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Case Report

Acute lymphoblastic leukemia complicating with adrenal insufficiency due cytomegalovirus infection

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Introduction

Adrenal insufficiency, also known as Addison's disease (AD), is a rare endocrinopathy, resulting from the destruction or complete dysfunction of the adrenal cortex. It has an estimated prevalence between 100 and 140 cases/million and an incidence of 4 cases per million/year.[1] The main causes of AD are autoimmunity, metastasis, bleeding and infectious diseases, such as tuberculosis, fungi and cytomegalovirus (CMV). Addison's disease due to CMV has been reported in infants through maternal-fetal contamination and in immunosuppressed patients with AIDS.[2–4]

Acute lymphoblastic leukemia (ALL) is a malignant disease that affects adults and children. Thirty years ago, it was an invariably fatal condition but today, with the appearance of modern therapies based on high doses of polychemotherapy and prophylaxis for the central nervous system, the cure rate in children was raised to about 85–90%. Despite the improvement in the survival rate, the treatment presents several complications, such as chemotherapy-induced immunosuppression.[5]

CMV Infection in patients undergoing treatment for acute leukemia and organ transplantation is very common. In general, the virus is acquired in transfusions of

contaminated blood or through a donor in transplantations, in this cases the main clinical manifestations are: pneumonia, retinitis and colitis.[6,7]

The following is the first case describing an adolescent with ALL who had an acute CMV infection and, despite being submitted to early therapy with ganciclovir, evolved with manifestations of acute adrenalitis that culminated in Addison's disease.

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Case report

An 8-year-old, brown, male, was admitted to the pediatric oncology center, in May 2013, for diagnosis and treatment of acute leukemia. The patient was diagnosed with acute lymphoid leukemia, CALLA +, with high risk of relapse (ALL-HR). He was submitted to treatment with the ALL-BFM 2002 protocol.

In October 2015, during maintenance treatment phase, he was admitted with high and persistent fever (39 °C), skin redness, asthenia, but otherwise good condition. Several laboratory tests, such as hemogram, biochemical, blood cultures (fungi and bacteria) and viral serological tests were performed. The patient was started on antibiotics – cefepime and ganciclovir – due to high suspicion of cytomegalovirus. He then developed severe abdominal pain in a band-like distribution around his upper abdomen to his back, nausea, vomiting and arterial hypotension. On this occasion, the diagnosis of acute pancreatitis was ruled out. Laboratory tests revealed amylase, lipase and transaminases normal levels, but also severe hyponatremia, hypoglycemia and hyperkalaemia. Urine and blood cultures were negative to bacteria and fungi, but serology for CMV showed positive IgM:4.6 (N-1.4 UA/mL), IgG:206.1 (N-15 UA/mL), and PCR identified 115,000 copies, confirming the acute cytomegalovirus. The severe hyponatremia (119 mEq/L) was corrected with hydroeletrolitic reposition. It was suspected to be due to SIADH for CMV infection or to side effect of ganciclovir. The patient continued with intravenous ganciclovir for three weeks, but the following week he already showed a significant reduction in the viral load. The patient was discharged from hospital and prescribed with oral ganciclovir until complete CMV negativation.

In December 2015, during an outpatient review, the patient had reported adynamia and it was observed cutaneous hyperpigmentation and arterial hypotension (80 × 50 mmHg). Laboratory tests results still revealed hypoglycemia (60 mg/dL) and hyponatremia (125 mEq/L). On this occasion, under suspicion of Addison's disease, the patient was referred to an Endocrinology Center to obtain a more complete diagnosis and therapeutic guidance.

Endocrinology investigation revealed a normal abdominal tomography, without adrenal glands abnormalities, reduction in cortisol level −2.4 μg / dL (N = 5.3–22.5 μg/dL) and high ACTH level of 581 pg/mL (<46 μg/dL). The patient was diagnosed with primary adrenal insufficiency and treated with oral prednisone (dose of 5 mg) for continuous use. He was discharged from hospital with improvement in blood pressure and of adynamia. After 3 months of treatment, as the patient showed only a small clinical improvement, prednisone was changed by fludrocortisone acetate. After that, the patient gained weight, showed signs of improvement on the skin hyperpigmentation, and the latest results revealed normal levels of blood pressure and blood glucose, the patient has concluded treatment to ALL, is currently fine in remission of disease.

Discussion

Immunosuppressed patients when infected by CMV suffer from symptomatic disease when their viral load reaches high levels.[2] CMV disseminates through the bloodstream to all organs and, in the case of AIDS patients, it can cause an acute adrenal crisis (adrenalitis), that is described as the first clinical manifestation in more than 50% of these cases and cause: sensory alteration, severe arterial hypotension and risk of hypotensive shock.[1]

The patient described in this report had a high fever (39 °C) and presented reddish skin. The ward evolved with abdominal band pain and signs of hypotension, suggesting acute pancreatitis, but this hypothesis were ruled out by laboratory tests, which showed normal level of transaminases, lipase and amylase.

Therefore, in reality, the arterial hypotension, hyponatremia and hypoglycemia that the patient has developed was due to acute adrenalitis and not to an inappropriate antidiuretic hormone syndrome (SIADH), as also previously thought.[8]

The tropism of the CMV by adrenal gland is unknown, but it has been suggested that

this gland could be an infection reservoir. Inside the adrenal gland, the virus reduces the reserve of the gland, predisposing the patient to adrenal insufficiency. However, clinical manifestations only appear when more than 90% of the adrenal gland has been destroyed.[9,10] Thus, the functional impairment of the gland develops slowly and is often not diagnosed until a complete onset of adrenal insufficiency, which is life-threatening for this kind of patient. The classic symptoms of AD are insidious and nonspecific, such as: anorexia, fatigue, nausea, fever, lethargy and postural hypotension.[1]

The diagnosis of AD described on this report was only done during an outpatient return visit, when cutaneous hyperpigmentation, weight loss and hypotension were associated with laboratory findings of hypoglycemia and hyponatremia. The patient was seronegative for HIV, had not undergone organ transplantation, but was in the maintenance treatment taking mercaptopurine daily and methotrexate weekly. So, it is possible to consider that the patient's immunosuppression favored opportunistic CMV infection, which in turn caused the destruction of the adrenal gland, leading to Addison's disease.

Addison's disease due to CMV is often described in immunosuppressed individuals with AIDS, and had not yet been described in patients with acute leukemia. Since it is a rare and highly complex disease, the diagnosis of Addison's disease is difficult, and in this particular case, it was complicated by the infrequent causality of this complication.

Conflicts of interest

The authors declare no conflicts of interest.

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