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Clinical Features and Autopsy Findings in Fulminant Hepatic Failure by Exertional Heat Stroke: Case Report

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Authors' contributions

This work was carried out in collaboration between all authors. Authors SRSS and YASS are the clinicians. Author PCBM are the hepatologist who accompanied the patient and made major contributions to the manuscript. The manuscript was prepared by authors SRSS and TFMT under the supervision of author YASS. Author CLL are the pathologist who performed and described the autopsy. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

A healthy 48 year-old man became unconscious suddenly, with a corporal temperature of 43ºC when participating in a strenuous motorcycle off-road competition in the last 2 days in southeastern Brazil on a very hot and humid summer. Once the first 6 hours of in-hospital he had dysfunction of several organ and systems. During the following days, he developed fulminant hepatic failure (FHF), disseminated intravascular coagulation, rhabdomyolysis and multiple organ failure. Despite the use of immediate conventional core body temperature control methods and support of organ-system function, the patient died on 11th day. Autopsy findings: there was significant jaundice impregnation, petechial and hemorrhagic suffusions in the skin and in visceral organs as well as generalized edema. The microscopic exam showed cytotoxic and vasogenic brain edema and encephalic death. The liver and the pancreas were diffusely necrotic and hemorrhagic, besides rhabdomyolysis, cardiac failure and acute tubular necrosis in the kidneys. The immunohistochemistry exam showed diffuse liberation in the lung and other viscera tissue of tumor necrosis factor-α (TNFα). In spite of being a rare occurrence, FHF should be included in the complications induced by exertion and commonly progresses to death.

Keywords: Heat stroke; induced hyperthermia; physical exertion; multiple organ failure; acute liver failure; autopsy.

1. INTRODUCTION

Heat stroke is a life-threatening disease characterized by elevated central body temperature exceeding 40ºC with associated dehydration and predominant central nervous system dysfunction resulting in delirium, convulsion or coma [1,2]. In many clinical and pathogenic aspects, heat stroke resembles sepsis and there is growing evidence that endotoxemia and cytokines may be implicated in its pathogenesis [3], and it has been defined as "a form of hyperthermia associated with a systemic inflammatory response leading to multiple organ dysfunction in which encephalopathy predominates" [1,4]. Hyperthermia itself is considered the main pathogenic factor for liver damage in heat stroke [5]. The clinical manifestations of heat stroke are variable. Hyperthermia and central nervous system dysfunction must be present for a diagnosis of heat stroke. Hepatic injury in most cases of EHS is usually asymptomatic and can be reversed [5]. Approximately 5% of EHS experienced fulminant hepatic failure (FHF), which might be fatal [2]. Acute liver failure is an uncommon condition in which rapid deterioration of liver function results in coagulopathy, usually with an international normalized ratio (INR) of greater than 1.5, and alteration in the mental status (encephalopathy) of a previously healthy individual. It is characterized as fulminant hepatic failure, when encephalopathy develops within 8 weeks after onset of symptoms.

In literature there are few cases that describe autopsy findings of a heat stroke during exercise and liver failure [6,7]. We report the clinical features and autopsy findings of a patient who developed a fatal heat stroke with fulminate hepatic failure (FHF) and multiple organ dysfunctions during physical exhaustion in motorcycle off-road competition on a hot and humid summer day in a tropical country.

2. CASE REPORT

A 48 year-old man was admitted to the emergency room of a hospital in the coastal area because he was unconscious during participation a strenuous motorcycle off-road two days competition on a mountainous section of the coastal area in southeastern Brazil, on a very hot and humid day, the second day of the summer endurance test. There was an environment temperature of 36ºC (96,5ºF) and relative humidity > 80%, producing a heat index of approximately 133ºF, an extremely high risk range for heat stroke during continuous exposure to sunlight and strenuous physical activity. The day before, he had run about 120 km in 7 hours. On the second day of this competition he felt tired and unwell. He practiced this sport frequently. Beyond this, he had no former medical history, was in good physical shape, and had a body mass index of the 24 kg/m^2. He took no medication, nor illicit drugs. He started the race at 9 hours and collapsed after approximately 3 hours of race, having covered approximately 60 km. He was rescued by other

competitors. He was found conscious, inside dirty mire, with no apparent signs of trauma. He was taken to a local hospital immediately, where he arrived in approximately one hour later, due to the difficult access. On examination, the Glasgow coma scale score was 6, core body temperature of 43ºC, blood pressure 110/80 mmHg, heart rate 110/min, respiratory rate 30/min, severely dehydrated, without another alteration in his physical examination. He required immediate orotracheal intubation and ventilatory support. The patient was monitored and started conventional temperature control methods including both external (sheet, ice water, and fan) and cooled endovascular saline solution cooling to combat hyperthermia.

After 6 hours, he was delivered to the intensive care unit of a tertiary care hospital for further diagnosis and management. On admission, he remained unconscious, requiring mechanical ventilatory support, was moderately dehydrated, with a core body temperature of 39ºC. Arterial blood gases during mechanical ventilation were PaO_2 150.6 mmHg (FiO_2 0.30), $PaCO_2$ 28.1 mmHg, pH 7.30, HCO_3 13.4 mEq/L, and oxygen saturation of 98%. A chest X-ray revealed no pulmonary or cardiac abnormalities. The initial cerebral computed tomography (CT) scan and subsequent magnetic nuclear resonance (MNR) showed no abnormalities. To exclude an infectious origin for the central nervous system dysfunction, a lumbar puncture was made which revealed normal cerebrospinal fluid. The ECG showed sinus tachycardia (140 beats/min), and cardiac enzymes were normal, including troponin. The laboratory results revealed a white cell count of $9.2x10^3/mm^3$ with 91% neutrophils, 5% lymphocytes, 4% monocytes, and a platelet count of $36x10^3/mm^3$ (normal range 142–424x $10^3/mm^3$), red blood cells $4.91x10^6/mm^3$, hemoglobin 13.7g/dL and hematocrit 40.7%;serum creatinine 2.0 mg/dL (normal ≤ 1.3 mg/dL), blood urea nitrogen 67 mg/dL (normal ≤ 40 mg/dL), urinalysis showing reddish brown urine. Serum lactate was 46.6 mmol/L (0.5–1.6 mmol/L), ionized calcium 1.02 mg/dL (4.4-5.3 mg/dL), potassium 3.4 mEq/L (3.5–5.1 mEq/L), sodium 152 mEq/L (135–145 mEq/L), magnesium 1.5 mg/dL (1.5–2.6 mg/dL). Elevated serum levels of creatinine kinase (CK) 3.931 U/L (normal ≤ 190 U/L), lactate dehydrogenase (LDH) 806 U/L (normal 208-378 U/L), serum aspartate aminotransferase (AST) 935 U/L (normal ≤ 35 U/L) and alanine aminotransferase (ALT) 1.315 U/L (normal ≤ 40 U/L) were observed. Serum albumin was measured at 3.2 g/dL (3.4–4.8 mg/dL) and total bilirubin 2.4 mg/dL (normal ≤ 1.2 mg/dL), prothrombin time(PT) 44.2% (normal range 70% - 100%), international normalized ratio (INR) 4.60 (normal ≤ 1.25), activated partial thromboplastin time (aPTT) of 60.5 sec (normal ≤ 38 sec), D-dimer test of 2.0 µg/mL (normal ≤ 0.5 µg/mL) and fibrinogen 103 mg/dL (normal 200-400 mg/dL), showing rapid deterioration of hepatic function, disseminated intravascular coagulation (DIC) and multiple organ dysfunction. The laboratorial analises can be checked in Table 1. An echocardiogram showed normal heart function and structure.

Forced diuresis was performed for 48 hours using fluids to prevent renal failure. Gram stain and culture of the tracheal aspirate, blood and urine were negative for bacteria and fungi. Other causes for hepatic failure were investigated, including an abdominal ultrasound with duplex Doppler ultrasonography, but they showed no alterations. Serology was positive for IgG HAV, but negative for IgM HAV, leptospirosis, hepatitis C and B, and human immunodeficiency virus (HIV). In addition, a drug screening was negative. On day 3, there was a great increase of hepatic enzymes with AST 6,598 U/L, ALT 11,989 U/L and total bilirubin to 8.2 mg/dL, a worsening of coagulation with PT of 9.8%, INR 5.89, aPTT 49.6 sec, and a platelet count of 44 x $10^3/mm^3$, in spite of an improvement in the renal function (serum creatinine 1.2 mg/dL and urea 28 mg/dL), when the CK level was 1,921 U/L. At this moment, liver transplantation was considered but it was contraindicated due to severe involvement of multiple organs. On day 4, a significant decreasein hepatic enzymes AST 175 U/L, ALT 2,009 U/L and an increase in total bilirubin 21.3 mg/dL were observed. On day 6, he showed extensive bilateral fluffy alveolar shadows, suggestive of acute respiratory distress syndrome, and hemodynamic instability. Echocardiography was normal, and evaluation of central venous oxygen saturation was 81%. On this day, a vasoactive drug (norepinephrine) was started in addition to the empiric broad spectrum antibiotics, intravenous corticosteroids (hydrocortisone 400 mg/day), maintenance of parenteral nutrition and daily sessions of extracorporeal hemodialysis due to oliguria with a progressive increase in serum creatinine (4.2 mg/dL). At this moment, newly collected culture samples showed negative. The peak elevation of the CK was 6,630 U/L on day 8. On day 9, there was marked decrease in the serum fibrinogen (80 mg/dL), and red cell concentrate transfusion was performed due hemoglobin decreased (8.5

g/dL). On day 10, he had reentrant focal seizures (face) that did not improve with phenytoin, requiring intravenous thiopental. Hisserum ammonium was 95 µmol/L (normal ≤ 32 µmol/L), AST 316 U/L, ALT 272 U/L, total bilirubin 30.6 mg/dL, platelet count of 46 x 10^3/mm^3, PT 15%, INR 5.75 and Factor V 38% (normal range 50-150%). The laboratory tests of 10 days of hospitalization were collected before section dialysis (Table. 1). The patient remained unconscious and died on day 11. The brain weighted 1525 grams, diffused soft with intense edema, with uncal and cerebellar tonsil herniation. The microscopic exam showed diffuse edema - neuron cytotoxic, interstitial and vasogenic edema; red hypoxic neurons and intense vascular congestion (Fig. 1). The lungs had diffuse alveolar damage with edema, pneumocyte 2 hyperplasia and alveolar macrophages with hemosiderin. The heart weighted 450 grams, with intense vascular congestion and, diffuses cardiac chambers dilatation. The liver and the pancreas were diffusely necrotic and hemorrhagic (Fig. 2). There were also rhabdomyolysis, cardiac failure and acute tubular necrosis in kidneys. The immunohistochemistry exam showed diffuse extracellular TNF- α immunostaining in the lung (The primary antibody TNF- α was polyclonal from RD System). We collected several samples to performed microbiological culture and there were no bacterial agents in any of them.

3. DISCUSSION

We described one case of heat stroke due to physical exhaustion in a motorcycle off-road competition during a hot and humid summer day in a tropical country. The patient initially presented hyperthermia and coma, FHF, progressing to acute respiratory distress syndrome, disseminated intravascular coagulation and acute renal failure. The presence of hyperthermia (core body temperature higher than 40ºC) and coma, followed by laboratory evidence of multiple-organ failure in healthy and active people who engage in strenuous exercise, often in hot and humid climates, supported the diagnosis of heat stroke [8]. There are two forms of heat stroke: the classic or nonexertional and the exertional. The non exertional occurs during environmental heat waves, most commonly in elderly persons and infants, as that which occurred in a very hot summer in the United States and Australia or during a heat wave in France [9-11]. The exertional heat stroke (EHS) occurs in healthy and active people who engage in strenuous exercise, often in hot and humid climates [8], and it has been rarely reported [12]. Clinical markers of disseminated intravascular coagulation, prolonged elevation of serum liver and muscle enzymes, multiple-organ failures, and prolonged coma are associated with a grave prognosis and an expected mortality rate of 7.1% to 50% [1,13].

Many studies indicate that heat stroke occurs precisely when the core body temperature rises and the thermoregulatory system fails to respond adequately [14]. Excessive environmental heat denatures proteins, phospholipids and lipoproteins, and also liquefies membrane lipids, leading to cardiovascular collapse, multiple organ dysfunction and death [1]. The efficacy of evaporation as mechanism to promote body´s heat loss, may not take place when ambient humidity is greater than 75% [15].

Hyperthermia due to passive heat exposure or to exercise may facilitate the leakage of endotoxin from the intestine to the systemic circulation as well as the movement of interleukin-1 or interleukin-6 from the muscles to the systemic circulation. The result is excessive activation of leukocytes and endothelial cells, manifested by the release of proinflammatory and anti-inflammatory cytokines (tumor necrosis factor-α, interleukin-1, interleukin-6, and interleukin-10), up-regulation of cell-surface adhesion molecules, and shedding of soluble cell-surface adhesion molecules [e.g., E-selectin, L-selectin, and ICAM-1 (intercellular adhesion molecule)] as well as activation of coagulation (with decreased levels of proteins C and S and antithrombin III) and inhibition of fibrinolysis. The inflammatory and coagulation responses to heat stroke, together with direct cytotoxic effects of heat, result in injury to the vascular endothelium, microthrombosis and multiple organs damage [1].

In the present case, the patient presented a very high core body temperature and when he was admitted to the emergency room he was already presenting coma. The central nervous system (CNS) is especially sensitive to the damaging effects of hyperthermia. Neurological dysfunction of varying degrees is common feature of heat stroke, frequently including seizures, delirium, lethargy, and coma. Different mechanisms have been postulated in the pathogenesis of the brain damage observed in heat stroke. These include injury of the thermoregulatory centers and reduced cerebral perfusion pressure due to

arterial hypotension and intracranial hypertension [16]. Others uncommon CNS complications described in patients with heat stroke include intracerebral hemorrhage, central pontine myelinolysis, peripheral polyneuropathy and Guillain-Barre syndrome [17-19].

Acute renal failure in heat stroke is usually multifactorial and includes direct thermal injury, rhabdomyolysis, disseminated intravascular coagulation, and renal hypoperfusion due to volume depletion and arterial hypotension. In our patient, acute renal failure was an early feature. On admission he had already shown serum creatinine kinase and creatinine elevated, and progressively developed oliguria with reddish brown urine. Rhabdomyolysis may follow strenuous physical exertion, particularly when associated with extremely hot and humid climate conditions, causing renal vasoconstriction, tubular toxicity, and tubular obstruction. The heme of myoglobin caninitiate lipid peroxidation and renal injury [20]. There is a direct relationship between acute renal failure and mortality in heat stroke [10].

Table 1. Serum laboratory findings collected during the course of 10 days of survival

Serum parameters	Laboratory findings							Reference interval
	First 24 h	D3	D4	D6	D8	D9	D10	
Hemoglobin	13.7	14.0	11.5	11.3	11.4	8.5	10.7	14–18 g/dL
White blood cell count	9.2	9.1	7.5	7.8	11.5	18.6	16.5	4–10 x 10^3/mm^3
Platelet count	36	44	39	38.5	79	75	46	142–424 x 10^3/mm^3
Bilirubin (total)	2.4	8.2	21.3	28.8	27.7	31.2	30.6	≤ 1.2 mg/dL
Bilirubin (direct)	1.4	3.4	18.4	20.7	25.3	22.2	26.9	≤ 0.6 mg/dL
Aspartate aminotransferase	935	6,598	175	108	139	155	316	≤ 35 U/L
Alanine aminotransferase	1,315	11,989	2,009	653	253	253	272	≤ 40 U/L
Alkaline phosphatase	67	142	313	311	238	-	-	50 – 136 U/L
γ-glutamyl transpeptidase	52	77	56	55	68	74	-	15 – 85 U/L
Albumin	3.2	3.5	2.9	2.4	2.1	2.0	2.0	3.4 – 4.8 g/dL
Ammonia							95	32 – 48 µmol/L
Creatinine phosphokinase	3,931	1,921	2,640	3,361	6,630	3,535	2,200	≤ 190 U/L
Blood urea nitrogen	67	28	54.6	81	103	141	161	≤ 40 mg/dL
Creatinine	2.0	1.2	2.5	4.2	6.4	8.2	10.3	≤ 1.3 mg/dL
Potassium	3.4	4.6	4.2	4.5	4.8	4.0	7.0	3.5 – 5.1 mEq/L
Sodium	152	149	150	146	142	141	140	135–145 mEq/L
Magnesium	1.55	1.6	2.8	3.2	-	-	-	1.5 – 2.6 mg/dL
Ionized calcium	1.02	2.8	3.6	4.1	4.2	3.9	3.2	4.5 – 5.3 mg/dL
Lactate	46.6	-	9.0	11.6	9.3	7.0	6.1	0.5 –1.6 mmol/L
Lactate dehydrogenase	806	4,310	961	1,143	1,797	3,307	4,662	208 – 378 U/L
Prothrombin time (PT)	44.2%	9.8	9	17	20	16	15	70–100%
International normalized ratio (INR)	4.60	5.89	12.40	5.20	4.15	5.27	5.75	≤ 1.25
Activated partial thromboplastin time (aPTT)	60.5	49.6	51.1	33.9	35.8	43.1	50.8	≤ 38 sec
D-dimer test	2.0	-	-	-	-	-	-	≤ 0.5µg/mL
fibrinogen	103	-	-	-	-	80	103	200–400 mg/dL

D, day of the exam, after the first 24 hours

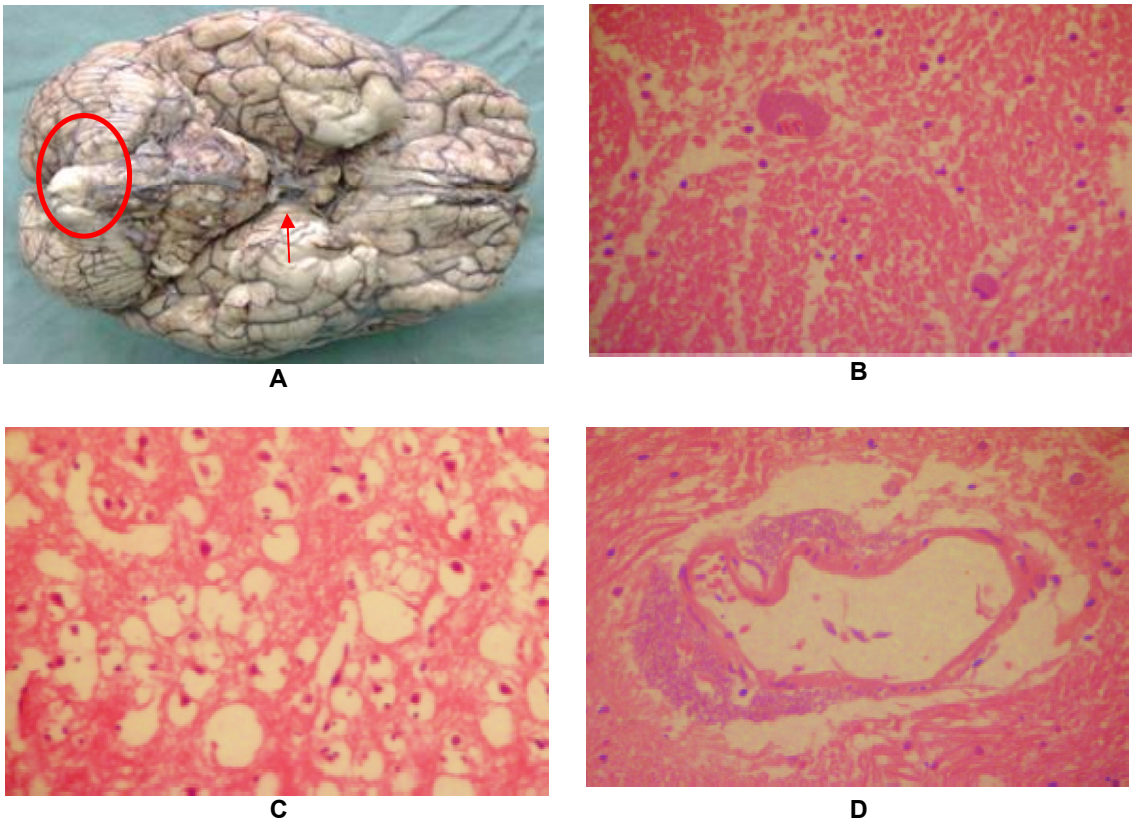

Fig. 1. CNS findings. A) Macroscopy showing cerebelar tonsil (circle) and uncal (arrow) herniation; B) Interstitial and vasogenic edema.HEX200; C) Cytotoxic edema HEX400; D) Vasogenic edema HEX400

Acute respiratory distress syndrome is a frequent complication in heat stroke, as well as liver dysfunction in various degrees, whereas FHF is a rare event and carries a worse prognosis [21], as observed in the present case.

The patient presented progressive deterioration of hepatic function followed by rapid decrease in serum hepatic enzymes (ALT and AST), with an abrupt decrease of over 60% on day 4, associated with an increase in total bilirubin, hyperammonemia and coagulopathy. The diagnosis of FHF was made based on findings of a rapid installation of coagulopathy, with international normalized ratio (INR) 4.60 early in the first 6 hours, accompanied by encephalopathy with persistent coma during the course of acute hepatocellular lesion in an individual who had not presented previous hepatic disease. As reported autopsy findings from this, the development of cerebral edema is the major cause of morbidity and mortality in patients with acute liver failure. The mechanism underlying liver failure in heat stroke patients is not totally understood. It could be an initial systemic or intrahepatic circulatory disturbance, and at this moment therapeutic application of vasoactive substances to increase intrahepatic blood flow could be beneficial. Hyperammonemia may be involved in the development of cerebral edema. Brain edema is thought to be both cytotoxic and vasogenic in origin. Cytotoxic edema is the consequence of impaired cellular osmoregulation in the brain, resulting in astrocyte edema. Vasogenic edema results from an increase of intracranial blood volume and cerebral blood flow is a factor in acute liver failure. The increased cerebral blood flow results because of disruption of cerebral autoregulation. The disruption of cerebral autoregulation is thought to be mediated by elevated systemic concentrations of nitric oxide, which acts as a potent vasodilator. Cytokine profiles are also deranged. A reduced splanchnic blood flow can result in dysfunction and increased permeability of the gastrointestinal barrier, relasing endotoxins, causing immune reactions and organ damage. Elevated serum concentrations of

bacterial endotoxin, tumor necrosis factor–alpha (TNF-α), and interleukin (IL)–1 and IL-6 have been found in fulminant hepatic failure. Another consequence of fulminant hepatic failure is multisystem organ failure, which is often observed in the context of a hyperdynamic circulatory state that mimics sepsis (low systemic vascular resistance); therefore, circulatory insufficiency and poor organ perfusion possibly either initiate or promote complications of fulminant hepatic failure.

In a revision published by Martins et al. in 2004, there are less than 20 cases of acute liver failure associated with heat-stroke. In 2/3 of cases there was spontaneously recovery and 1/3 died [22]. There are only few previous cases of liver transplantations for heat stroke in the literature, and there are no guidelines available to guide transplantation. Conservative management appears to be justified in heat-stroke associated liver failure even in the presence of accepted criteria for emergent liver transplantation. It is of crucial importance to rule-out irreversible brain damage before listing these patients. Long-term neurologic sequelae occur in approximately 20% of patients [22].

The primary, immediate therapeutic goal must be to lower the core body temperature as soon as possible, which should have a positive effect on prognosis. This seems to be the most effective way of preventing multiple-organ failure in these patients, along with fluid application and rebalancing of acid-base and electrolyte disorders. Various methods for rapid cooling in heat stroke have been used: immersion in ice water, iced peritoneal and gastric lavages, and evaporative techniques. However, there is no evidence to support the superiority of either any cooling method or any target temperature for safe cessation of cooling [23].

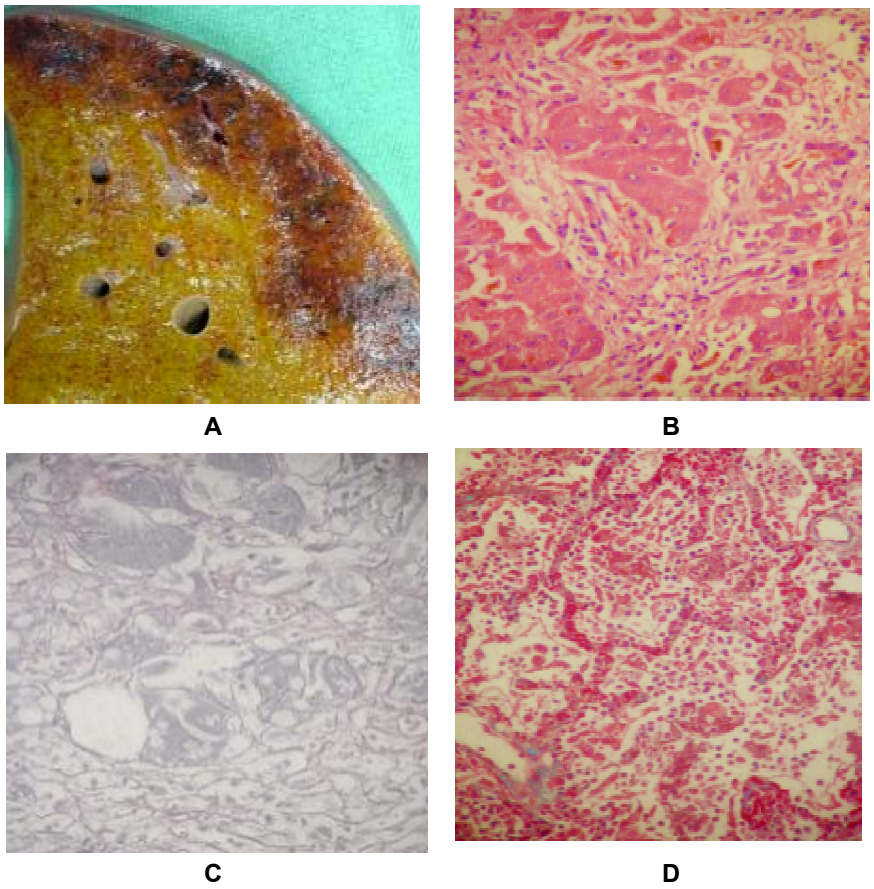

Fig. 2. A) Liver showing necrosis and hemorrhagy; B) Liver necrosis with cholestasis.HEX400; C) Liver showing collapsed reticulin fibers. Reticulin stainX400; D) Lung with diffuse alveolar damage. MassonTrichromeX200

Despite the aggressive use of conventional temperature control methods, including surface cooling techniques, we could not control the patient's core body temperature. Physical means to lower temperature, including surface cooling, have been shown to be ineffective in many studies because these methods can have limited efficacy as a result of skin vasoconstriction and shivering [24].

4. CONCLUSION

In spite of being a rare occurrence, fulminant hepatic failure should be included in the complications induced by exertion and commonly progresses to death. In the present case, autopsy showed multiple-organ failure and systemic inflammatory response syndrome, confirming heat stroke syndrome (HSS).

Systematic review based in related cases, and prospective studies based on protocol, both in the out-of-hospital and in-hospital, will be needed to offer a better prognosis for this patients.

CONSENT

Author has declared that 'written informed consent' was obtained from the patient's adult brother for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared there are no competing interests.

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