patients with hereditary hemolytic anemia suggests B19 infection.*

Key-words: *Human parvovirus B19. Sickle-cell disease. Transient aplastic crisis. Reticulocytopenia.*

Resumo *Descreve-se um caso de crise aplástica devida ao parvovírus B19 num paciente adulto, manifestando-se por palidez, cansaço, lipotímias e dispnéia. A ausência de reticulócitos chamou a atenção para o diagnóstico. Detectaram-se IgM e IgG anti-B19. Reticulocitopenia em pacientes com anemia hemolítica hereditária sugere infecção por B19.*

Palavras-chaves: *Parvovírus B19. Doença falciforme. Crise aplástica transitória. Reticulocitopenia.*

Parvovirus B19 is the only pathogenic parvovirus in humans. It is a DNA virus that infects and destroys erythroid cell progenitors. Cossart and coworkers[3] discovered parvovirus B19 fortuitously in 1974, when they were trying to detect HBsAg in panels of human sera. Unexpectedly, the serum numbered 19 in panel B showed an anomalous precipitin line in a counter immunoelectrophoresis (CIE) employing another human immune serum. This same B19 serum showed no reactivity when tested for HBsAg with much more sensitive radio-immuno or hemagglutination assays using animal sera. Cossart excised the precipitin line from the CIE gel and, examining it under electron microscopy, saw 23-nanometer particles resembling parvovirus. The new virus did not react with antisera to adeno-associated viruses or to rat parvovirus, and the virus was labeled *serum-parvovirus-like particle*. Retesting the sera from their panels, which were obtained mainly from British adults, Cossart and coworkers demonstrated that 30% of them had antibodies to the virus.

The virus was identified again two years later in two blood donors[12], and six years later in two British soldiers returning from Africa[15], all of which suffering from nonspecific febrile illness. These patients were probably examples of the many instances in which parvovirus determines asymptomatic infection or nonspecific febrile disease. Nonetheless, the virus was subsequently associated with specific clinical pictures and syndromes.

The first clinical syndrome doubtlessly linked to parvovirus B19 was transient aplastic crisis

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occurring among patients with sickle-cell disease[11]. The virus was demonstrated in plasma by electron microscopy during the aplastic crisis, and there was evidence of seroconversion at convalescence — a time in which the virus was no longer detectable. Direct invasion and destruction of erythroid cell progenitors in bone marrow results in transient interruption of erythropoiesis. Clinical manifestations of acute anemia occur only in patients with great erythrocyte turnover (as in sickle-cell disease and other hemolytic anemias). In otherwise healthy individuals, the erythrocytes circulate for fully 120 days and the infection is cured spontaneously before any hematologic symptoms occur[11].

The appearance of techniques for the detection of IgM class antibodies enabled the conclusion that parvovirus B19 was the only etiologic agent of an old common exanthematic benign disease of childhood: erythema infectiosum. This disease was described at the end of the seventeenth century, and has been known variously as fifth disease, slapped cheek disease, academy rash, Sticker's disease, and infectious megaloerythema. There are no hematologic symptoms[1].

Among those suffering from AIDS, the immunodeficiency can render the infection chronic. The destruction of erythroid cell progenitors, continued beyond the maximal life span of erythrocytes, results in severe and protracted anemia that responds to the intravenous administration of standard human immune globulin, which generally contains sufficient amounts of antiviral antibodies[7 18].

In the case of pregnant women, infections caused by parvovirus B19 can produce severe fetal damage, despite it's little, or perhaps absent, teratogenic potential[5]. During fetal life, particularly in the second trimester, there is normally a great increase in the fetal total red cell mass. The infected fetus, unable to keep the rate of erythropoiesis needed for such an increase, develops severe intrauterine anemia. This is usually followed by heart failure (also caused to a certain extent by myocarditis) and anasarca, in a picture denominated erythroblastosis fetalis, or non-immune hydrops fetalis[1].

CASE REPORT

This is the case of a 28-year-old, male, afro-Brazilian, born in Rio de Janeiro state, living with his female companion and three children in a poor neighborhood of Niterói, Rio de Janeiro State, Brazil. He worked as a restaurant attendant, without social insurance of any type. He was neither a smoker, nor a drinker. He had sickle-cell disease diagnosed at the age of 5 months. This also affected a maternal uncle, and two sisters out of his six siblings. Both parents are diabetic, and the father was hypertensive. At the age of three, he was admitted to the Infectious Diseases Department of Hospital Universitário Antônio Pedro with jaundice and elevated aminotransferases, and was given a diagnosis of hepatitis. Since then, he has attended the Hematology outpatients' service on an irregular basis, suffering from frequent acute respiratory infections and hemolytic crises. He takes folic acid continuously.

He was admitted on March 16, 1999, complaining of tiredness, dyspnea and fainting, and was provisionally diagnosed as having hemolytic crisis. Six days before admission, he had had symptoms attributed to a bout of tonsillitis, and improved after being treated with a benzathine penicillin injection. However, after three days, he began to faint and to feel increasingly tired. By the time of admission, he was restricted to the emergency room stretcher, with dyspnea, generalized pains, and fainting on attempting to sit up. He was awake, fully conscious, but rather pale and somewhat jaundiced. Submandibular and pre-auricular adenopathy was noted. His respiratory rate was twenty-eight. There was a third heart sound, and a mitral systolic murmur. He had audible peristalsis, no visceral enlargements, and his abdomen was not tender to palpation. He had a chronic eschar on the right malleolus, and there was no calf tenderness. A blood count showed no reticulocytes and the diagnosis was changed to aplastic crisis. He was transfused with three units of packed red cells, and his painful and cardiovascular symptoms rapidly improved. He was discharged on March 25, 1999, afebrile, well hydrated, and normotensive, for follow-up as an outpatient. In a blood sample collected this day, using immunofluorescence and a m-capture enzyme immunoassay, it was possible to detect specific IgG and IgM antibodies against parvovirus B19[4 13]. A dot blot assay[9] detected no parvovirus B19 DNA in this sample. The blood counts performed at admission can be seen in Figure 1, which include also the only three earlier counts available for comparison.

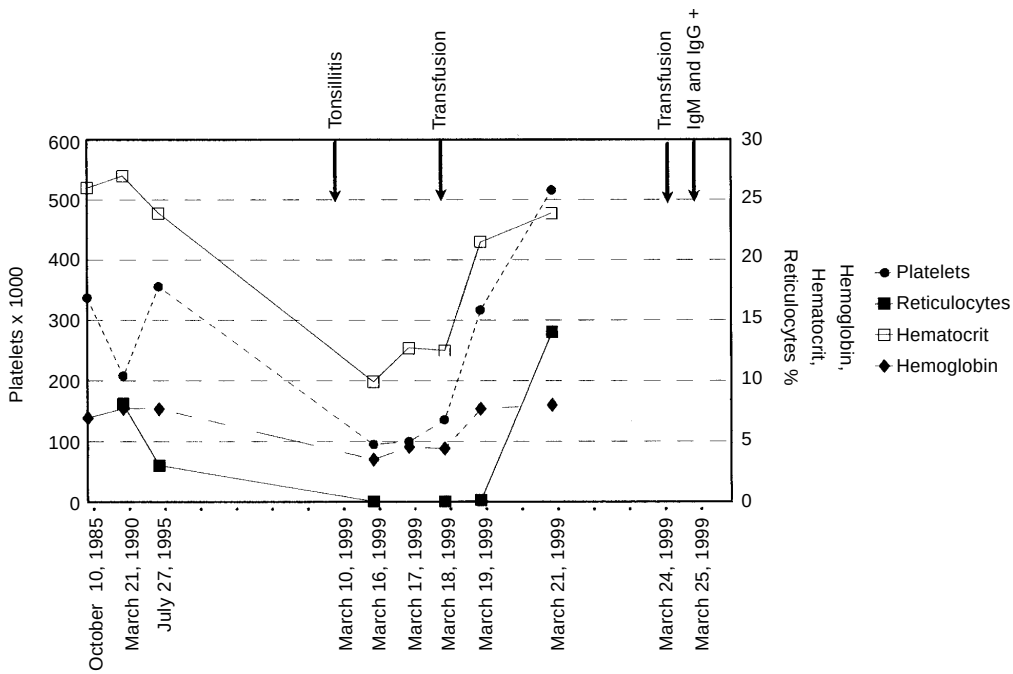

Figure 1 - Evolution of some laboratory findings of a patient with sickle cell disease (1985-1999).

DISCUSSION

Parvovirus B19 is considered the most important cause of aplastic crisis in sickle-cell patients. Aplastic crisis due to parvovirus B19 was also described in a wide range of other hemolytic disorders, as hereditary spherocytosis, thalassemia, red cell enzyme disorders (as pyruvate kinase deficiency) and auto-immune hemolytic anemia. An aplastic crisis may be the first manifestation of a hemolytic disorder in a patient who was well compensated until that moment. An aplastic crisis may also occur under certain conditions marked by an *erythroid stress*, such as hemorrhage, malaria, iron deficiency anemia, or following renal or bone marrow transplant. Acute anemia following parvovirus B19 infection has been described even in normal people. A fall in red cell count was described in infected healthy volunteers, but a generally good erythroid reserve precludes the appearance of symptoms[1].

Although suffering from a disease which is, at last, self-limiting, the patient with aplastic crisis may progress to an appalling situation, or even die. Signs and symptoms include not only dyspnea and tiredness resulting from the worsening anemia, as experienced by our patient, but also confusion and evidence of congestive heart failure. Parvovirus B19 infection is frequently associated with changes in blood lineages other than the erythroid: different degrees of neutropenia occur and thrombocytopenia, due to the cytopathic effect on megakaryocytes, is not uncommon. Some patients have massive bone marrow necrosis[1 8 17].

In Rio de Janeiro, parvovirus B19 was first detected in 1988, during a blood donor survey[16]. For the general population living in this city the seroprevalence ranged, in the 1980's, from 35% in children to more than 90% in adults over 50 years old[10]. In a study performed in 1994 on a large group of sickle cell patients attending the Sickle Cell Service in the Instituto Estadual de Hematologia, the prevalence of anti-B19 IgG was very low when compared to the general population matched by age[14]. An epidemiologic surveillance study for exanthematic diseases, presently in course in Niterói, detected an increase in the rate of parvovirus B19 infection between December 1998 and January 1999[2].

Cases of hydrops fetalis, transient aplastic crises, and febrile illnesses with joint manifestations are described sporadically in the local population[5].

In our patient, two of the three prior blood counts available for comparison displayed an increase in the reticulocytes count, as would be normally expected in people with sickle-cell disease. Indeed, a normal reticulocytes count would indicate possible bone marrow failure in such a patient. Nevertheless, in our patient the reticulocytes count was found to be zero in three out of the four initial exams performed after admission (Figure 1). The fifth exam showed a count that would be considered low even for a healthy individual. Only in the last exam, performed eleven days after the onset of symptoms, did the count return to the ordinary levels for the patient. Interestingly, the platelet count showed a parallel decrease. This was probably a consequence of cytopathic effect on megakaryocytes, as stated above.

As can be inferred from the seroprevalence profile in Rio de Janeiro and elsewhere, in which the number of previously infected individuals increases according to the age strata, transient aplastic crises caused by parvovirus B19 are not to be expected in an adult patient. It is very likely that the symptoms of tonsillitis experienced by the patient six days before admission were a consequence of the parvovirus B19 infection.

During transient aplastic crisis, the patient is acutely infected and eliminates a huge quantity of virus, mainly through respiratory secretions. As our patient stayed in a shared ward for 9 days before the diagnosis, there might be some concern regarding his role as a potential source of nosocomial parvovirus B19 infection[6].

A low or zero reticulocyte count in patients with hereditary hemolytic anemia must draw attention to the possibility of transient aplastic crisis caused by parvovirus B19, indicating a serologic diagnostic test. From the nosocomial epidemiology standpoint, promptness in making the diagnosis would lessen the risk of a possible nosocomial outbreak.

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