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Case Report

Brucellosis infection presenting with cholestasis

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SUMMARY

Brucellosis is a relatively common disease in the Mediterranean area and may present with prolonged fever without focus, however it remains an important diagnostic challenge to most pediatricians. We report the case of a 10-year-old male patient who presented with fever without a focus of 10-day duration, hepatomegaly, ascites, a small elevation in transaminases and acute-phase reactants indicating cholestasis, leukopenia, and thrombocytopenia. Imaging tests showed many small, rounded, hypodense focal lesions in the liver and spleen. After eliminating a wide range of diseases, positive results for the Rose Bengal test and indirect immunofluorescence assay for *Brucella melitensis* made it possible to establish a diagnosis of hepatosplenic brucellosis. A review of the family history revealed direct contact with farm animals. The patient made good progress on treatment with doxycycline and streptomycin, with complete resolution of both clinical symptoms and imaging signs. The prevalence of brucellosis is gradually increasing, mainly due to migratory movements. It should always be eliminated as a source of unknown fever in endemic areas and should also be taken into account in other geographical areas where it is not common whenever a patient presents with prolonged fever and unspecific symptoms. Standard therapy is highly effective, even in relapse cases, and early diagnosis leads to a rapid recovery and favorable outcome. The unusual presentation in the case reported here reminds us that it is possible to encounter a Brucella infection in a case of fever without a focus, irrespective of the existence of a clear epidemiological history, which is very often omitted by the family. All differential diagnostic protocols for fever without a focus should include a diagnostic test for Brucella in order to achieve early detection of the disease and initiate therapy promptly.

1. Introduction

Fever is the main cause of attendance to pediatric emergency services and primary care clinics in most industrialized countries. In general, symptoms are clear and the most common cause is a mild viral infection, such as a respiratory infection affecting the upper airways. These processes are usually of a short duration and self-limiting, only requiring symptomatic treatment. On other occasions, fever is an isolated symptom and there are no other signs to help establish an accurate diagnosis. Most often, these processes are also self-limiting. When fever is the only symptom and it is continuous and lasts for more than 7 days, pediatricians are more concerned.

Prolonged fever without focus is a well-known clinical entity to most pediatricians. Its etiologic spectrum ranges from unimportant viral processes to malignant hematological processes, and covers a wide range of infections. Occasionally, the patient's clinical history may help us to determine the source of the fever. Many different protocols are used to manage children with prolonged fever without a focus, but we must not forget that irrespective of all the tests we can perform, a detailed and accurate clinical history can help us, if we are aware of the possible causes, to reach an accurate diagnosis.

Brucellosis is a relatively common condition in the Mediterranean area and may present with prolonged fever without a focus, however due its wide spectrum of clinical symptoms it remains an important diagnostic challenge for pediatricians.

2. Case report

During the month of April, a 10-year-old Caucasian male presented at our institution with fever of intermediate duration. The week before admission the patient had experienced episodes of high fever (39–40 °C) occurring at different times of the day and occasional vomiting. Two weeks before the fever episode the patient had been given antibiotics due to a bacterial tonsillitis, and this had resolved without complications.

The patient's clinical history was unremarkable. His mother did not report any recent travel, contact with animals, or the

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consumption of unpasteurized dairy products. A physical examination revealed that he was in good general condition, without signs of constitutional syndrome; there was frank jaundice of the skin and mucosa, fever of 38.2 °C, heart rate of 95 beats/min, respiratory rate of 18 breaths/min, and arterial tension of 100/65 mmHg. Cardiopulmonary auscultation and examination of the ears, nose and throat showed no alterations. An abdominal examination revealed discreet painless hepatomegaly of 2 cm, with an increase in abdominal diameter and ascites. A neurological examination yielded negative results.

Laboratory tests showed low hemoglobin levels (11.8 g/dl, hematocrit 33.6), leukopenia (leukocytes 2.69×10^9/l, polymorphonuclear leukocytes 1.30×10^9/l), and thrombocytopenia (platelets 25×10^9/l). Peripheral blood smears were normal. The coagulation test yielded an activated partial thromboplastin time of 42.9 s. Biochemical tests revealed elevated liver enzymes (alanine aminotransferase 368 U/l, aspartate aminotransferase 290 U/l, gamma-glutamyl transferase 118 U/l), alkaline phosphatase of 633 U/l, hyperbilirubinemia suggestive of cholestasis (total bilirubin 7.77 mg/dl and direct bilirubin 6.05 mg/dl), elevated acute-phase reactants (C-reactive protein 7.77 mg/l and erythrocyte sedimentation rate 83 mm/h), and a sodium level of 127 mEq/l. Epstein–Barr virus, cytomegalovirus, hepatitis A virus, hepatitis B virus and hepatitis C virus, blood cultures, and viral serology were all negative. A bone marrow biopsy was also normal; the proteinogram showed hypergammaglobulinemia, and was negative for autoimmune antibodies, copper, and celiac disease studies . A Mantoux test was negative, as were studies for chronic granulomatous disease.

In view of the results of the analyses performed, we carried out a series of imaging tests. Chest and abdominal X-rays were normal, but abdominal ultrasound (US) revealed discreet liver hepatomegaly and free peritoneal fluid. An abdominal computed tomography (CT) scan showed mild hepatosplenomegaly with many small round and hypodense focal lesions (between 1 and 1.5 cm in size), some of them exhibiting mild peripheral enhancement, a small amount of intraperitoneal fluid, and a small rounded focal lesion similar to the splenic ones in the medial parenchyma of the middle third of the right kidney.

On further questioning, the mother made reference to a one-day school trip to a farm two weeks before the onset of fever. At this farm the children had come into contact with farm animals such as cows, sheep, goats, etc. This new information prompted us to perform the Rose Bengal test for *Brucella melitensis*, and a positive result was obtained. By means of an indirect immunofluorescence assay we obtained an IgG value of 1:8000 and an IgM value of 1:1000 for *B. melitensis*.

We initiated combined antibiotic therapy with doxycycline and streptomycin. We observed a favorable response to the treatment: the fever and clinical symptoms resolved within a few days and some weeks later all laboratory tests were normal and imaging tests showed no alterations. At subsequent follow-up visits as an outpatient, this subject showed a satisfactory recovery without sequelae or complications.

3. Discussion

Brucellosis is a zoonotic disease found worldwide,[1] with a high morbidity rate.[2,3] Humans become the accidental hosts of this organism through direct contact with infected animals or through the consumption of untreated derivative products. Although it may appear in almost any geographical area, there are some endemic areas such as the Mediterranean basin, India, Arabian Peninsula, Mexico, and Central and South America.[4,5] In our country, the annual incidence of brucellosis is 50–500 new cases/year, approximately 10% of which occur in infants.[6]

B. melitensis remains the main etiologic agent, followed by *Brucella abortus* and *Brucella suis*.[5] The intracellular characteristics of Brucella allow it to reside in the cells of the phagocytic mononuclear system causing an insidious clinical course with poorly specific symptoms, which may delay an accurate diagnosis. The clinical symptoms are like those associated with other systemic conditions. Although there is a classic triad of fever (mainly in the evenings), arthralgia, and hepatosplenomegaly, the most common form of presentation is fever without a focus.[6]

Liver and/or spleen involvement is seen in about 30–60% of brucellosis cases.[2] In most patients the clinical symptoms of this infection are minimal: discreet swelling of the organ involved and elevated transaminase values. The presence of cholestasis and/or visceral abscesses is uncommon (1–3% of patients according to the largest series of brucellosis patients in the literature reported by Colmenero et al. in the Hospital Carlos Haya in Málaga, Spain). In the case of children, the incidence is even lower. Hepatosplenic abscesses associated with brucellosis are rare complications usually occurring in adult patients with chronic forms of the disease and infrequently in children with acute brucellosis. In the case reported here we did not observe large abscesses, but microabscesses, which are relatively more common. These lesions are not diagnosed in non-complicated forms of brucellosis as imaging tests are not necessary in these cases. In the series of patients studied in the literature, hepatosplenic abscesses are those lesions >5 cm in size with subacute or chronic presentation. The US performed for our patient showed abdominal lesions of <2 cm in size affecting the spleen and the kidney. Vallejo et al. gave the first description of a hepatosplenic abscess due to a *Brucella* species in a child. They remarked on the importance of this rare entity because of its difficult evolution and showed many similarities between affected patients.[7]

There are several reports in the literature on chronic hepatosplenic suppurative brucellosis.[8–10] Ariza et al. reported the clinical and radiological findings of their series. They detected localized lesions of 1.5–9 cm obtained in 15 of 985 CT scans of patients affected with brucellosis. Multiple lesions were detected in one of 14 patients. In all cases, a calcium deposit was found in the middle or in the periphery of lesions.[8] Carazo et al.[9] carried out a retrospective analysis of the CT and US presentation of hepatosplenic brucelloma in five patients. On US, brucellomas were iso- or hypoechogenic with the liver. Hyperechogenic masses were seen in one patient. Brucellomas were very poorly defined and contained small scattered cystic areas. All lesions showed central or marginal gross focal calcification, except multiple lesions in one patient. Contrast-enhanced CT showed predominantly solid masses with irregular borders and fine or thick enhancing trabeculations separating hypodense solid areas and/or small cystic areas.[11–13] They highlighted the favorable results obtained through combined therapy with doxycycline and streptomycin (from both a clinical and pharmacokinetic point of view, as rifampin diminishes doxycycline levels, and from the point of view of resistance, as rifampin resistance hinders the management of brucellosis).[14] As a result, we may conclude that the current gold standard management of *B. melitensis* infections consists of the combined administration of tetracyclines and streptomycins for a period of 2–3 weeks. Depending on the particular characteristics of each region, we can use other alternative therapies such as the combination of doxycycline and gentamicin (level of evidence BII) or either trimethoprim–sulfamethoxazole or quinolones, which may also be another possibility if the first regimen cannot be employed (level of evidence CII). On the other hand, some cases of visceral abscesses (no microabscesses) have been reported that have required surgical resection due to the failure of therapy, even after the application of percutaneous drainage.

4. Conclusions

Brucellosis is an infectious disease with an increasing incidence, mainly due to the effects of migration. It should always be considered as a possible source of fever of unknown etiology in endemic areas and it should be taken into account in geographical areas where it is not endemic whenever a patient presents with prolonged fever and unspecific symptoms. The above mentioned therapeutic guidelines have proved effective, even in cases of disease relapse. Early diagnosis of the infection favors a rapid recovery and a satisfactory outcome. Chronic forms of brucellosis provoke asthenia, arthralgia, and in general a constitutional syndrome in patients that is difficult to diagnose and with a high morbidity rate.

The unusual presentation of brucellosis in the case reported here reminds us of the possibility of Brucella infection in any patient with fever without a focus irrespective of the presence of a clear epidemiological history, as this is very often omitted by the family. All protocols for the differential diagnosis of intermediate duration fever without a focus should include a diagnostic test for brucellosis in order to achieve early detection of the disease and initiate prompt therapy.

Conflict of interest: No conflict of interest to declare.

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