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Case Report

Klebsiella Infection oxytoca in Bone Marrow as a Cause of Prolonged Febrile Syndrome, in Relation to a Case

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ABSTRACT

Introduction: Prolonged febrile syndrome (PFS) is a clinical entity where fever persists after at least one week of detailed evaluation or exhaustive study, without reaching an etiological diagnosis.

Clinical Case: A 6-year and 3-month-old female schoolgirl, characterized by an increase in body temperature quantified at 39 °. In view of the persistent continuous fever and associated liquid stools, numbering 6 per day, her admission was decided. After an exhaustive realization of studies for the etiological search, the myeloculture reported growth of Klebsiella oxytoca, instituting treatment with favorable clinical resolution.

Conclusion: This case represents a lesson for medical personnel in the proper management of protocols for patients with PFS, which makes it necessary to understand it and apply it to reduce the time of diagnosis and indication of timely treatment, improving the patient's quality of life and reducing the anxiety generated in caregivers.

KEYWORDS

Immunization, Hospitalized pediatric patient, Missed vaccination opportunities.

Introduction

Fever in the pediatric population is associated with acute diseases and benign etiology in most cases, physiologically defined as a self-regulation and self-limiting response of the hypothalamus, to an acute inflammatory response in the patient and although it is usually pointed out as harmful, evidence shows that fever does not cause tissue damage [1,2]. Despite being a frequent reason for consultation in pediatric emergencies, it generates a lot of anxiety in parents and caregivers, which causes them to consult with undiagnosed or poorly evolved febrile symptoms, especially in infants [3-5].

From an etiological point of view, fever is due in most cases to self-limited viral infections and uncomplicated bacterial infections, which can resolve in a week or less [2,4]. In a small number of cases, fever may be prolonged or reappear, defining recurrent

fever as febrile episodes that are separated by periods of normal temperature (cyclical fever) [3,6]. On the other hand, fever without source is a process of less than 72 hours of evolution, in which the cause is not identified after the history and physical examination [7]. PFS is a clinical entity, where fever is prolonged after at least one week of detailed evaluation or an exhaustive study, without reaching the etiological diagnosis [8-10].

The etiological study, management and final diagnosis represent a challenge for physicians in charge of child health, considering the etiological variability according to the geographical location and the scarce reports in the literature [8,11]. The diagnostic approach should always include a directed anamnesis and a complete physical examination, aimed at finding the most common causes, resulting in determining the cause of SFP in 90% of cases [4,7]. In the pediatric population, the three main causes are: infectious (> 50% of cases), autoimmune and oncological [12,13].

A 4-level scale of etiological investigation is described in the SFP, the first level rules out frequent infectious causes and should include laboratory studies such as blood count, blood and urine cultures or other cultures according to clinical manifestations, as well as acute phase reactants, kidney and liver function tests, chest x-ray, if no pathological findings are found, the search for less common infectious diseases such as tuberculosis, cytomegalovirus infection, Epstein Barr virus, malaria, shigellosis, among others should be included [8,14]. If there is no defined etiology, the next level of care should be continued, in search of immunological diseases, for which directed tomographic studies, echocardiogram and bone marrow aspiration should be performed, likewise, complement studies, directed antibodies such as ANA, ANCA, Anti DNA, Anti Smith should be included [8,10]. The fourth and final level includes exploratory laparotomy, which is left for cases of extreme SFP and if there is no level of suspicion at the second and third levels [1,15].

Due to the great uncertainty that comes with not having a final diagnosis, in the context of SFP, both for family members and medical staff, it is really important to keep in mind the concept of SFP, which as its name indicates, is a clinical syndrome with varied forms of presentation and multiple etiologies, so everything professionally possible should be done to achieve the correct diagnosis, indicate a correct treatment and achieve complete resolution of the condition [8,14]. We present the clinical case of a schoolgirl who went to the pediatric emergency room, due to a clinical picture characterized by prolonged fever, of more than 1 month of evolution, without an etiological diagnosis, despite having gone to a physician, generating great debate about its management protocol, as well as its therapy, reminding medical staff about the great etiological variety in patients with SFP.

Clinical Case

A 6-year and 3-month-old female student, born and raised in Flor de Patria, Pampán municipality, Trujillo state, reported the onset of a current illness of 1 month's duration, characterized by an increase in body temperature measured at 39 ° C, which was attenuated by the administration of antipyretics, concomitant vomiting of food content, once a day for a week, going to the physician, who prescribed symptomatic treatment, without improvement. In view of the persistent continuous fever, without hourly predominance, without a characteristic clinical pattern and associated with liquid stools, numbering 6 per day, without mucus or blood, she went to the pediatric emergency service of the University Hospital of Valera (HUV), where her admission was decided. The patient had no significant medical history; however, her mother reported no prior immunizations against chickenpox and influenza, as well as no COVID-19 and pneumococcal boosters. She also reported a family history of systemic lupus erythematosus in a maternal aunt who worked in the pediatric surgery department at HUV. There was no history of oncological diseases.

On admission, the patient's physical examination revealed a heart rate of 84 bpm, respiratory rate of 20 rpm, temperature of 38.4 °C, blood pressure of 110/70 mmHg (50th percentile for age), and arterial oxygen saturation of 98%. Anthropometry: Weight of 17,000 g, height of 113 cm, left arm circumference of 19 cm. The patient was in stable clinical condition, with mild cutaneous-mucosal pallor, hyperthermic to the touch and febrile, eupneic, and tolerating ambient oxygen. Bilateral cervical lymphadenopathy <0.5 cm was palpated, mobile, not adherent to deep planes, and non-tender. Heart sounds were rhythmic; no murmurs were heard. Breath sounds were audible, symmetrical, and without aggregates. No signs of respiratory distress were evident. The abdomen was soft and depressible. No visceromegaly was palpable, and there were no signs of peritoneal irritation. Bilateral inguinal lymphadenopathy measuring <0.5 cm was palpable, mobile, not adherent to deep planes, and non-tender. Symmetrical and mobile extremities were present, without edema. Neurological: active, cooperative with physical examination, with preserved muscle strength with a Daniels scale of 5/5. There were no signs of meningeal irritation, no ictal events, and isochoric pupils that were normoreactive to light. There were no motor or sensory deficits.

Given the clinical evolution of the current disease and its duration, it was decided to initiate a protocol for SFP. The patient was admitted with laboratory studies requested by primary health care, reporting a complete blood count: white count 17,100 /mm3, segmented 77%, lymphocytes 13.9%, platelets 494,000 /mm3, hemoglobin 10.4 g / dl, hematocrit 35.7%. Acute phase reactants: ESR 83 mm / Hr, CRP 96 mg / dl, SGOT 31 U / L, SGPT 22 U / L. Urinalysis: leukocytes 0-1 xC, negative nitrites, negative leukocyte clusters. IgM serology for Toxoplasmosis, Cytomegalovirus, Epstein-Barr: negative. Upon admission, a decision was made to request a complete blood count, lactate dehydrogenase, alkaline phosphatase, uric acid, HIV and VDRL Test Pack, thick blood smear, blood culture, BK of gastric contents, RDT for COVID-19, chest x-ray, and abdominal and pelvic ultrasound. A lumbar puncture was requested to take a cytochemical sample and, after taking the same, to associate third-generation cephalosporins and aminoglycoside, cefotaxime and amikacin at doses of 200 mg/kg/day and 15 mg/kg/day respectively, and an evaluation by the pediatric hematology service was requested.

Subsequently, the result of the blood culture and fungal culture was received, which was negative for bacterial and fungal growth after 72 hours of incubation. Likewise, the result of the sputum BK plus KOH reported positive for budding yeast, so fluconazole was indicated at a dose of 6 mg/kg/day once a day, complying for 10 days. The result of the cerebrospinal fluid cytochemistry was received, which reported: colorless, clear appearance, pH 8.0, alkaline reaction, cells 0 x mm3, polymorphonuclear cells

0%, mononuclear cells 0%, glycemia 49 mg/dl, protein 18.5 g/dl, negative PANDY, interpreted as negative for neuroinfection, and the culture reported negative for bacterial growth. The result of the blood count was received, which reported: white count 9,800. /mm3, segmented 75%, lymphocytes 21%, monocytes 4%, hypochromia (+), anisocytosis and mild poikilocytosis. The LDH result was 429 U/L, the HIV and VDRL Test Pack results and the thick film were negative. Given the persistence of undiagnosed SFP, 10 days after admission, an evaluation by the pediatric infectious disease service was requested.

The peripheral blood smear was evaluated in conjunction with the hematology service, where anipoikilocytosis and hypochromia from + to ++ were observed, with a predominance of atypical lymphocytes and multiple polysegmented lymphocytes with giant band cells, so they decided to perform a bone marrow aspiration and myeloculture study. On day 12 of hospital evolution, the patient presented arthralgias in symmetrical joints of the upper limbs, predominantly at night, so she was evaluated by the rheumatology service who, in view of the blood culture results, within the protocol for SFP, suggested performing an echocardiogram, as well as serum ferritin to rule out hyperferritinemic syndrome. The results of the abdominopelvic ultrasound and chest x-ray showed no pathological findings.

The myeloculture was received, which reported the growth of *Klebsiella oxytoca*, ESBL strain, with a count of 100,000 CFU, being sensitive to meropenem, imipenem and levofloxacin, so in conjunction with the hematology and infectious disease service, it was decided to indicate broad-spectrum antibiotic therapy, since it represented a bone marrow infection with a gram- negative bacillus, likewise it was decided to omit the rest of the antimicrobials and the rest of the studies, in view of the disappearance of the fever and associated symptoms within 48 hours of treatment with meropenem at a dose of 100 mg/kg/day. Compliance with antibiotic therapy with Meropenem for 14 days was suggested. Finally, the diagnosis of *Klebsiella infection was established oxytoca* in Bone Marrow, as the cause of the patient's PFS.

Discussion

The prevalence of carbapenemase -producing Enterobacteriaceae remains a threat to public health, as it continues to increase worldwide and is associated with significant morbidity and mortality [15]. Among the Enterobacteriaceae of global epidemiological importance, the genus *Klebsiella* is considered an opportunistic pathogen linked to serious diseases, including urinary tract infections, septicemia, and pneumonia [14,15]. The most common species of this genus are *Klebsiella oxytoca and K. pneumoniae* representing approximately 8% of cases of opportunistic infections in the United States and Europe, as described by Gedebjerg and collaborators [15], as was the case of the patient presented, where her final diagnosis was *K. oxytoca infection* in bone marrow, after an exhaustive clinical search for the etiology following the protocol for SFP.

Although bone marrow studies constitute an important element in the study and investigation of patients with a high index of suspicion of benign or malignant hematological pathology, the clinical study to identify the etiology of SFP is less clear, as reported by Sharvit et al. [10]. In the clinical case studied, myeloculture was performed in view of the absence of a diagnosis of more than 2 weeks of in-hospital evolution without absence of fever, suggested by the hematology service. Although multiple authors consider *Klebsiella oxytoca* as an opportunistic germ, the vast majority agree that it is pathogenic with varying degrees of intensity, especially in intestinal infections, bacteremia, complicated urinary tract infections and pneumonia [10-13].

K. oxytoca infection in bone marrow has been reported in the medical literature, as was diagnosed in the clinical case presented, however, as mentioned by Sharvit and others [10], the most common etiologies in myelocultures are *Mycobacterium avium, Leishmania spp, Mycobacterium kansasii, Bartonella henselae, Coxiella burnetti,* cytomegalovirus, as well as autoimmune etiologies such as lymphohistiocytosis hemophagocytic, juvenile rheumatoid arthritis and malignant entities such as lymphoma. In parallel, Stewart et al. [4] mention that *Klebsiella* isolates *The most common oxytoca* samples are urine, respiratory and wound secretions, with a high rate of resistance.

The antimicrobial resistance studied by Pérez et al. [2] between 2016 and 2017 of *K. oxytoca* in 22 Spanish hospitals shows the appearance of carpenemases in 80 of the cultures, as well as the case of bacteremias represented 28% of the isolations of this gram-negative bacterium, with a predominance of the male sex in all patients. In the case of the patient studied, *K. oxytoca* was isolated. strain BLEE, for which Meropenem was indicated at usual doses, according to the reported antibiogram, having a satisfactory clinical evolution, management that does not coincide with that reported by Walkty and collaborators [7], where they used cefotaxime at usual doses in the treatment of complicated UTI, where *K. oxytoca* was isolated producer of OXY β- lactamase, as well as reported by Brooks [6], where *K. oxytoca was reported* in a patient with urosepsis, using ceftriaxone.

Although the incidence of *K. oxytoca infections is unknown in our environment*, it is truly necessary to understand it as a bacteria that can cause serious complications in immunocompetent patients, as was the case presented, as well as in immunocompromised patients and in pediatric patients with PFS, especially when empirical antibiotic therapy has been used, generating resistance if the exact etiology is unknown. Likewise, this case represents a lesson for medical personnel on the proper management of protocols in patients with prolonged febrile syndrome, which makes it necessary to know it and apply it to reduce the time of diagnosis and indication of timely treatment, improving the quality of life of the patient and reducing the anxiety generated in caregivers.

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