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A severe acute cholestatic hepatitis due to visceral leishmaniasis in a child using monoclonal antibodies and systemic steroids

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Abstract

Acute cholestatic hepatitis is a rare but potentially severe manifestation of visceral leishmaniasis. There are few described pediatric cases of acute hepatitis due to leishmaniasis, and to our knowledge, this is the first reported case in a pediatric patient with associated monoclonal antibody therapy. The novelty of monoclonal antibodies requires further investigation of their potential involvement in systemic infections. The development of haemophagocytic syndrome in visceral leishmaniasis is very rare and can represent an additional challenge in diagnosis and management.

Introduction

Leishmaniasis is caused by the protozoa leishmania, whose reservoirs are mammals, and its vector is the Phlebotomus mosquito. The world`s annual incidence is 700,000 cases per year and it is more common among immunocompromised and young infants. It is endemic in tropical and subtropical areas, and southern Europe, being more frequent in rural areas; however, it has been described in urban suburbs [1]. Clinically, leishmaniasis can have mucocutaneous or visceral presentations. Visceral Leishmaniasis (VL) is characterized by fever, splenomegaly, and pancytopenia. Acute hepatitis is an exceptional presentation, which despite being uncommon, can be severe or even fulminant. It has a cholestatic pattern that can be associated with abdominal pain, vomiting, and jaundice [2]. After reviewing the literature, 13 published cases of pediatric VL with acute hepatitis around the world were found [3,4]. On the other hand, the use of targeted monoclonal antibody therapy is rapidly increasing in frequency and variety, though the side ef-

fects [4] and complications of its use are still a broad and undiscovered field. It should be noted that some monoclonal antibodies block the Th2 lymphocytes pathway, which can increase the theoretical risk of parasitic infections [5].

Methods

We report the case of a 16-year-old boy with acute severe cholestatic hepatitis secondary to VL. He was born and lives in Sant Boi, a middle-income, developed urban municipality next to the delta of Llobregat river, in the metropolitan area of Barcelona, Spain. He presented in the emergency room with a 3-day history of vomiting, diarrhea, abdominal pain, and low-grade fever (37.8°C). His past medical history was notable for Attention Deficit Hyperactivity Disorder (ADHD) in treatment with methylphenidate (54 mg/day) and severe persistent asthma initially treated with ß2 agonists (salmeterol 50 mcg/day), inhaled steroids (fluticasone 500 mcg/day), and tiotropium (5 mcg/day) that was uncontrolled and required oral steroids (prednisone 10 mg /12 hours) for the past 4 years and monoclonal anti-interleukin 5 antibody (Mepolizumab 100 mg every 28 days) for the past 9 months. On admission, he had normal vital signs, cushing syndrome appearance, and right hypochondriac tenderness. The initial blood analyses revealed severe cholestatic hepatitis (alanine aminotransferase (ALT) 901 UI/L (normal range (NR 2-30)), aspartate aminotransferase (AST) 467 UI/L (NR 2-38), gamma-glutamyl transferase (GGT) 165 UI/L (NR 10-22), total bilirubin 1.5 mg/dl (NR 0.2-1), direct bilirubin 1.1 mg/dl (NR<0.2, thrombocytopenia (97,000 /uL, (NR 150,000-500,000)), and hypergammaglobulinemia (17,520 mg/L, (NR 6,500-15,000). Alkaline phosphatase, prothrombin time, INR, C reactive protein and blood smear were normal. An abdominal doppler-ultrasound revealed splenomegaly of 17 cm without hepatomegaly, intrahepatic biliary radical dilatation was excluded or there were no signs of portal hypertension. The initial microbiologic study of hypertransaminasemia included viral serologies for Cytomegalovirus, Epstein Barr, hepatitis B, hepatitis C, hepatitis A, hepatitis E, adenovirus, parvovirus B19, and enterovirus that were negative and the only positive result was a weak positive polymerase chain reaction (PCR) for human herpes 6 virus. Other causes of hypertransaminasemia were ruled out, including thyroid dysfunction, alpha 1 antitrypsin deficiency, Wilson's disease, and celiac disease. The liver autoimmune study was negative, except for anti-smooth muscle antibodies that were positive in low titers (1/40) with a negative anti-actin pattern, suggesting low autoimmune hepatitis specificity. On the following days, he experienced marked worsening of hepatic cytolysis (maximum ALT 1,755 UI/L (NR 2-30)) so a liver biopsy was performed.

Results

Histological examination revealed marked centrilobular inflammation with lymphoplasmacytic aggregates containing plasma cells and necrotic hepatocytes. Histocytes showed epithelioid morphology with foamy cytoplasm containing structures suggestive of intracellular microorganisms. There was a slight fibrous expansion with reticuline collapse in the necroinflammatory areas. PAS, Giemsa, and Ziehl-Neelsen stains as well as immunohistochemistry for cytomegalovirus were negative. Immunohistochemistry for VL was performed containing structures suggestive of amastigotes. On the following days, he presented persistent daily fever, thrombocytopenia (minimum 85,000/uL (NR 150,000-500,000)), leukopenia, ele-

vated ferritin (maximum 11,838 ug/L (NR 10-120)), and hypertriglyceridemia (286 mg/dl (NR 40-201)). The presence of 5 out of 8 diagnostic criteria was compatible with secondary haemophagocytic syndrome (sHLH) which was supported by findings in bone marrow aspiration [6]. Although no hemoparasites were detected in the microscopic examination of bone marrow samples, PCR for Leishmania was positive in the bone marrow and blood samples. Mepolizumab was suspended, and he received systemic low-dose prednisone (60 mg/day) for sHLH and intravenous amphotericin B (3 mg/kg/day) for VL. His subsequent evolution was excellent, with normalization of liver enzymes after 6 doses of amphotericin B.

Discussion

There are very few described cases of VL with liver involvement in pediatric patients. To our knowledge, this is the first reported pediatric case of severe hepatitis due to VL in a patient in treatment with monoclonal antibodies and systemic steroids. Acute hepatitis due to VL has been described in adult and pediatric populations but it is rare. Although leishmania is endemic in Spain, there are only three published case reports of hepatitis due to VL in the area of Barcelona (Spain), all of them adults [2,7]. When present, acute hepatitis due to VL tends to be severe, with a cholestatic pattern that can manifest with portal hypertension. VL is much more common among immunosuppressed patients. In our case, both the prolonged use of systemic steroids and the anti-IL 5 monoclonal antibody could modify the immune response of the patient and increase the risk of parasitic infection. Immunosuppression caused by steroids at doses >20 mg/day or 2 mg/kg/day during more than 14 days is well established. Cases of leishmaniasis in adult patients in treatment with steroids have been published [8]. Mepolizumab, on the other hand, is a new generation drug whose possible infectious complications are unknown. It acts by blocking IL-5 and preventing its attachment to the eosinophilic surface, thereby blocking eosinophilic maturation, differentiation, migration, and function. Eosinophils are key in the innate immune response and have an antiparasitic function, so by blocking eosinophils, the theoretical risk of parasitic infection increases [5]. For this reason, Mepolizumab´s pharmacological prospect includes a warning regarding the risk of parasitic infections, generally localized, and recommends its screening before starting treatment, but beyond this reference, there is no published scientific data. Following the recommendation to rule out parasitic infections before starting Mepolizumab, our patient was performed a stool analysis for parasites that was negative. Upon literature review, only one case report was found of an adult receiving treatment with a monoclonal antibody (anti-IgE Omalizumab) with a parasitic infection by Echinococcus [5]. Unfortunately, parasitic infections are considered exclusion criteria in many safety clinical trials, so the real risk of parasitosis might be underestimated.

Conclusions

This case presents a rare manifestation of an infrequent systemic infection in a pediatric patient in treatment with Mepolizumab and systemic steroids. The association of monoclonal antibodies with important systemic infections requires further investigation. Hopefully, this case can contribute to raise suspicion of parasitic infections in patients under treatment with monoclonal antibodies, especially when combined with other immunosuppressive treatments, such as steroids. Furthermore, this case highlights the importance of reporting individual cases of rare concurrent infections in patients with novel drugs that act by

modulating the immune system. It is through multiple individual reports that potentially association can be investigated and identified.

Declarations

Author's contributions: Conception and design of study: María Clara Jijón, Cristina Molera, Estefanía Ortega, Javier Martín de Carpi acquisition of data: María Clara Jijón, Estefanía Ortega, Carlota Rovira Analysis and interpretation of data: Cristina Molera, Claudia Fortuny, Carlota Rovira, Maria Cols drafting the manuscript: María Clara Jijón, Estefanía Ortega, Cristina Molera, María Solsona revising the manuscript: Claudia Fortuny, Maria Cols, Fabriella Quesada, Carlota Rovira Approval of current version: María Clara Jijón, Cristina Molera, Estefanía Ortega, Claudia Fortuny, Maria Cols, Fabriella Quesada, Carlota Rovira, Maria Solsona, Javier Marín de Carpi agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or work are appropriately investigated and resolved: María Clara Jijón, Cristina Molera, Estefanía Ortega, Claudia Fortuny, Maria Cols, Fabriella Quesada, Carlota Rovira, Maria Solsona, Javier Marín de Carpi

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