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Case Report

Fever of Unknown Origin in Children: The Challenge of History Taking

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Abstract

A fever of unknown origin (FUO) in children is usually described as a fever of at least 8 days duration with no apparent diagnosis after initial investigations, including taking medical history and preliminary laboratory assessment. Infectious diseases are the most common cause of FUO, followed by rheumatologic and neoplastic conditions.

In this report, we present a case of a 15-year-old Caucasian boy with a silent past medical history, who presented at our Pediatric ER department with a three-day history of fever, fatigue, and abdominal pain with diarrhoea. Initial laboratory testing and microbiological work-up were non-significant.

At hospital admission, a broad infectious diagnostic work-up was pursued, including serologies and polymerase-chain-reaction (PCR) for CMV, EBV, HAV, Parvovirus, Toxoplasma gondii and Adenovirus, all negative.

Given mild splenomegaly and linfadenopathy, systemic Juvenile Idiopathic Arthritis (s-JIA) was suspected, as well as Multi-inflammatory Syndrome in Children (MIS-C), but the patient did not meet their main diagnostic criteria. Malignancy was ruled out by a negative bone marrow fine-needle aspiration cytology and whole-body PET-CT scan.

On hospital day 8, *Brucella* was identified on a new set of blood cultures and a combined antibiotic therapy was started with IV Gentamicin plus per os Doxycycline. The patient's general conditions rapidly improved, and both fever and diarrhoea resolved. A reassessment of the patient's medical history before discharge revealed exposure to unpasteurized soft cheese in the weeks prior to the onset of symptoms. This case underlines the importance of taking a complete medical history, as well as a full diagnostic work-up to unveil unusual infectious etiologies behind FUO. After the preliminary negative microbiological tests, a connective tissue disease was ruled out (i.e. lack of cutaneous or articular involvement), as well as malignancy, which led to a closer evaluation for infection and the diagnosis of Brucellosis.

More Information

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Introduction

Although there is a lack of consensus for a definition, fever of unknown origin (FUO) in children is usually described as a fever of at least 8 days duration with no apparent diagnosis after preliminary investigations, including a detailed history evaluation and initial laboratory assessment [1], which can vary upon different epidemiological and resource-related background.

Some definitions of FUO made a distinction based on the setting (inpatient versus outpatient) [2-4], the immune status of the host, or the duration of temperature, which ranges from five days to three weeks.

Viral infections are usually self-limited benign diseases, but they often cause prolonged unexplained fever in children. Human herpes viruses (CMV, EBV, HSV1-2, HHV-6, HHV-7) may cause a febrile illness with skin rash, elevated aminotransferase levels, leukopenia, or other hematologic abnormalities [5]. Mononucleosis in pediatric patients is typically characterized by fever, pharyngitis, lymphadenopathy, and splenomegaly, while older patients often present with prolonged fever and more pronounced leukopenia [6]. Immunocompromised patients with FUO should be tested for HHV6 and

HHV-8, while the role of HHV-7 is still to be clarified [7]. Significant exposure and travel history may suggest some zoonotic viral etiology, especially when meningoencephalitis is suspected [8].

Connective tissue disorders and rheumatic diseases (rheumatic fever, SLE, vasculitis, etc.) are the second most

common cause of FUO in children. Systemic Juvenile Idiopathic Arthritis (sJIA) should be considered in pediatric patients who present with unexplained fever, arthritis, evanescent skin rash, and lymphadenopathy [9].

In a 2011 systematic review of 18 cases of pediatric FUO [10], malignancy represented approximately 6% of cases, of which 44% had leukemia, 17% had lymphoma and 24% were diagnosed with other types of malignancy, including neuroblastoma, Wilms tumor and myelodysplastic syndrome. Other less common causes of FUO in children may be Kawasaki disease, immunodeficiency, inflammatory bowel disease, and hemophagocytic lymphohistiocytosis [10]. Drugs may also cause unexplained fever, such as topical preparation of atropine [11] or other drugs interfering with thermoregulatory control mechanisms, such as phenothiazines, anticholinergic drugs, epinephrine, and related compounds. We present a case of a 15-year-old boy with prolonged fever and non-specific gastrointestinal symptoms to emphasize the importance of taking a full medical history, with a special focus on dietary and animal exposure.

Case report

A 15-year-old Caucasian boy with a silent prior past medical history arrived at our Pediatric ER department with a three-day history of fever (maximum body temperature 38.6 °C), fatigue, malaise, decreased appetite, and abdominal pain with diarrhoea. His travel and exposure history were not significant. He was discharged with a diagnosis of infectious gastroenteritis and no therapy other than supportive treatment.

Due to persisting symptoms, he presented again a few days later in poor general conditions, with some mild signs of dehydration, and diffuse abdominal tenderness, but no signs suggestive of peritoneal irritation. No lymphadenopathy nor skin rash were observed. Vital signs were: body temperature T 39°C, HR 88 bpm, BP 116/57 mmHg.

Initial diagnostic workup in the ER included a normal complete blood count with mildly elevated inflammatory markers (CRP 7.89 mg/dL, ESR 36 mm, ferritin 272 ug/L) and liver enzymes (AST 56 U/L, ALT 60U/L). Blood, urine, and stool cultures (*Shigella, Salmonella, Campylobacter Jejuni*) were negative, as well as polymerase-chain-reaction (PCR) for gastrointestinal viruses and respiratory pathogens and Sars-CoV-2 on nasopharyngeal specimens.

Due to the deterioration of clinical conditions in the following days (persistent fever, abdominal pain, and diarrhea), a surgical consult was asked to exclude intestinal obstruction or appendicitis, but physical examination and abdominal ultrasound were negative. He was initially managed with an IV rehydrating solution and empirical antibiotic therapy (Ceftriaxone 1g/die IV) to treat possible infectious gastroenteritis.

Due to persisting fever (with a peak of 39.5 °C) and abdominal pain despite antibiotic therapy, the patient was admitted to our hospital for further evaluation.

A review of systems was pertinent for intermittent abdominal pain, non-bloody loose stools, and fatigue. No weight loss was recorded. Physical examination was negative for signs of Kawasaki Disease. He was afebrile at admission having recently received ibuprofen, but he was febrile to 39 °C a few hours later. On hospital day 1, inflammatory markers were: CRP 7.43 mg/dL, PCT 0.22 ug/L, ESR 36 mmhr; and ferritin was stable.

A wide-range antibiotic treatment was started (Piperacillin-Tazobactam 3.3 mg for three times/day IV) and a broad infectious diagnostic work-up was pursued, including serologic and polymerase chain reaction for CMV, EBV, HAV, Parvovirus, *Toxoplasma gondii* and Adenovirus. One new set of stool samples was obtained for *Salmonella, Shigella, Campylobacter* cultures, and *Clostridium Difficile* toxins as well as fecal occult blood tests and calprotectin. All tests were unremarkable. Also, one new set of blood cultures resulted in contamination by *Staphylococcus hominis*.

An abdominal ultrasound revealed some mild splenomegaly and linfadenopathy, while a chest X-ray showed no abnormalities.

Given the persisting fever, increased inflammatory markers, and negative infectious preliminary diagnostic work-up, a pediatric rheumatologic consult was asked.

A full rheumatic panel was obtained (ANA, ANCA, ASCA, dsDNA, C3-C4), but no significant findings occurred. Given mild splenomegaly and linfadenopathy, systemic Juvenile Idiopathic Arthritis (s-JIA) was suspected but rapidly excluded due to the lack of cutaneous and articular involvement. Serology for Sars-CoV-2 was suggestive of a previous infection, so we evaluated the hypothesis of a multi-inflammatory syndrome in children (MIS-C), which was excluded with normal findings at echocardiography (no valvular abnormality nor pericardial effusion), as well as lack of other diagnostic criteria.

To rule out malignancy, bone marrow fine-needle-aspiration cytology was performed, as well as a whole-body PET-CT scan, both with negative results.

On hospital day 8, we obtained a control set of blood cultures which resulted in a positive for *Brucella*.

The patient was immediately started on a combined antibiotic therapy (IV gentamicin 315 mg/day plus per os doxycycline 100 mg/day). Minimum Inhibitory Concentration (MIC) was determined for gentamicin [MIC50 >4.0 ug/mL, resistant(R)], doxycycline [MIC50 = 2 ug/mL, intermediate (I)], tigecycline [MIC 50 = 0.5ug/mL, sensitive (S)] rifampicin and ampicillin [both sensitive, MIC50 = 1 ug/mL].

Therefore, we rapidly adjusted the combined treatment to per os rifampicin 600 mg/day plus doxycycline 100 mg/day. His general conditions rapidly improved, and both fever and diarrhea resolved. The last blood culture before discharge from the hospital on day 16 was negative.

Eventually, we found out that our patient had been exposed to unpasteurized soft cheese in the weeks prior to symptoms' onset. He completed the 6-week long antibiotic treatment with full resolution of symptoms.

Discussion

Transmission of brucellosis usually occurs through the consumption of infected, unpasteurized animal milk products, especially raw milk, soft cheese, butter, and ice cream [12]. It can also occur through direct contact of skin or mucous membranes with infected animal products (placenta, miscarriage products) or fluids (blood, urine, or milk), and through the inhalation of infected aerosolized particles [11-14]. *Brucellae* are usually taken up by local tissue lymphocytes, replicate within regional lymph nodes, and then enter the circulation, with an incubation period of two to four weeks [12].

The disease generally occurs with an insidious onset of fever, which can be spiking and accompanied by rigors or may be relapsing, mild, or protracted. It is often associated with malaise, arthralgias, low back pain, and malodorous night sweats [12,19]. Less specific symptoms include weight loss, anorexia, abdominal pain, cough, and depression [12,17]. Physical examination may be normal, but hepatomegaly, splenomegaly, and/or lymphadenopathy may be observed.

In our case, relapsing fever was accompanied by non-specific physical findings, such as abdominal pain and diarrhea. The patient did not complain of arthralgia or night sweats, however, mild splenomegaly and hepatomegaly were found at the abdominal ultrasound during hospitalization.

When Brucellosis is suspected, blood cultures and serologic testing should be obtained. Laboratory workers should be informed about the diagnostic possibility of brucellosis in order to implement appropriate precautions to avoid exposure to *Brucella* [13].

A diagnosis of brucellosis usually requires a positive culture of blood, body fluids (urine, cerebrospinal fluid, synovial fluids, pleural fluid) or tissue specimen (bone marrow or liver biopsy), or positive serologic testing for *Brucella* [12,20-22]. In the early stages of the disease, serological test results are often negative or show low or borderline antibody titers [14,15]. In addition, laboratory studies including complete blood count and liver function tests should be obtained.

Our patient's first two sets of blood cultures were either negative or contaminated, while blood tests showed some mild increase in aminotransferase levels, as well as inflammatory markers.

The patient had already received two different antibiotic therapies (ceftriaxone first, piperacillin-tazobactam later) when the diagnosis was made with a third set of blood cultures finally positive for *Brucella*. After hospital discharge, he completed a 6-month long follow-up at our Infectious Disease clinic, with good results and complete resolution of symptoms and normalisation of blood tests.

Brucellosis is a systemic infection that may affect multiple tissues and organs of the body, consisting of the musculoskeletal system, reproductive system, central nervous system, liver, heart, and lungs [23]. Misdiagnosis or delayed treatment may lead to multiple clinical complications from brucellosis, as well as the possibility of chronicity or recurrence of the disease [23].

Brucellosis is the most common zoonosis worldwide and represents both a diagnostic challenge and a serious public health issue. Diagnosis of brucellosis may reveal exposure to sick animals, consumption of contaminated dairy products, or breach of laboratory safety practices as well as intentional release of *Brucellae* as a biological weapon [23].

Our case underlines the importance of a complete diagnostic work-up along with a thorough past medical history to unveil the unexpected etiology of FUO in children. When first-line microbiological tests resulted in nonsignificant, we hypothesized a rheumatologic disease due to the persisting fever, increased inflammatory markers, lymphadenopathy, and mild hepatosplenomegaly. However, the lack of articular and cutaneous involvement led us to consider malignancy as a possible cause of persisting fever in our patient, but both bone marrow fine-needle-aspiration cytology and whole-body PET-CT scan resulted inconclusive. A second round of microbiological investigations leads eventually to the diagnosis of Brucellosis.

Conclusion

This case report underlines the importance of taking a complete medical history when assessing a case of unknown fever associated with nonspecific symptoms in pediatric patients. A full travel and exposure history must be taken from the patient or his/her parents so as not to miss any unusual cause of FUO, including zoonosis. Exposure to contaminated products may occur when animal safety health measures are not respected, leading to rapid disease spreading in urban settings as well as in the countryside. Improving diagnostic accuracy is fundamental to avoiding treatment delays and reducing the risk of complications from the disease.

Ethical considerations: The authors declare that they have obtained all appropriate patient's informed consent.

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