

## Bone marrow necrosis and fat embolism: an autopsy report of a severe complication of hemoglobin SC disease

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### ABSTRACT

Sickle Cell Disease encompasses a group of disorders related with the hemoglobin S and other hemoglobin genotypes. The clinical manifestation and the severity of symptoms are dependent on the specific genotype. In this setting, homozygous genotype (HbSS) presents an early onset of symptoms and a low expectancy of lifetime. However, the SC genotype (HbSC), which apparently shows a less severe clinical course, may exhibit the same complications of HbSS. These complications are usually manifested late in the course of life, when compared with the HbSS patients. It is noteworthy that HbSC may present a normal hematocrit, and therefore stays unknown until the first complication, that may be disastrous. The authors report a case of an African-Descendant woman, aging 65 years, with no previous diagnosis of anemia who sought medical attention because of a thoracic back pain followed by fever and altered mental status. The clinical picture deteriorated very fast with multiple organ failure and death. The autopsy findings concluded by generalized vaso-occlusive crisis, bone marrow necrosis and bone marrow and fat embolism, mainly to the lungs and kidney. The authors call attention for the knowledge of this severe life threatening complication, mainly in a country with a high Afro-Descendant population.

### Keywords

Anemia, Sickle Cell; Hemoglobin SC Disease; Embolism, Fat; Multiple Organ Failure; Acute Chest Syndrome.

### CASE REPORT

A 65-year-old black female patient, previously diagnosed with diabetes mellitus and hypertension, was admitted at the emergency room with the history of continuous and intense thoracic pain, mainly in the back, followed by high-grade fever and altered mental status. Two days after the initial painful symptoms the patient started with obtundation and stupor soon after, reason why she did not take her regular medication namely: antihypertensive medication, oral hypoglycemic drugs and insulin.

The initial examination showed an ill-looking patient, pale, icteric, and dehydrated. Coma Glasgow scale was 10, blood pressure was 130/74 mmHg, pulse was regular 110 beats per minute, respiratory frequency was 26 respiratory movements per minute, room air oximetry was 86%, axillary temperature was 38,3° C and capillary glucose determination was 556 mg/dl. Nuchal stiffness was absent. Cardiac examination was unremarkable, but scarce rales and rhonchi were audible in the right lung. The abdominal examination

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disclosed hepatosplenomegaly, and lower limbs examination was normal. The initial laboratory workup is shown in Table 1.

Peripheral blood film showed some target red cells, others cell figures as shrunken and elongated forms, folded cells as well as 150 erythroblasts/ 100 leukocytes (Figure 1).

The patient was treated with antibiotics (empirically for a probable pulmonary infection, although chest radiography was doubtful on this diagnosis) transfusion of packed red blood cells, intravenous insulin, and mechanical ventilatory support. Soon after the admittance, the patient presented hemodynamic instability requiring continuous noradrenalin infusion. Despite the adopted therapeutic regimen, the patient died on the third day of hospitalization. After death the hemoglobin electrophoresis was available and showed the SC pattern by alkaline and acid electrophoresis and high performance liquid chromatography (HPLC). Diagnosis of HbSC was unknown *antemortem*.

## AUTOPSY FINDINGS

Gross examination of the cephalic segment showed an edematous and congested brain (Figure 2), weighing 1340,0g (RV 1178 g). Microscopically, there was a hematopoietic cell thrombus interspersed

with fibrin and red blood cell in meningeal vessels, intraparenchymal vascular congestion, scattered small foci of recent hemorrhage with few sickled red cells and some pyknotic neurons in cerebral cortex (Figure 3).

On gross examination, the thoracic cavity contained congested and edematous lungs more prominent on the inferior lobes, (right lung: 451,0g; left lung: 476,0g [RV 450 g and 375 g respectively]) (Figure 4).

Microscopic examination showed viable and necrotic bone marrow embolism in pulmonary artery branches and arterioles, fat embolism in alveolar septa capillary and focal fibrin thrombi.

There were also areas of pulmonary infarction, diffuse congestion, foci of hemorrhage, alveolar edema, and small areas of fibrin deposition with mild foci of desquamating pneumocytes representing mild diffuse alveolar damage (Figures 4, 5 and 6).

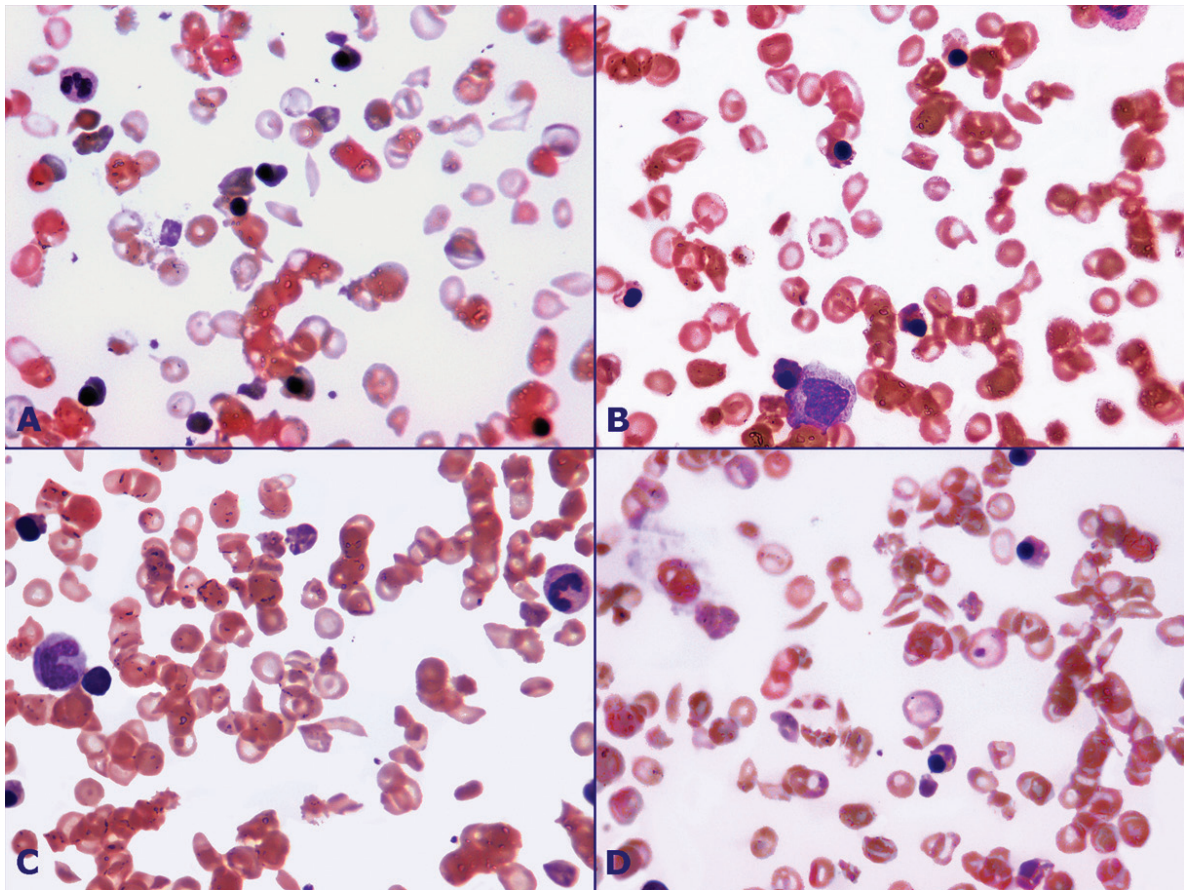
Thin slices stained with toluidine blue and electronic microscopy confirmed the presence of fat droplets within pulmonary capillaries (Figure 7).

At the opening of the abdominal cavity, the liver was enlarged and purplish in color, weighing 1674,0 (RV 1780g) (Figure 8).

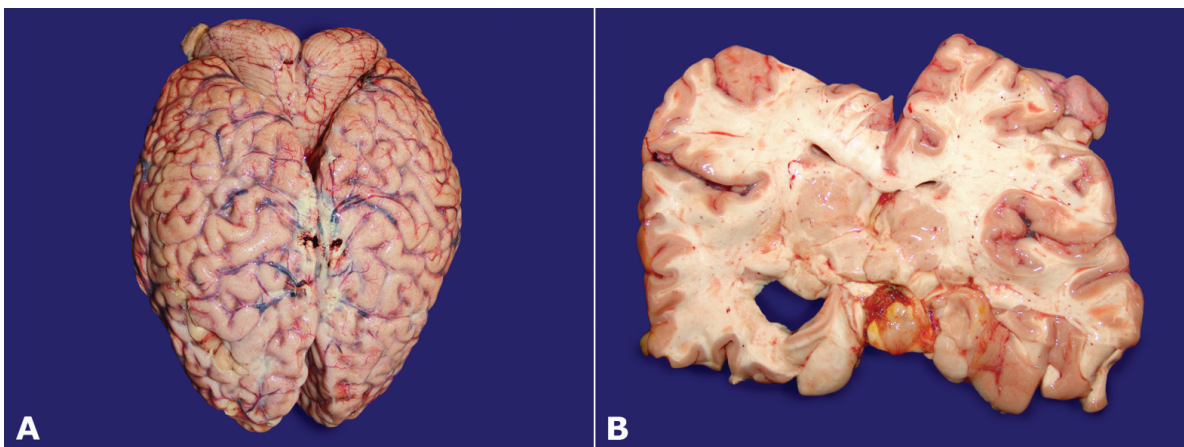
**Table 1.** Initial laboratory workup

		VR			VR
Hemoglobin	7.1	12.3-15.3 g/dL	Urea	228	5-25 mg/dL
Hematocrit	20.3	36.0-45.0%	Creatinine	1.51	0.4-1.3 mg/dL
Leukocytes	21.000	4.4-11.3 × 10 <sup>3</sup> /mm <sup>3</sup>	Potassium	4.1	3.5-5.0 mEq/L
Bands	6	1-5%	Sodium	150	136-146 mEq/L
Segmented	72	45-70%	ALT	495	9-36 U/L
Eosinophils	0	1-4%	AST	381	10-31 U/L
Basophils	0	0-2.5%	Total protein	6.3	6-8.5 g/dl
Lymphocytes	10	18-40%	Albumin	3.2	3.0-5.0 g/dL
Monocytes	12	2-9%	TB/DB	4.12/2.4	1/0.3 mg/dL
Platelets	86	150-400 × 10 <sup>3</sup> /mm <sup>3</sup>	CK/CKMB	267/0.6	140/<10 mg/L
INR	1.59	1.0	Lactate	24.9	4.5-19.8 mg/dl
CRP	24.9		Glucose	540	70-99 mg/ml

ALT= alanine aminotransferase; AST= aspartate aminotransferase; CRP= C-reactive protein; CK= creatine kinase; CKMB= creatine kinase - fraction MB; DB= direct bilirubin; INR= international normalized ratio; TB= total bilirubin.



**Figure 1.** Peripheral blood film showing elongated, target and folded red cells. Note the presence of erythroblasts.

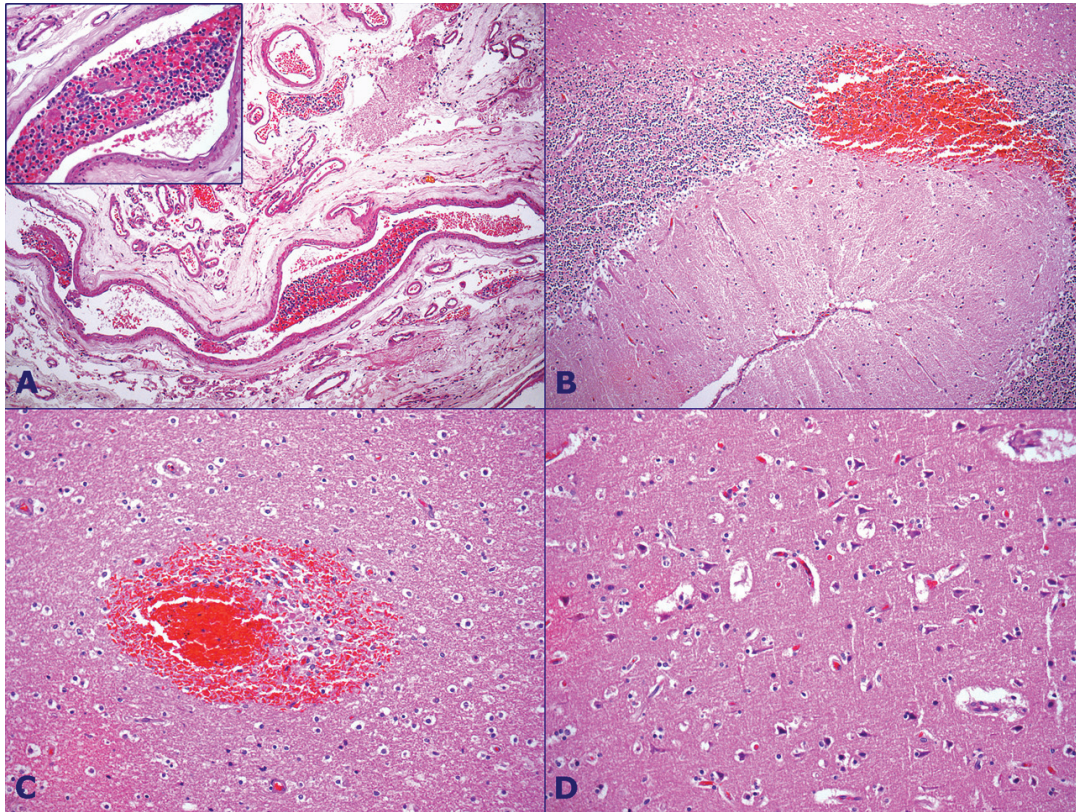


**Figure 2.** Gross examination of the brain showing edema and congestion.

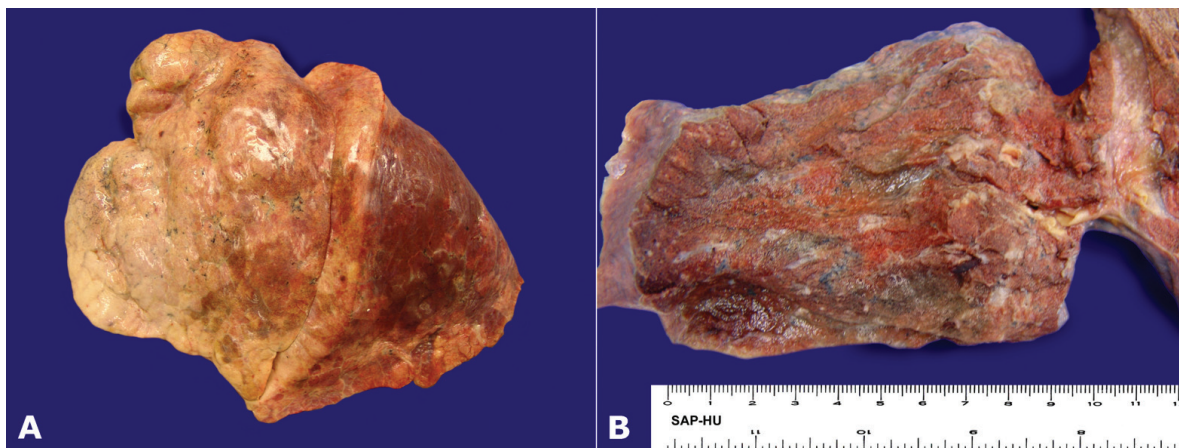
Microscopically the liver was cirrhotic with many sites of atrophic or disappearing portal branches (veno-occlusive pattern) and sinusoidal fibrosis. There was diffuse sinusoidal congestion, with aggregation and impactation of sickled red cells and also prominent foci of liver cell necrosis in all zones. There was mild siderosis (Figure 9).

The spleen was enlarged and congested, weighing 743,0g (RV 112g), represented by red pulp congestion and areas of necrosis, with focal vascular thromboembolism and small subcapsular nodule suggestive of Gamma-Gandy body (Figure 10).

The right kidney weighed 227 g, and the left kidney 225 g (RV 280 g each), both presenting granular



**Figure 3.** Photomicrography of the brain, showing in **A** – (HE – 100x) hematopoietic cell thrombus in meningeal vessel; **B** – (HE – 100x) small foci of recent hemorrhage in cerebellum; **C** – (HE – 200x) intraparenchymal vascular congestion with hemorrhage and sickled red cells; **D** – (HE – 200x) presence of pyknotic neurons, showing eosinophilic and shrunken cytoplasm, in cerebral cortex.



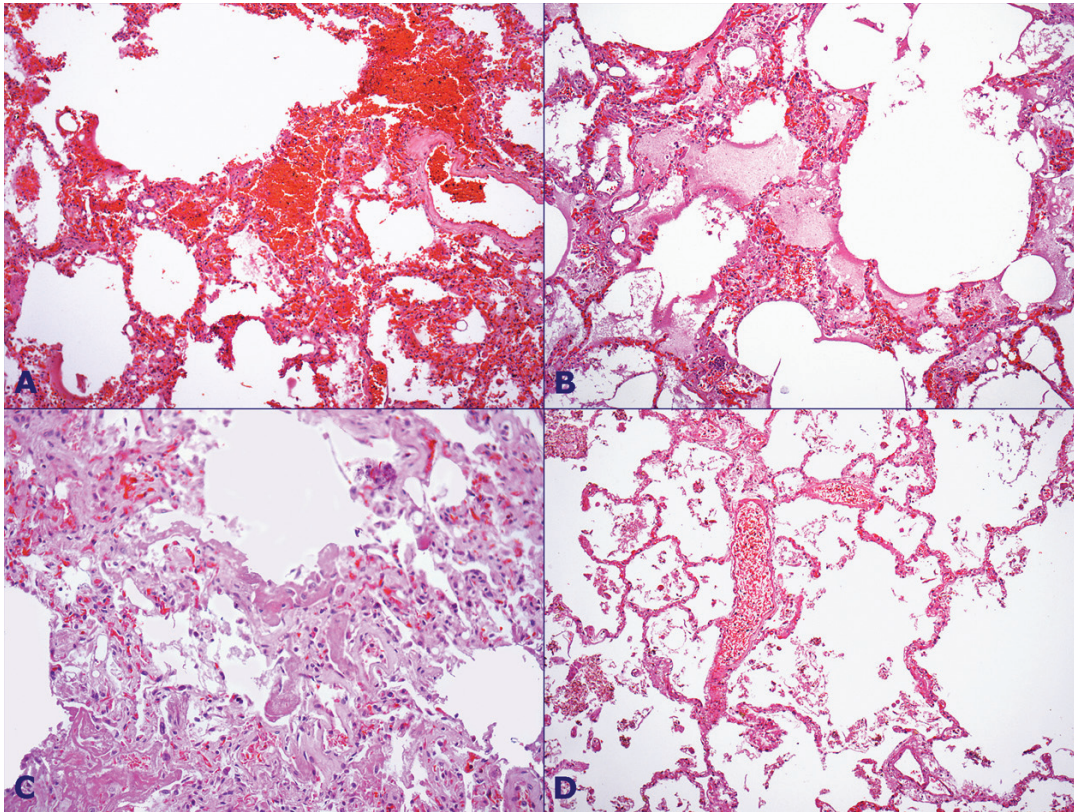
**Figure 4.** **A** – Gross findings of the lung showing reddish pleural surface on the lower lobe of the left lung; **B** – presence of reddish congested pulmonary parenchyma on the cutting surface.

surface. On cut-section, they showed congestion suggestive of acute tubular necrosis and a simple cyst measuring 1,5 cm in the right kidney (Figure 11).

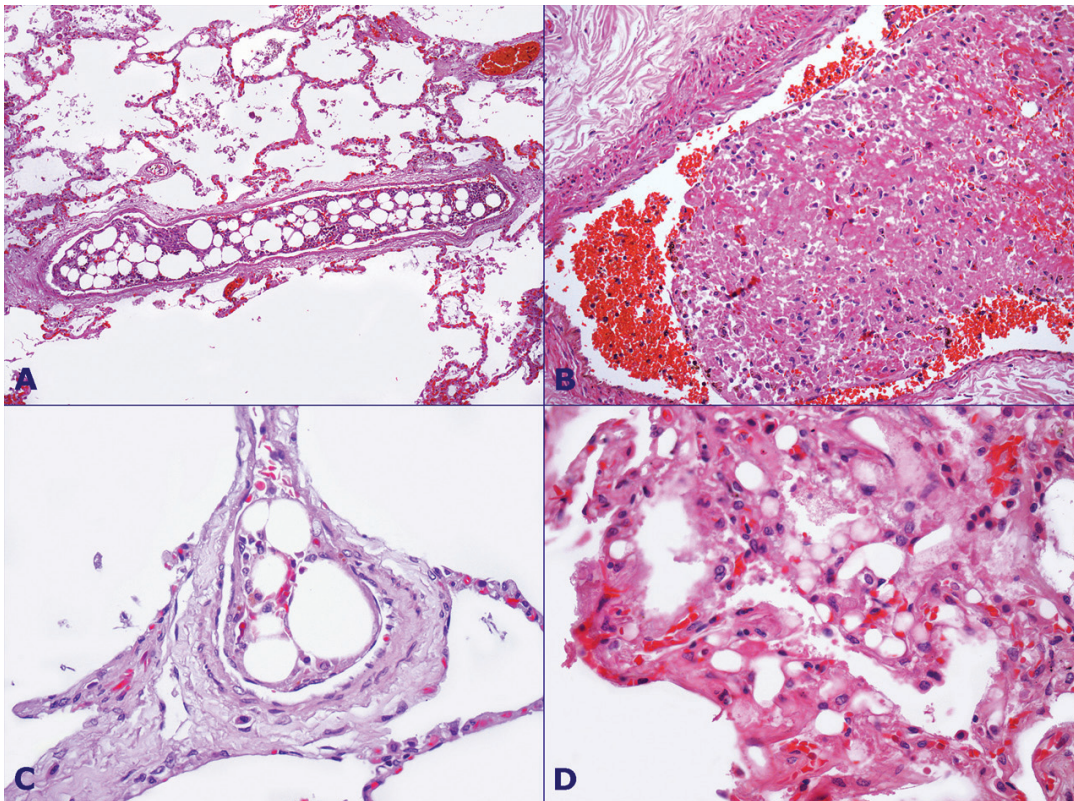
Microscopic examination showed diffuse congested glomeruli with scattered foci suggestive of fat embolism, focal Kimmelstiel Wilson nodule (nodular glomerulosclerosis) consistent with diabetic

nephropathy, mild foci of mesangial proliferation, foci of benign nephrosclerosis and also acute tubular necrosis (Figure 12).

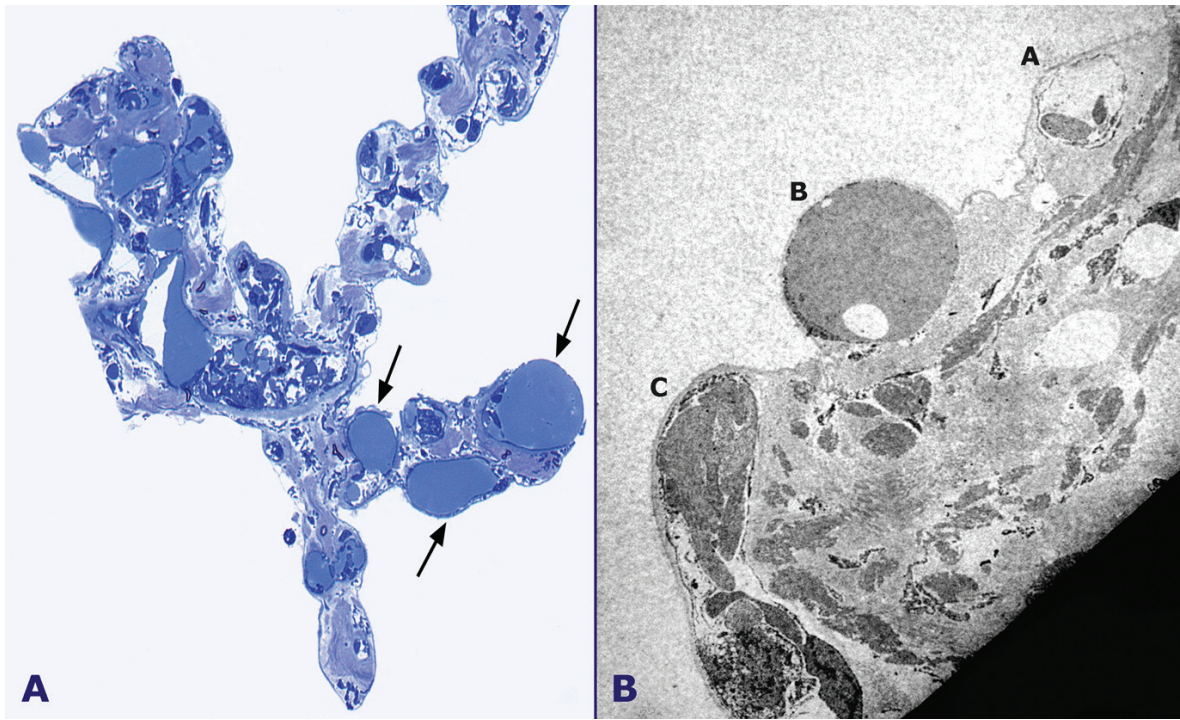
The bone marrow was hypercellular, represented by 70% of hematopoietic cells, showing large areas of infarction (about 50%) and areas of hemorrhage with sickled erythrocytes (Figure 13).



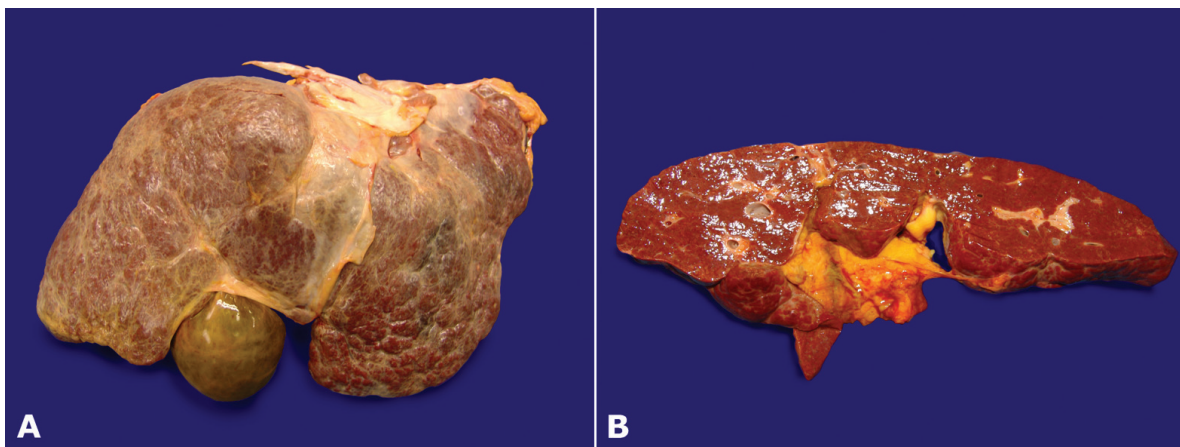
**Figure 5.** Photomicrography of the lung. **A** – (HE – 100x) pulmonary parenchyma showing capillary congestion and hemorrhage intra alveolar; **B** – (HE – 100x) presence of areas of edema alveolar; **C** – (HE – 200x) focus of deposition of fibrin on the alveoli; **D** – (HE – 100x) presence of a congested vessels with sickled red cells in an area of infarcted parenchyma.



**Figure 6.** Photomicrography of the lung. **A** and **C** – (HE – 100x; 200x) presence of bone marrow and fat tissue embolism in pulmonary arteriole branch; **B** – (HE – 200x) presence of necrotic bone marrow embolism in pulmonary artery lumen; **D** – (HE – 400x) presence of adipocytes in the capillaries of alveolar septa.



**Figure 7.** Photomicrography of the pulmonary septa. **A** – showing capillary loops obstructed by fat droplets (some of them are pointed with arrows) (toluidine blue stained tissue representing a 1u section for a plastic-embedded sample, 400x). **B** – Electronic microscopy of the pulmonary septum showing three capillaries (A, B and C). Note in B a fat droplet fulfilling the entire capillary circumference and in C cellular debris (6000x).



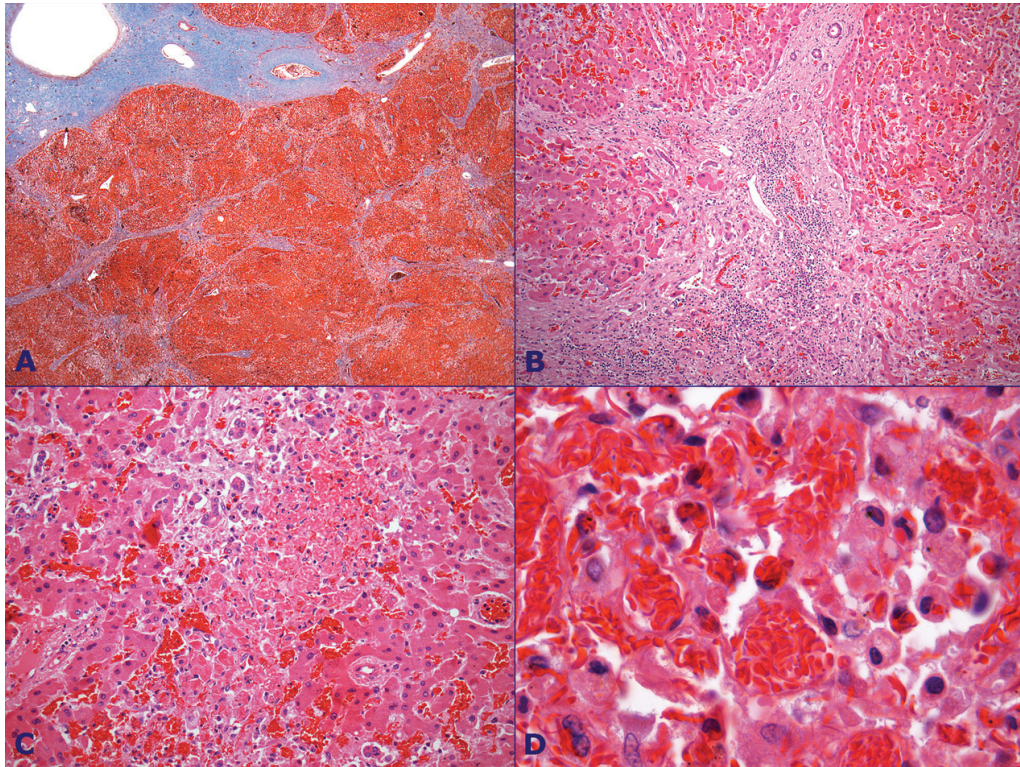
**Figure 8.** **A** – Gross findings of the liver showing nodular irregularity of the external surface suggestive of cirrhosis; **B** – presence of congested liver parenchyma on the cutting surface.

The cause of the death was attributed to sickle cell disease crisis complicated by extensive bone marrow necrosis and fat embolism syndrome, leading to multiple organ failure, and shock.

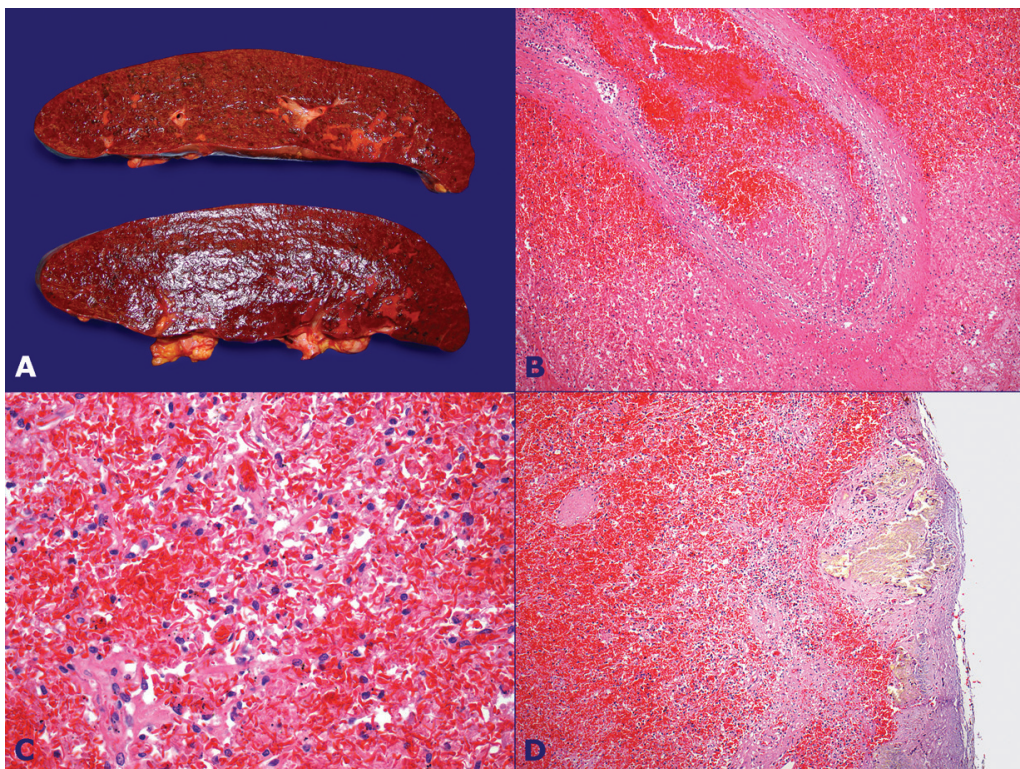
## DISCUSSION

Sickle cell disease (SCD) comprises a group of disorders, which include homozygous hemoglobin

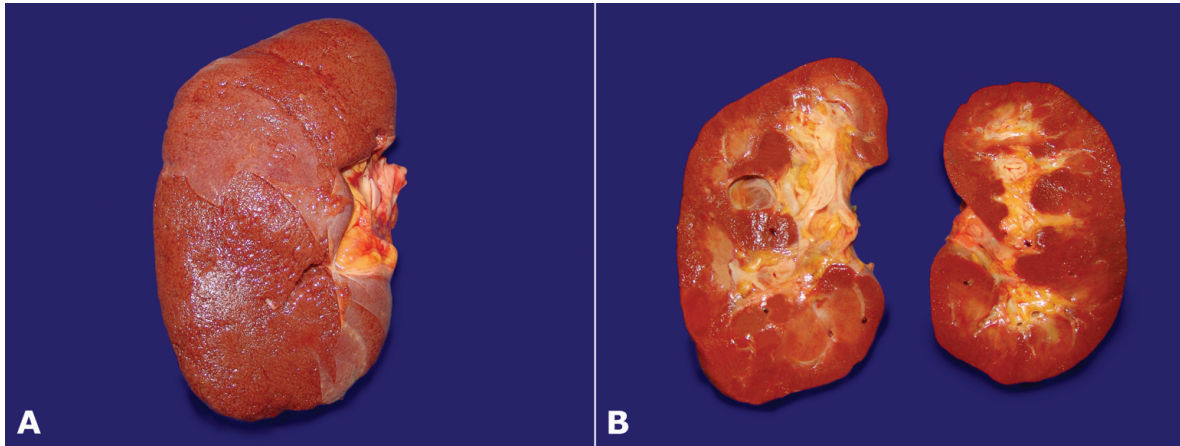
(Hb) S, and heterozygous genotypes of hemoglobin S and others hemoglobinopathies like Hb C, D, E, G, O. Hemoglobinopathy S may also be coinherited with thalassemia. Originally brought from Africa during the slave market, SCD spread throughout Brazil; remaining more prevalent among the Afro-Brazilian population.<sup>1</sup> The genotypes SS and SC are the most common, followed by SThal (when  $\beta$ -thalassemia is coinherited). The SS disease or sickle cell anemia



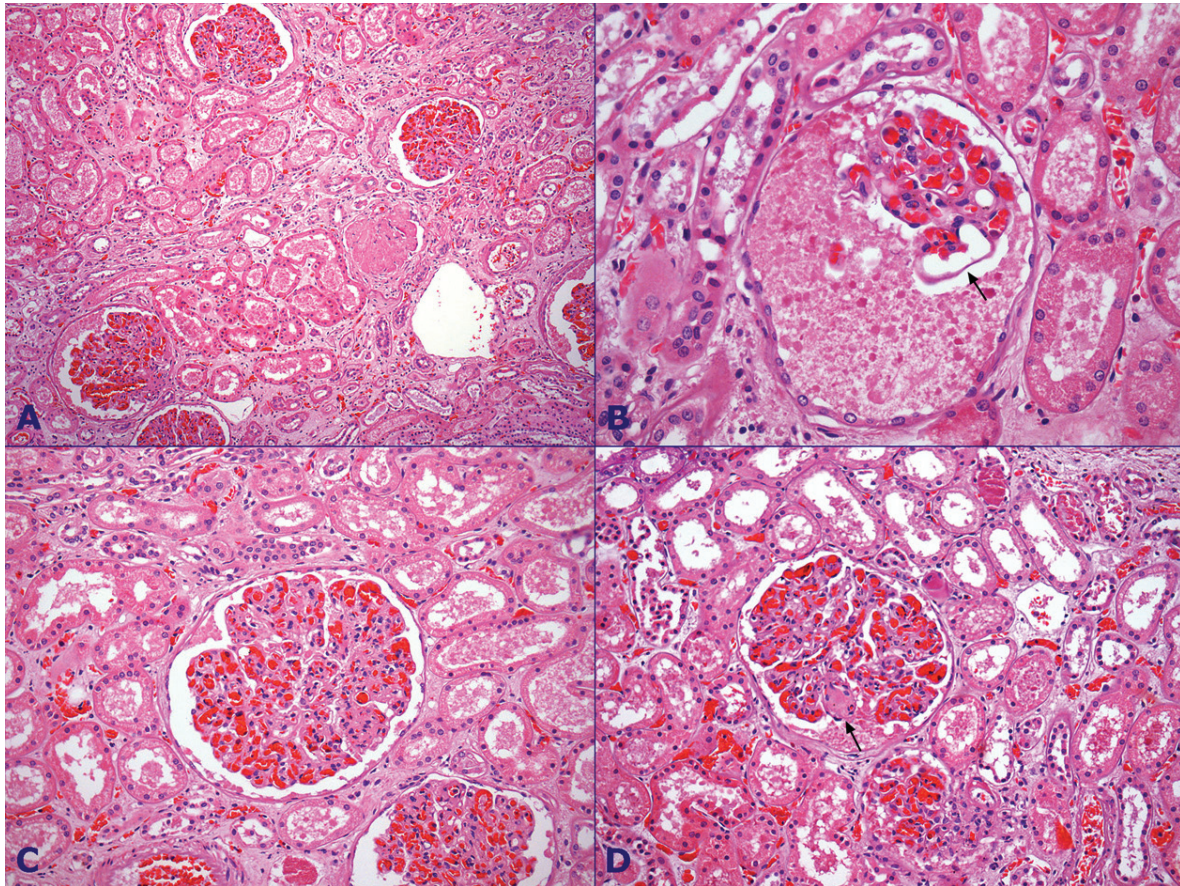
**Figure 9.** Photomicrography of the liver. **A** – (Masson – 25x) liver cirrhosis showing sinusoidal fibrosis and numerous septa delimiting nodules in the parenchyma; **B** – (HE – 100x) portal tract showing mild chronic inflammatory infiltrate, fibrous expansion and atrophic or disappearing portal branches (veno-occlusive pattern); **C** – (HE – 200x) presence of sinusoidal congestion and focus of ischemic infarction in the hepatic lobe; **D** – (HE – 400x) presence of sickled red cells in the Kupffer cells cytoplasm.



**Figure 10.** **A** – Gross findings of the spleen showing congested parenchyma with areas of necrosis. Photomicrography of the spleen – **B** – (HE – 100x) vascular thromboembolism near an area of necrosis; **C** – (HE – 200x) congested red pulp showing sickled red cells; **D** – (HE – 100x) presence of Gamna-Gandy nodule in the under the capsule.



**Figure 11.** **A** – Gross findings of the kidney showing granular surface suggestive of vascular kidney. **B** – presence of congested kidney parenchyma and a small retention cyst in the right kidney.

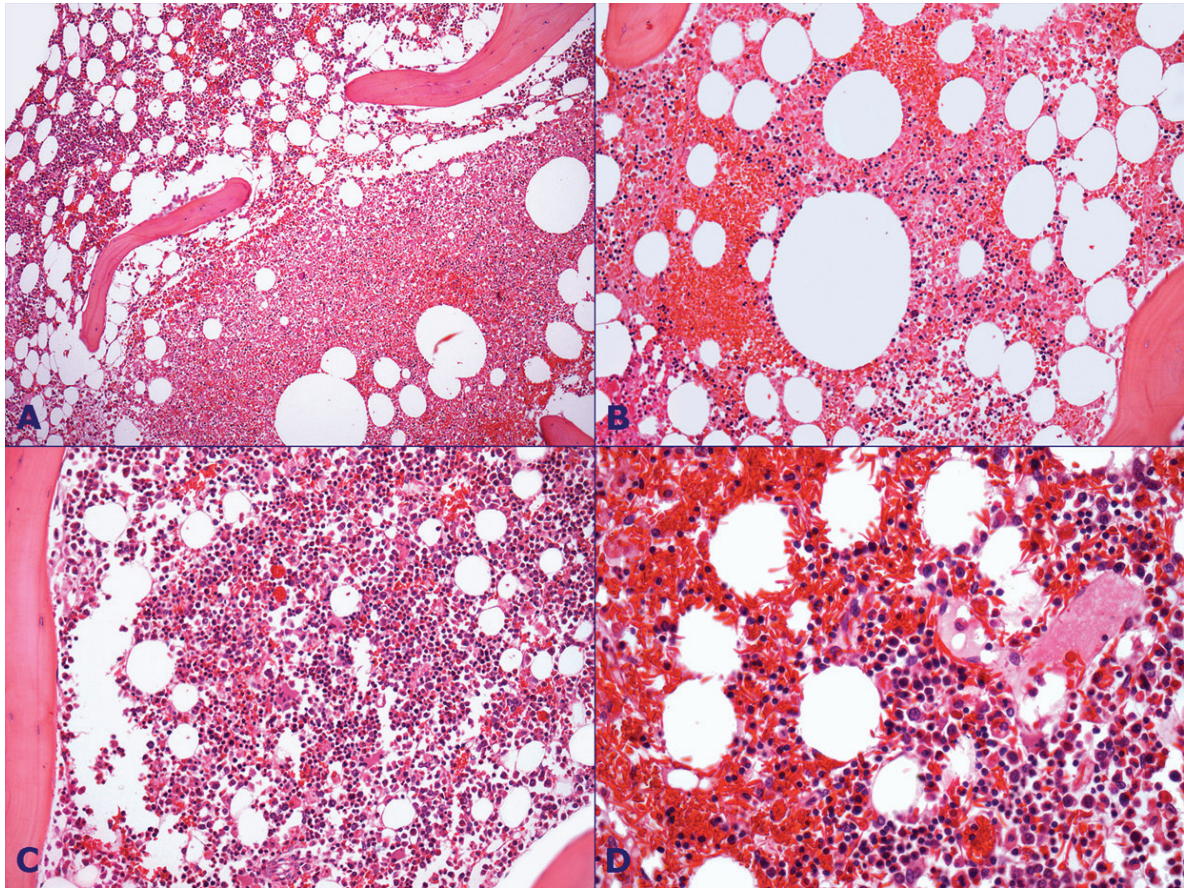


**Figure 12.** Photomicrography of the kidney showing in **A** – (HE – 100x) congested glomeruli, focus of hyaline glomerulus and acute tubular necrosis; **B** – (HE – 400x) glomerular capillary loop with sign suggestive of fat embolism (arrow); **C** – (HE – 200x) glomerulus showing mild mesangial proliferation; **D** – (HE – 200x) presence of focal Kimmelstiel Wilson nodule in the glomerulus (arrow).

(inheritance of 2  $\beta^S$  alleles) is a debilitating disease with severe pain crisis, hemolysis, increased susceptibility to infection, cerebrovascular events, and chronic organ damage<sup>2</sup> and consequently low expectancy of life (42 year for men and 48 years for women).<sup>3</sup> The

mutation  $\beta^C$ , most likely originated in Burkina Faso, is responsible for the synthesis of hemoglobin C ( $\beta^6$  Glu6Lys), which is related to the lost of potassium and consequently intracellular water due to activated  $K^+/Cl^-$  cotransport, event that increases the mean





**Figure 13.** Photomicrography of the bone marrow showing in **A** – (HE – 100x) large area of necrosis besides preserved tissue; **B** – (HE – 200x) detail of necrotic bone marrow parenchyma with hemorrhage; **C** – (HE – 200x) area of reactive hyperplasia of hematopoietic cells; **D** – (HE – 400x) area of hemorrhage with sickled red cells.

corpuscular hemoglobin concentration, increasing the tendency of Hb S polymerization in the double compound S and C inheritance. In some West African regions (Ghana, Burkina Faso, Nigeria) about 25% of the population may have HbSC disease.<sup>4</sup> Although SC hemoglobinopathy usually shows a more benign clinical behavior, both SS and SC may present similar complications.<sup>5,6</sup> However, hemolysis is less intense and aplastic episodes as well as cholelithiasis are less frequent in HbSC. On the other hand, proliferating retinitis, osteonecrosis, and acute chest syndrome may present equal or higher incidence in Hb SC compared with HbSS.<sup>6</sup> Generally, HbSC patients manifest appreciable pathology after 20 years of life<sup>6</sup>, and the median age of irreversible organ failure is 10-35 years later than sickle cell anemia.<sup>7</sup> In the USA, the median survival of HbSC patients was reported to be 60 years for men and 68 years for women.<sup>3</sup>

Patients with SC hemoglobinopathy presents Hb S and Hb C in a ratio 1:1, have mild anemia or normal

hematocrit, and the peripheral blood smears shows target cells and poikilocytes. Diagnosis of hemoglobin C requires more than one diagnostic methodology since HbA<sub>2</sub> and HbO<sub>arab</sub> may comigrate with HbC on acetate electrophoresis; therefore, in our case, acid and alkaline electrophoresis and HPLC were used to assure the diagnosis of HbC.<sup>5</sup>

Complications of SCD are severe, generally associated with high mortality and not infrequently misdiagnosed. Among them are pulmonary hypertension and bone marrow necrosis (BMN) followed by fat embolism syndrome (FES). Pulmonary hypertension, with a prevalence of 20-30% can be related to chronic hemolysis, nitric oxide deficiency, chronic hypoxemia, endothelial dysfunction and proliferative vasculopathy, or vaso-occlusive events due to sickling erythrocytes and hyperviscosity.<sup>8-10</sup> In addition, SCD patients are at increased risk of developing large vessels thrombosis and more rarely intracardiac thrombus.<sup>11-13</sup>

Bone marrow necrosis and fat embolism was described as a sickle cell disease complication in 1941.<sup>14</sup> Since then, other cases have been reported. Tsitsikas et al.<sup>15</sup> was able to find 58 such cases in a review of the English literature on BMN and FES. These cases fulfilled the criteria of histologically proven bone marrow necrosis and multi or single organ histologically proven involvement by fat and/or necrotic marrow emboli, or development of acute respiratory distress and neurological manifestation or multiorgan failure with evidence of bone marrow necrosis. In this report, 57% of the cases were diagnosed at autopsy, and in 33% the diagnosis of SCD was unknown, what raises the suspicion of *ante-mortem* underdiagnoses. FES was related to HbSC in about half of the cases<sup>15,16</sup>, and a slight predominance among females was also observed. It seems that the higher prevalence of FES among HbSC patients is associated with the higher hematocrit (resulting in higher viscosity) compared to that in HbSS.<sup>15,17</sup> Pain (most often starting in the back) and fever are the main initial symptoms due to a vaso-occlusive crisis, which suddenly deteriorates in a space of few hours with respiratory distress, altered mental status, a significant drop in hemoglobin, thrombocytopenia, leukocytosis and varying degrees of other organs failure. Lungs and kidneys are the most affected organs by fat emboli at autopsy.<sup>15,16</sup>

Although the pathogenesis of FES in SCD is still not fully understood, it is thought that fat emboli arise from necrotic (infarcted) bone marrow, which enters the circulation through the passage into bony venous vessels, possible by the anatomical structure of cancellous bone containing red marrow.<sup>16</sup> Vaso-occlusion and increased bone marrow blood flow seems to be adequate to dislodge necrotic marrow material into the circulation. Perhaps not only the mechanical obstruction by fat globules is sufficient to explain the development of FES. Another biochemical theory, which involves chylomicrons, platelets, fibrin, and other blood elements form the substance of the emboli eliciting an inflammatory response.<sup>18,19</sup> Moreover the free fat acids liberated from marrow deposits and chylomicrons directly cause lung injury.<sup>20</sup>

Diagnosis of FES is based on clinical grounds since currently no laboratory test is pathognomonic. In this setting, it is important to notice that, although PaO<sub>2</sub> may be normal on admission, hypoxemia ensues within the first 72 hours often accompanied by the development of the clinical syndrome. Chest

X-Ray may be normal in mild cases but may show diffuse bilateral infiltrate. Brain lesions may not be diagnosed by computed tomography, in these cases magnetic resonance imaging showed to be superior in diagnosing abnormal signs.<sup>16</sup>

A challenging question that remains without a convincing response is what sort of triggering events are associated with BMN and FES. In Tsitsikas et al. publication<sup>15</sup> a substantial number of cases were observed during pregnancy (25% of all females) related or not with medication infusion (prostaglandins and oxytocin). Other interesting finding was the evidence of human parvovirus B19 infection, which was documented by serology or protein chain reaction in 24% of cases. These authors also concluded that serology for parvovirus B19 may not be positive during the BMN/FES, suggesting the research of the virus in the bone marrow by immunohistochemistry reaction.<sup>15</sup> In our case we searched for the presence of parvovirus with the aid of polymerase chain reaction (PCR) using in one reaction the material of a blood smear kept in the laboratory, and paraffin embedded bone marrow slices. Both reactions were negative.

The case reported herein is in accordance with the findings of the reported cases of the literature. Our patient, a 65-year-old Afro-Descendant woman with no previous known diagnosis of HbSC disease presented, apparently without known triggering event, a thoracic back pain. We inferred this complain as an initial mild manifestation of vaso-occlusive crisis, followed by fever, neurological manifestation, much probably as part of FES. When she was brought to the emergency unit she also presented a hyperosmolar nonketotic hyperglycemic state, what should have enhanced the vaso-occlusive phenomenon, but we do not believe this diabetic decompensating complication could be the triggering phenomenon. She was admitted already presenting a severe clinical picture with multiorgan failure what did not permitted a favorable outcome. The pathological findings, the clinical and laboratory features were unequivocally of BMN and FES. The autopsy also showed liver and spleen findings that were consistent with a HbSC phenotype of SCD, and no pathological signs of infection.

Due to the rarity of this syndrome and the high index of unawareness of HbSC many cases may continue to be undiagnosed. The familiarity with this syndrome and its diagnosis, in a country where the Afro-Descendants population are so expressive, is the

only way to diagnose it early and diminish the high mortality index.

This report illustrates once again the usefulness of the autopsy as a diagnostic tool. By the recognition of this diagnosis, the family of the deceased patient could be further studied and received proper genetic counseling.

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