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CLINICAL CASE

Hyperferritinemic sepsis secondary to invasive *Toxoplasma gondii* in a child with untreated HIV

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Abstract

Background: *Untreated human immunodeficiency virus (HIV)-immunosuppressed pediatric patients show high morbidity and mortality from opportunistic infections. Limited cases of hyperferritinemic sepsis have been described in patients with toxoplasmosis.* **Case report:** *We describe the case of a 13-year-old female patient with a history of untreated HIV who presented with hyperferritinemic sepsis secondary to Toxoplasma gondii infection and Pneumocystis* jirovecci *pneumonia. She received ventilatory support, inotropic drugs, treatment for opportunistic germs, and high-dose corticosteroids, but with unfavorable evolution.* **Conclusions:** *The global approach to sepsis with elevated ferritin guides to using of therapies aimed at neutralizing the severe inflammatory response. A timely diagnosis would allow prompt treatment and minimize complications.*

Keywords: *Sepsis; Ferritin. Lymphohistiocytosis. Hemophagocytic.Child. Human immunodeficiency virus.*

Sepsis hiperferritinémica secundaria a Toxoplasma gondii *invasiva en un paciente pediátrico con virus de inmunodeficiencia humana sin tratamiento*

Resumen

Introducción: *Los pacientes pediátricos inmunodeprimidos por el virus de la inmunodeficiencia humana (VIH) sin tratamiento presentan una elevada morbilidad y mortalidad por infecciones oportunistas. Se han descrito limitados casos de sepsis hiperferritinémica en pacientes con toxoplasmosis.* **Caso clínico:** *Se describe el caso de una paciente de 13 años con antecedente de VIH sin tratamiento que presentó sepsis hiperferritinémica secundaria a una infección por Toxoplasma gondii y neumonía por Pneumocystis jirovecci. Recibió soporte ventilatorio, uso de inotrópicos, tratamiento para gérmenes oportunistas y corticoides en altas dosis, pero su evolución fue desfavorable.* **Conclusiones:** *El abordaje global de la sepsis con ferritina elevada orienta a utilizar terapias dirigidas a neutralizar la respuesta inflamatoria severa, por lo que un diagnóstico oportuno permitiría iniciar el tratamiento prontamente y minimizar las complicaciones.*

Palabras clave: *Sepsis. Ferritina. Linfohistiocitosis hemofagocítica. Niño. Virus de la inmunodeficiencia humana.*

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Introduction

Immunosuppressed children represent a subgroup of critically ill patients who account for a substantial fraction of mortality in pediatric intensive care units (PICUs) due to sepsis[1].

Toxoplasma gondii infection is due to an intracellular protozoan parasite transmitted via cyst-ridden meat or fecal-oral route that causes an asymptomatic or mild self-limited infection[2]. Although the prevalence of toxoplasmosis in the population is declining, considerable regional heterogeneity in seroprevalence persists[3,4]. In immunocompromised patients, toxoplasmosis can cause a primary disseminated infection, but most often, reactivation of a previous infection occurs. The most common clinical manifestations of toxoplasmosis are neurological[5]. Other features often include fever and nonspecific signs, including respiratory and neurological symptoms that overlap with other opportunistic infections[2,5].

Hyperferritinemic sepsis has previously been reported in patients with *Toxoplasma gondii* infection[6]. Ferritin is a critical molecule that limits the prooxidant stress of inflammatory conditions such as sepsis. The primary source of serum ferritin is tissue macrophages[7]. When CD4+ T-lymphocyte count in patients with human immunodeficiency virus (HIV) is < 100 cells/μL, there may be a risk of disease reactivation or severe acute toxoplasmosis[4].

This report aimed to describe the case of a 13-year-old female patient with active *Toxoplasma gondii* infection and untreated HIV who developed hyperferritinemic sepsis and failed to improve despite treatment.

Clinical case

We report the case of a 13-year-old female patient from the jungle of Huancayo-Peru, who came to the emergency department accompanied by her maternal aunt. The family member reported that the patient presented with severe headaches associated with fainting episodes, fever, and abdominal pain for two weeks. The patient had a history of horizontally transmitted HIV infection and had never received antiretroviral therapy. She had not been exposed to COVID-19 (coronavirus disease 2019) positive individuals.

Physical examination revealed multilobulated and umbilicated papules on the skin of the scapular region, cervical lymphadenopathy, and ulcerative and whitish bleeding plaques in the oropharynx. Lung sounds were abolished at the bases with basal rales in both lungs. The patient manifested pain on palpation of the lower abdomen, with sonographic signs of mesenteric adenitis, ascites, hepatosplenomegaly, and splenic calcified granuloma. On neurological evaluation, Glasgow 15/15 with no motor deficit was found. The patient presented pupillary anisocoria with the right eye pupil of 1.5 mm and the left eye pupil of 2 mm; the fundus was normal. Bleeding ulcerative lesions were present in the perianal region.

Admission test results reported thrombocytopenia (74 x 10^3 cells/uL), leukocytopenia (2800 cells/uL), lymphocytes (500 cells/uL), hemoglobin (9.9 g/dL), D-dimer > 5 ug/ml. Biochemistry tests showed C-reactive protein (40 mg/dL), procalcitonin (2.07 ng/mL), elevated alkaline phosphatase (1452.6 U/L), lactate dehydrogenase (1789.8 U/L), lactate (2 mmol/L), lipase (247.8 mg/dL), triglycerides (344.7 mg/dL), ferritin > 2000 ng/mL, sodium (130 mEq/L), creatinine (0.42 mg/dL), alanine aminotransferase (88 U/L), aspartate aminotransferase (173.81 U/L), and albumin (2.7 g/dL). Coombs' test was positive. Quantification of HIV-1 viral load by real-time polymerase chain reaction (PCR) resulted in 2,230,000 copies/mL, and the CD4+ T lymphocyte subpopulation count was 9 cells/uL; CD8+, 141 cells/uL; CD3+, 156 cells/uL; CD4+/CD8+, 0.07; CD4+/CD3+, 0.06; and CD8+/CD3+, 0;90; resulting in the diagnosis of childhood HIV infection. Serology for *Toxoplasma gondii* was positive IgG > 650 IU/mL (negative < 9 IU/mL). The molecular reverse transcription (RT-PCR) panel for SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), influenza, and respiratory syncytial virus RNA was negative. On admission, the patient received prophylactic (trimethoprim-sulfamethoxazole) and antiretroviral (emtricitabine/tenofovir and efavirenz) treatments.

During the second week of hospitalization, studies for hepatitis A, B, C, cytomegalovirus, herpes simplex 2, and Epstein Barr virus were performed, all with negative results for acute infection. Sputum real-time PCR for *Mycobacterium tuberculosis* and rifampicin sensitivity tests were negative. In addition, sputum, urine, and gastric aspirate smears were also negative.

In the third week of hospitalization, the presence of *Pneumocystis jirovecci* was detected by Giemsa staining in a bronchoalveolar lavage sample, and the second serology for *Toxoplasma gondii* was also positive (IgG > 650 IU/mL). Due to the positivity for *Toxoplasma gondii* and the initial manifestation of headache with fainting, a contrast-enhanced CT scan was performed. The results showed a hypodense image in the right thalamus with a hyperdense central ring and an apparent small subarachnoid hemorrhage

at the level of the cerebral sulci in the left frontal cortical region, images compatible with cerebral toxoplasmosis at the level of the thalamus (Figure 1). Due to the positive result for toxoplasma in blood and brain imaging, trimethoprim-sulfamethoxazole dose was increased to 160 mg/800 mg every 6 hours for 15 days, and fluconazole 350 mg every 24 hours for 5 days was added.

Three weeks after hospitalization, the patient presented with neurological deterioration and hypoxia (oxygen saturation of 75% on room air). Oxygen was administered by high-flow cannula at 20 L/min improving to 85%. The oxygen saturation/inspired oxygen fraction index was < 100. Due to persistent severe respiratory distress, a thoracic CT scan was performed, which was compatible with *Pneumocystis jirovecci* infection (Figure 2). The patient was then intubated and placed on assisted mechanical ventilation in the PICU, where antibiotic coverage was initiated with vancomycin 60 mg/kg/day and meropenem 120 mg/kg/day for 14 days. Echocardiography showed a cardiac ejection fraction of 62% with severe vasoplegia; thus, a vasoactive drip (epinephrine and norepinephrine) was administered with a vasoactive-ionotropic score of 30.

Assisted ventilatory management consisted of pressure control mode, maximum peak pressure 33, inspiratory pressure 20, expiratory pressure 13, respiratory cycle 15, inspiratory time 1, inspired oxygen fraction 70%, mean pressure 18, distending pressure 30, expiratory tidal volume 5 cm^3/kg. The patient had an initial arterial blood gas with pH 7.37, partial pressure of carbon dioxide (pCO_2) 33.3 mmHg, partial pressure of oxygen (pO_2) 50.4 mmHg; bicarbonate (HCO_3) 19.2 mmol/L; arterial oxygen saturation 79.6%; oxygenation index 25; PaO_2/FiO_2 (arterial oxygen pressure/inspired fraction of oxygen) 72. Forty-eight hours later, the patient was placed in prone decubitus for 96 hours, with no improvement in oximetry, for which persistent hypoxemia was considered refractory.

In the initial cerebrospinal fluid study, the outflow pressure was > 25 mmHg; adenosine deaminase was 9.4; lactate dehydrogenase, 34.77 U/L; leukocytes, 1 cell/mm^3; red blood cells, 1 cell/mm^3; glucose, 73.8 mg/dL; protein, 42.5 mg/dL; Chinese ink and Gram's test results were negative. Ferritin concentration was > 2000 ng/mL at hospital admission, remaining elevated at 4000 ng/mL during the fourth week after admission. A bone marrow aspirate was requested for suspected hemophagocytic lymphohistiocytosis.

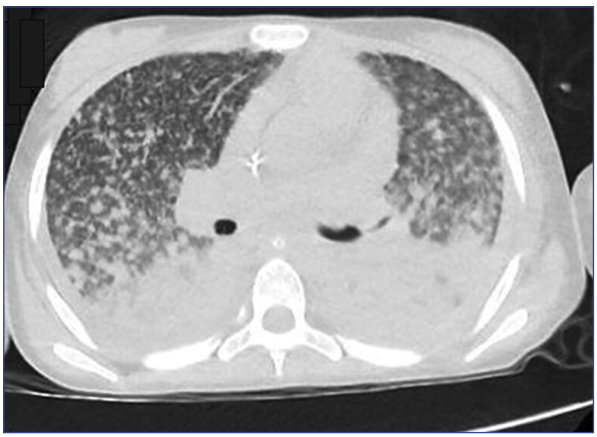

Figure 1. Contrast-enhanced brain CT scan: hypodense image in the right thalamus with a hyperdense central ring. In the left frontal cortical region, there is a small apparent subarachnoid hemorrhage at the level of the cerebral sulci. These images are compatible with cerebral toxoplasmosis at the thalamus.

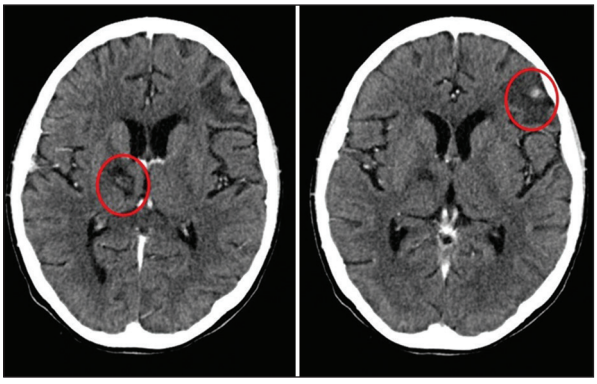

Figure 2. A lung CT scan showing ground-glass and alveolar patterns affecting 90% of both lungs. These images are compatible with *Pneumocystis jirovecci.*

Unfortunately, it could not be performed due to hemodynamic instability.

The patient was managed for hyperferritinemic sepsis due to persistent elevation of ferritin associated with clinical deterioration showing hematological and biochemical alterations. Therefore, amphotericin B 35 mg/day and voriconazole 200 mg orally every 12 hours for 10 days were added to the treatment. After 4 weeks in PICU, the patient continued with further clinical deterioration. Given the persistence of hyperferritinemic sepsis, it was decided to initiate methylprednisolone pulses 1 g/day for 3 days and endocranial hypertension control

therapy with mannitol at 0.5 g/kg/dose every 4 hours. However, the patient developed massive bleeding from the nostrils and oropharynx, resulting in consumption coagulopathy and refractory metabolic acidosis. The patient died 3 weeks after admission to the PICU.

Discussion

Elevated ferritin levels characterize hyperferritinemic syndrome in the context of an inflammatory process, including macrophage activation syndrome, Still's disease, catastrophic antiphospholipid syndrome, and septic shock[8].

Toxoplasma gondii can produce hyperferritinemia directly due to some virulence factors, such as chitinase, and indirectly by macrophage activation[9]. Hyperferritinemic syndrome associated with toxoplasmosis has been described after hematopoietic cell transplantation with fatal outcomes[6] and in patients with HIV[10,11].

Our patient, with a history of untreated HIV, was admitted to our hospital to complete studies because she presented headaches and fainting. However, 3 weeks after hospitalization, she showed severe hypoxemia, thrombocytopenia, lymphopenia, hypoalbuminemia, and tomographic images compatible with *Pneumocystis jirovecci* infection (Figure 2). The neurological level, the two elevated IgG serological tests for toxoplasmosis, weeks apart, correlated with the tomographic image, concluding in the diagnosis of cerebral toxoplasmosis with thalamic involvement (Figure 1).

Hemophagocytic lymphohistiocytosis was considered an alternative diagnosis due to persistent elevation of ferritin associated with the patient's clinical deterioration, pancytopenia, elevated ferritin, fever, splenomegaly, elevated triglycerides, and low fibrinogen. However, due to the patient's critical condition, bone marrow aspirate could not be performed to confirm the diagnosis, so hyperferritinemic sepsis was finally considered. Zhou et al. reported a 33-year-old male with a history of HIV under treatment who presented with respiratory failure due to *Pneumocystis jirovecii* and primary *Toxoplasma gondii* infection. The patient developed hemophagocytic lymphohistiocytosis with good clinical evolution after therapy with immunoglobulin, methylprednisolone, and sulfamethoxazole/trimethoprim[10]. In contrast, Guillaume et al. reported another 33-year-old male with HIV treatment and *Toxoplasma gondii* infection who also developed hemophagocytic lymphohistiocytosis; however, the patient died despite treatment with immunoglobulin and corticosteroids[11]. These cases demonstrate that hyperferritinemic syndrome should be suspected in immunosuppressed and critically ill patients, as it has been reported that a ferritin level > 500 ng/mL is associated with 58% mortality in patients with sepsis[12].

Treatment of hyperferritinemic sepsis differs from that of sepsis without hyperferritinemia[13], as the goal of treating hyperferritinemic syndrome is to suppress the inflammatory process. Intensive care units promote hemodynamic stability, support specific organ dysfunction, and correct coagulopathy to achieve that goal[14]. Treatment includes intravenous immunoglobulin, high-dose corticosteroids, plasmapheresis, and even IL-1 (interleukin-1) receptor antagonists[15,16]. In the present case, antibacterial, antifungal, antiparasitic, antiviral treatment, and high-dose corticosteroid administration were used, but without favorable response. Immunoglobulin or plasmapheresis was not administered because they were unavailable in our hospital. Despite coverage against opportunistic microorganisms, hemodynamic support, and assisted ventilation[17], the outcome was fatal, and the patient died.

In conclusion, hyperferritinemic sepsis may be caused by *Toxoplasmosis gondii*. Therefore, it is necessary to suspect hyperferritinemic syndromes in critically ill patients when initial therapies are not favorable, particularly in immunosuppressed patients.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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