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Case Report

Use of Oral Gentamicin in Children with Primary Immunodeficiency and Recurrent *Campylobacter coli* Bacteremia: A Case Report

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Abstract

Immunosuppressed patients are more at risk of suffering bacteremias due to atypical microorganisms such as *Campylobacter coli*, which can colonize their intestinal mucosa due to the absence of IgA, the main immunoglobulin of the mucosa and which is not provided with intravenous or subcutaneous immunoglobulin treatment. We have recently had a case of a 5-year-old girl with autosomal recessive agammaglobulinemia with recurrent *Campylobacter coli* bacteremia and positive stool cultures for the same microorganism. She was treated with intravenous antibiotherapy and given the recurrence of bacteremia, oral gentamicin was associated with this treatment to try to achieve intestinal eradication of the germ. Oral gentamicin was well tolerated, gave no side effects, and managed to eradicate the microorganism 6 months after the end of treatment. We want to reflect the scarce literature on the use of oral gentamicin, the dose and duration of treatment, and the good evolution of our patient with the regimen used.

Introduction

Autosomal recessive agammaglobulinemia is a primary immunodeficiency characterized by an abnormal development of B lymphocytes, severe hypogammaglobulinemia, and therefore an increased risk of infections. Is a rare disease with a prevalence of <1 case/1,000,000 births and there are less than 100 cases in the world. Symptoms begin at 6 months of age, at which time maternal immunoglobulins are lost. It can be caused by multiple mutations in several genes involved in humoral immunity, including IGHM (14q32.33), CD79A (19q13.2), BLNK (10q23.2-q23.33), IGLL1 (22q11. 23), CD79B (17q23), PIK3R1 (5q13.1) and TCF3 (19p13.3) [1,2]. Diagnosis is suspected on the basis of early susceptibility to severe recurrent or persistent infections. On laboratory work-up, they have low immunoglobulin levels and low or no mature B lymphocyte counts in peripheral blood. Genetic testing should be performed to confirm the diagnosis [1,2]. Treatment includes early intravenous or subcutaneous immunoglobulins every 3-4 weeks [1,2]. Screening for severe infections in fever is important in these patients as well as early antibiotherapy if needed. The prognosis is generally good but depends on adherence to treatment and the development of complications [1,2].

Campylobacter coli is a bacterium that in patients with humoral immunodeficiencies, due to the absence of IgA, can cause bacterial translocations from the intestine to blood and therefore intermittent bacteremia, being a difficult germ to eradicate [3]. The good results seen with the concomitant use of intravenous antibiotherapy and oral gentamicin in adults, which has no systemic absorption [3-5], allow us to use it in a 5-year-old girl with autosomal recessive agammaglobulinemia, with intestinal colonization by *C. coli* and repeated bacteremias caused by this germ, with very good results. With this case, we want to reflect on the use of oral gentamicin in a pediatric patient with autosomal recessive agammaglobulinemia to

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eradicate the intestinal reservoir, not described in the literature at the moment.

Case report

A 3-year-old patient from Pakistan newcomer to Spain, consulted in the emergency department for intermittent fever since she was 6-7 months old, with intermittent diarrhea, stagnant weight, abdominal distension, and asthenia. She was studied in Pakistan with normal abdominal ultrasound, leukocytosis with persistent lymphocytosis (other series normal), no other alterations, bone marrow without malignancy signs, normal pregnancy control, term delivery, and no incidents until 6-7 months of age.

In the emergency room physical examination was performed with good general condition, scarce adipose panniculus (weight $p < 3$), globular abdomen, hepatomegaly, and subcentimetric laterocervical, occipital, and inguinal lymphadenopathies. Laboratory tests show leukocytosis, lymphocytosis (11.000/mcL), hypertransaminasemia, microcytic anemia, elevated RDW, compatible with iron deficiency anemia, no elevation of Acute Phase Reactants (APR), and pathological urine analysis (positive nitrites and leukocytes with abundant bacteria in the sediment). Due to the hepatomegaly and analytical findings, abdominal ultrasound was requested. It showed pathological lymphadenopathies in the gastrohepatic ligament, hepatic hilum, and retroperitoneal, liver and kidneys were normal. Admission was decided to complete the study with oral cefixime for suspected febrile urinary tract infection. The urine culture was positive for Extended-Spectrum Beta-Lactamase (ESBL)-producing *Escherichia coli*, so treatment was changed to ertapenem for 10 days. The control urine culture was negative on the seventh day of treatment.

During the admission, the study was extended due to prolonged fever, hepatomegaly, and weight stagnation. In the analysis, there was an iron deficiency, malnutrition parameters (vitamin D, prealbumin, and RBP decreased), absence of all immunoglobulins and CD19 lymphocytes with normal peripheral blood morphology, and persistent lymphocytosis.

Suspected immunodeficiency, monthly intravenous immunoglobulins were started at 0.5 g/kg and increased to 0.8 g/kg to maintain adequate levels of IgG. A complete immunity study was performed (including Burst, maternal chimerism, LTT) and was normal. It was also observed the absence of adenoid tissue. Genetic study with IGHM gene mutation was compatible with autosomal recessive agammaglobulinemia type 1. The infectious study was negative except for the stool culture, positive for *C.coli* resistant to azithromycin (she received a single dose prior to the antibiogram result) [6]. She had no diarrhea or digestive symptoms and was in good general condition, so it was decided not to treat her despite being immunocompromised and to do a stool culture control, which was negative after one month.

Due to malnutrition, nutritional support was started with hypercaloric shakes, iron, and vitamin D. During admission there was weight gain, anemia improved and hepatomegaly decreased in the following months, same as lymphocytosis.

During follow-up, at 5 years of age, intermittent fever and diarrhea restarted. Blood and stool cultures were drawn without elevation of APR and sent home after 24 hours of admission with no fever, and the patient was notified of *C.coli* growth in all the samples taken. New cultures taken on admission prior to initiation of intravenous antibiotic with ertapenem were negative and the patient was de-escalated and sequenced to amoxicillin-clavulanic acid at high doses (due to increased sensitivity). The girl remained asymptomatic and with excellent general condition during the bacteremia, some febrile peak isolated at the beginning of the treatment which was maintained for 14 days. At discharge, stool and blood cultures were negative.

Four months later, she was reconsulted for intermittent fever. Blood tests were normal except for known hypertransaminasemia and lymphocytosis. Blood cultures were positive for *C.coli* and stool culture was negative on this occasion. Treatment was started with ertapenem which was de-escalated to amoxicillin-clavulanic acid at high doses after knowing the antibiogram. Blood cultures were negative and she was discharged after 14 days of treatment. Prophylaxis was started with trimethoprim-sulfamethoxazole three times a week.

Due to the consecutive bacteremias with the growth of *C.coli* in stool cultures and blood cultures and after the good results obtained in adult patients, it was decided to administer oral gentamicin as the patient was sensitive, to try to eradicate the germ that we believe colonizes her intestine (intermittent positive stool cultures) and is the cause of these intermittent bacteremias [3-5]. Oral gentamicin had no systemic absorption, thus avoiding the toxicity of this antibiotic. The dose used in adults is extrapolated to the patient's body surface area (dose administered in adults is 80mg every 6 hours, which is equivalent to a dose of 45-50 mg/m^2 of surface area every 6 hours). Serial plasmatic levels of gentamicin are performed to ensure no systemic absorption, being undetectable. Serial blood and stool cultures after 3 months of treatment were all negative, so it was decided to discontinue treatment [4]. The dose used was 30mg every 6 hours (45mg/m^2/dose) and had good results in the first 6 months of follow-up, continuing with negative cultures extracted on a monthly basis [4].

Discussion

Bacteremia due to *Campylobacter coli* (and *Campylobacter spp* in general) is very infrequent and is associated with immunosuppressed patients [3,6,7]. The involvement of the intestinal mucosa due to malnutrition and IgA deficiency in these patients may be risk factors for recurrent bacteremia due to bacterial translocation [3,5,8]. In addition, macrolide-resistant *Campylobacter coli* have been shown to have an increased risk of producing bacteremia [6]. We present a case of a girl with autosomal recessive agammaglobulinemia, with intestinal colonization by *Campylobacter coli* that causes repeated bacteremias due to this germ, which has been eradicated by associating oral gentamicin.

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Campylobacter coli is a gram-negative bacillus that in humans can infect the gastrointestinal tract, generally producing diarrhea after eating contaminated food and water, but it can also be in the soil. In immunocompromised patients, the infection can be more severe, such as bacteremia, due to the absence of B lymphocytes and immunoglobulins [3,5,6,8]. Colonization of the intestinal mucosa by *Campylobacter coli* may be the mechanism of recurrent infection in patients with agammaglobulinemia. In addition, low levels of the main intestinal immunoglobulin, IgA, which is not administered with intravenous or subcutaneous immunoglobulin therapy, prevent adequate elimination of intestinal pathogens [3,5,6,8].

In our patient, *Campylobacter coli* was isolated in all the episodes of intermittent fever observed in Spain, even in the stool culture extracted one month after her arrival from Pakistan (on arrival it was negative) within the study of immunodeficiencies and while she was asymptomatic. In this case, she received treatment with oral azithromycin before knowing that it was resistant. Given her good general condition and normal laboratory tests, despite being immunosuppressed, it was decided not to start treatment and to maintain close monitoring of the patient, achieving a negative stool culture at one month. Subsequent stool culture controls were negative until the first bacteremia, where *Campylobacter coli* was isolated in both blood and stool cultures, which led us to think of intestinal translocation. Treatment with ertapenem due to the previous antibiograms for fourteen days managed to negativize both blood and stool cultures. With the second bacteremia, it was decided to add oral gentamicin to ertapenem iv to try to eradicate the germ from the intestine and avoid recurrences [3,4,5], because the control blood cultures obtained in the first six days of treatment with ertapenem or high-dose amoxicillin were still positive. The first and subsequent blood cultures obtained three days after starting oral gentamicin were negative. Oral gentamicin in our patient has been shown effective for the remaining follow-up time and she has no toxicity and no neither secondary effects.

Curiously, all the patients described in the articles are unstable or severely affected while our girl always maintains excellent general condition, is asymptomatic except for fever, and has analytical tests without elevated APR [3,4,9].

Persistent intestinal colonization is a very important factor in bloodstream infections in immunocompromised patients. In our patient, the association of oral gentamicin for 3 months to the treatment of bacteremia has managed, for the moment, to eradicate *C. coli* from her intestine [4,9-11].

Oral gentamicin does not seem to have side effects since it has no systemic absorption. Our patient had no side effects and blood levels of gentamicin were found to be undetectable monthly during the 3 months of treatment [3,4]. The oral treatment allowed the eradication of the microorganism after 6 months of treatment suspension.

Conclusion

In conclusion, with this case, reflecting on the literature on the use of oral gentamicin in a pediatric patient with autosomal recessive agammaglobulinemia to eradicate the intestinal reservoir and prevent relapses [12], it was not described in the literature previously in children. In addition, gentamicin has once again been shown to be safe when administered orally. Due to the increased risk of recurrent *Campylobacter coli* bacteremia in immunosuppressed patients and the difficulty of its eradication, it seems advisable, despite the few cases described, in the case of bacteremia, to associate oral gentamicin to the intravenous antibiotic; even to treat *Campylobacter coli* colonization with oral gentamicin to prevent bacteremia, since it has been shown to be safe and effective because it has no systemic absorption.

Informed consent statement

Written parental consent was obtained for the intervention and publication of the case. A copy of this consent is scanned in the patient´s clinical history.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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