Fatal fungal superinfection complicating B19 virus-induced massive bone marrow necrosis in sickle-cell disease

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Manifestations of acute B19 virus infection in sickle cell disease range from transient and benign isolated anemia to life-threatening conditions. We report a case of a B19 virus-induced massive bone marrow necrosis with severe pancytopenia complicated by a fatal secondary acquired fungal superinfection.

A 29-year old woman was admitted to hospital for dizziness, muscular and diffuse bone pain, and fever as high as 40°C of one-week duration. Hemoglobin SC disease (hemoglobin [Hb] HbF 1%; HbS 50%; HbC 46%; HbA2 3%) was known since childhood with 1 to 2 annual episodes of musculoskeletal or abdominal pains, and 1 episode of acute chest syndrome. Baseline hemoglobin was 11.6 g/dL, and reticulocyte count 174×10^9/L (3.9%). Red cell transfusions had been needed twice during pregnancies. Symptoms began with malaise, muscular pain and fever. There was no history of recent medication. Similar symptoms occurred simultaneously within household members. Core temperature was 40°C, the liver and the spleen were not felt and no lymphadenopathy was found. Laboratory analysis revealed mild aregenerative anemia [Hb 8.4 g/dL; reticulocytes 10×10^9/L (0.3%)]. Despite non-steroid anti-inflammatory drugs and morphine intravenous administration, the patient remained dizzy and became dyspneic and comatose within the first day, whereas laboratory analysis evidenced severe hypoxemia and sudden drop of hemoglobin. The patient was referred to the respiratory intensive care unit (ICU). Clinical parameters worsened rapidly, the spleen became enlarged, and multi-organ failure occurred within few hours, with pancytopenia, disseminated intravascular coagulation, hepatic and renal dysfunction and shock (Table). Mechanical ventilation, hemodynamic and renal artificial support, as well as packed red cells, platelets and fresh frozen plasma were administered. Empirical antibiotics were initiated. Blood, urine and respiratory specimens cultures remained negative for bacteria, fungi and virus (HIV, Epstein-Barr virus and cytomegalovirus). Bone marrow aspiration and biopsy specimen (day 2) demonstrated a hyper cellular marrow with necrosis of all hematopoietic precursors, with pyknotic nuclei, *ghost cells* and nuclear debris (Figure 1). Special stains for acid-fast bacilli, fungi, spirochetes, and immunoperoxydase stains for cytomegalovirus and herpes simplex antigens were negative. There was neither granuloma formation nor lymphoma. The RBC folate level was normal. The serum collected on hospital admission was positive for B19 virus-specific IgM antibodies (parvovirus B19 enzyme immunoassay third generation; Biotrin, Dublin, Ireland). The B19 virus DNA was evidenced in serum, bronchoalveolar lavage and bone marrow, using PCR. Moreover, a previous 6-months serum assayed for B19 virus DNA and antibodies was negative. Clinical and biological parameters improved up to day 6, while the patient became febrile and hematologic variables worsened. Antibiotics were changed after repeated numerous samples for bacteria and fungi. A repeated bone marrow aspirate (day 7) demonstrated massive necrosis of virtually all hematopoietic elements (Figure 2). Immune globulin infusion (180 g over 5 days) was started. A single-sheathed plugged telescopic catheter culture yielded to rhizopus sp. Unfortunately, the patient died on day 15 despite the administration of ambisome. No autopsy was performed.

We report a fatal case of a documented acute B19 virus infection in a sickle cell disease patient. The clinical spectrum of B19 virus infection ranges from benign[1,2] to life-threatening presentation.[3-5] Several mechanisms may have contributed to death in our patient. First, there is a well recognized association between B19 virus infection and bone marrow necrosis, which may result from a direct bone marrow injury or be secondary to a primary lung injury.[4-7] In our patient, we could not evidence a direct viral cytopathic effect on bone marrow biopsy specimen, in part because of the massive bone marrow necrosis and hypoplasia. Although the commonly observed falls in neutrophils and platelets in B19 virus-infected patients are usually transient, recovery of neutrophils may be delayed for several days, which might further increase the risk of bacterial superinfection.[8] To

Table 1. Results of laboratory tests performed at 4 time points for a patient with acute human B19 virus infection.

Laboratory test	*Normal values*	*Baseline admission*	*Hospital hospital admission*	*12 hours after admission*	*ICU admission*	*24 hours after ICU*
Urea nitrogen level, μM/L	3-7	3	3	3	8	9
Creatinine level, μM/L	40-120	60	66	53	94	137
Total bilirubin level, μM/L	< 17	10	18	24	26	30
Aspartate/Alanine aminotransferase level, IU/L	2-60	19/12	81/33	355/53	622/63	346/117
Lactate dehydrogenase level, IU/L	160-500	400	1800	12100	11500	17000
Lactic acid, mM/L	0.60-2.40	1.20	1.20	5.30	5.30	18
Hemoglobin level, g/dL	12-18	11.6	8.4	4.3	4.1	3.4 (after 3 packed red cells)
Reticulocyte count, ×10^9/L (%)	30-120	174 (3.9)	10 (0.3)	12 (0.7)	-	-
Leukocyte count, cells ×10^9/L	4-10	5.2	7.3	10.1	12	12.8
Differential count, cells ×10^9/L						
Neutrohils	1.5-7	2.55	*5.77*	6.44	-	-
Lymphocytes	1.5-4	2.18	*1.05*	2.96	-	-
Monocytes	0.10-1	0.1	0.24	0.17	-	-
Eosinophils	0.03-0.7	0.26	0.06	0.09	-	-
Platelet count, cells ×10^9/L		192	207	100	68	93 (after 10 platelets units)
Prothrombin time, %	75-120	100	-	50	44	56 (after 3 plasma units)
Partial-thromboplastin time, ratio	0.90-1.26	1.11	-	1.64	1.80	1.42

Figure 1. A. (First sample, day 2). Hyper cellular marrow with ill-defined cytoplasmic borders and bare nuclei of hematopoietic precursors, most of which are unrecognisable (erythroblasts? lymphoid cells?); persistence of megakaryocyts. **B.** (first sample, day 2). High power view demonstrating loss of detail of mononuclear cells, consistent with marrow necrosis.

Figure 2. A. Bone marrow biopsy specimen (day 2) demonstrating extensive coagulative necrosis involving nearly all hematopoietic elements (due to Dr Mathilde Sibony from the Service d'Anatomie Pathologique). **B.** Repeated bone marrow aspirate (second sample, day 7) demonstrating *ghost* bone marrow, with scarce cells and pycnotic nuclei; megakaryocyts have also disappeared.

our knowledge, fungal superinfection has never been reported in this clinical setting. Second, systemic fat embolism syndrome may complicate bone marrow necrosis, sometimes leading to death in a setting of marked anemia, central nervous system depression, respiratory distress and multi-organ failure,[9] as we observed in our patient. Kolquist et al have reported the case of a sickle cell child (S/,+ thalassemia) with fatal fat emboli complicating B19 virus induced-marrow necrosis diagnosed at autopsy.[4] Last, TTP like illness might also have been considered, although unlikely because of the abnormality of the initial coagulation tests.[10] As no autopsy was performed in our patient, we can only hypothesize that death resulted from a fungal superinfection occurring during a massive viral-induced bone marrow necrosis, possibly complicated by systemic fat emboli.

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