International Journal of Research in Medical Sciences
Ali M et al. Int J Res Med Sci. 2023 Mar;11(3):1047-1049
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20230599

Case Report

A case report of pyrexia of unknown origin in a 15-year-old boy

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Received: 30 January 2023
Revised: 14 February 2023
Accepted: 15 February 2023

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ABSTRACT

We present a case of a 15-year-old boy presenting with a 3-week history of fever whilst visiting relatives in the United Sates (US). Despite extensive workup, a definitive diagnosis was not reached. The clinical history and course of the disease required consideration of broad range of differential diagnosis. This case highlights the importance of clinical history and examination in the assessment of fever of unknown origin (FUO).

Keywords: Pyrexia, Differential Diagnosis, Limitation of Invigoration, Bone marrow culture

INTRODUCTION

Fever is a common presenting complaint amongst children. Most febrile illnesses are self-limiting, resolving before developing distinguishing characteristics that lead to a definitive diagnosis. FUO was initially classified as prolonged fever higher than 38.3ºC on several occasions for at least three weeks without an identifiable cause despite more than one week of extensive investigation in a hospital setting.[1] It was subsequently modified to include evaluation in outpatient setting consisting of at least 3 visits or 3 days of inpatient investigation.[2] In developing countries FUO is commonly due to infection where is in developed countries it is due to non-infectious inflammatory disease.[3]

CASE REPORT

A 15-year-old boy of Pakistani origin and Qatar residency, presented to primary care clinic in Doha with a three-week history of fever. The fever began whilst he was on a two-month holiday in the US visiting relatives in Indiana and Chicago. The fever began whilst he was in Chicago in the last week of his stay in the US. He had not been in contact with any sickness and there was no history of tick or insect bite. He was seen by a doctor in the US and given a seven-day course of an oral antibiotic (co-amoxiclav) and an antihistamine. This was purely a precautionary measure as he was traveling back to Qatar. His medical history includes eczema and an MST01 genetic disorder.

He had developed a generalized rash which was maculopapular in nature. The rash started 2-3 days after his return to Qatar and lasted 2-3 days. Patient continued to spike fever after the rash has resolved. He was having high grade fevers three times a day in the early morning, mid-day, and late evening, lasting a few hours. It subsided with Paracetamol. Associated symptoms included shivering, myalgia, joint pain, headache and loose motions after eating.

Management and outcome

At the initial consultation in his primary health center in Doha, he was afebrile with a negative coronavirus rapid antigen test. A point of care urinalysis and CBC blood test was normal. His liver function tests (LFTs) and creatine kinase (CK) results were abnormal but within the expected range for the patient who was known to have an underlying MST01 genetic disorder.

Four days after his initial consultation, the patient presented to the emergency department (ED) of his local hospital, again complaining of intermittent fever, sweating, fatigue, reduced appetite, and loose motions. Observation and examination were unremarkable. A chest x-ray was reported as normal, and he was discharged with an urgent outpatient appointment three days later.

The next day, whilst awaiting outpatient review, the patient's mother sought a second opinion in the primary care clinic. A battery of tests weas requested including, full blood count (CBC), CRP, ESR, Blood culture, renal and Liver function, malaria, hepatitis A, B, and C, Tuberculosis, IGM cytomegalovirus, Epstein Barr virus, Herpes Simplex virus, human immunodeficiency virus, antinuclear antibodies, serum protein electrophoresis, antistreptolysin O (ASO) titer and stool and urine cultures.

The patient was reviewed in the outpatient clinic as planned, but given his unwell appearance was admitted to hospital for further assessment and management.

Aside from the raised CK and LFT's that were within expected ranges for the patient, the CRP was 21 (0-5), LDH 454 (130-250), ferritin 181 (23-70) and ASO 247 (0-150) were elevated. The remaining tests were normal. However, he was started on antibiotic (ceftriaxone) 3 days after admission as he continued to spike fever.

He had an ultrasound of the abdomen which showed prominent para-aortic lymph nodes with the largest measured at 1.2 cm without evidence of intracardiac masses or vegetations.

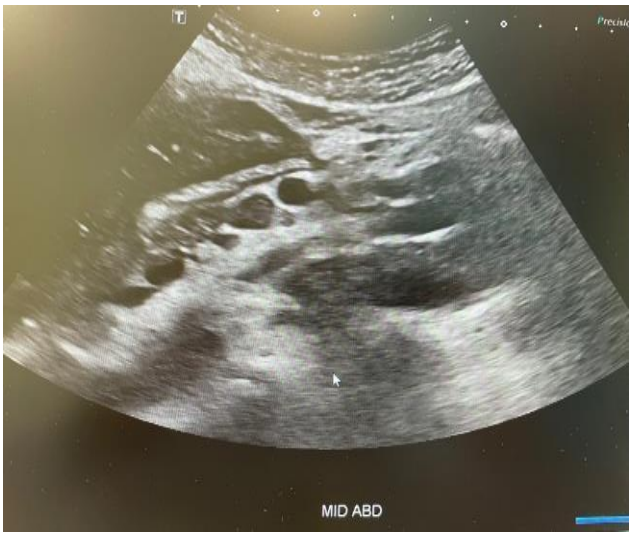

Figure 1: Ultrasound of the abdomen.

The patient was seen by an infectious disease specialist who ordered further tests including hepatitis E, treponema pallidum, brucellosis serology, respiratory virology panel and procalcitonin. These were normal. A rheumatological opinion was sought which ruled out lupus, juvenile arthritis or any other inflammatory arthritis.

His procalcitonin level was 0.09 ng/ml (≤0.1 ng/mL) with CRP and the white cell count were never significantly raised. Transthoracic echocardiography showed no vegetation or mass. A whole-body PET CT scan was carried out to identify a source of infection or malignancy. It revealed prominent lymph nodes in the paraaortic, superior mesenteric and ileoeoliac regions. It was felt that this could represent an infective process but could not rule out malignancy. An ultrasound of the neck to assess lymph nodes was carried out. Following a multidisciplinary meeting between internal medicine, infectious disease, and hematology specialists a bone marrow biopsy was advised due to the difficulty in performing the more suitable lymph node biopsy.

His antibiotic was stopped after 2 days of treatment after discussion with infectious disease specialist as his results such as blood culture was negative, and his inflammatory markers had improved. He was also said to be doing well even though he was still having fever. However, his fever had subsided the following day and he remained afebrile for 7 days after which he was discharged home. A working diagnosis of viral illness followed by drug fever was made on his discharge summary having excluded malignancies, inflammatory and infective processes. Subsequently, he had an outpatient bone marrow aspiration and biopsy under sedation which showed no definitive evidence of lymphoma.

The patient has remained well and afebrile after his discharge and is currently awaiting a repeat CT scan.

In summary, this young boy has had extensive investigations which included full septic screen, viral screen, respiratory viral panel, ultrasound, echocardiography, autoimmune profile with treponema and syphilis screen.

DISCUSSION

This case highlights the importance of thorough history taking and detailed examination as it can provide important valuable diagnostic clues.

Pyrexia of unknown origin requires consideration of broad range of differential diagnosis. This generally falls into Infection, Autoimmune and inflammatory causes, malignancies, and other miscellaneous causes. This requires a multi-disciplinary team approach. PHCC clinical practice guideline for the management of fever in children less than five years of age highlights the importance of detail history and examination. It also acknowledges the challenge of managing a febrile illness and defines PUO as: children with fever >38.3 for at least eight days with no apparent diagnosis after initially investigation in hospital or outpatient setting.[4]

Infectious causes of PUO should include typhoid illness. Typhoid is not endemic in Qatar but given large number of migrants from countries where Typhoid is endemic this should be considered as a possible differential diagnosis. In the United States typhoid causes 80% of the 400 to 500 cases of enteric fever yearly.[5] Whilst most of these cases are associated with travels to endemic part of the world, domestic acquisition still occurs.[5,6] Abdominal pain, fever, and chills are common presenting features of enteric fever and any associated gastrointestinal symptoms such as diarrhea should raise suspicion. However, the clinical presentation of enteric fever can be nonspecific.

There are several ways of diagnosing typhoid illness. Stool culture is readily done as its readily available. However, stool culture is said to be positive in 30-40% of cases.[7] Blood culture is available, but it can take several days to report. It is positive in 50-70% of cases of typhoid.[8] Moreover, it requires three sets of blood cultures from different sites several hours apart before staring antibiotic.[9]

Bone marrow culture is the most sensitive investigation but not usually clinically indicated.[10] It is positive in more than 90% of cases and may remain positive in 50% of cases after 5 days of antibiotic use.[11] It can be considered for suspected cases unresponsive to treatments and in complicated cases.

This case also shows the importance of travel history, it should be documented for the previous 2 years especially as he is a Pakistani national and typhoid is endemic in Pakistan. Furthermore, latency of certain infections can be very prolonged.

This patient had bone marrow investigation, but it was not cultured as the investigation was carried out almost 3 weeks after stopping his antibiotic in outpatient setting. The use of antibiotic early in the course of the disease may have skewed results and led to falsely negative stool and blood cultures.

CONCLUSION

This case illustrates the challenge of managing PUO. When managing such cases physicians need to be aware of limitations of certain investigations and to consider culture of bone marrow where it is indicated clinically. It may be worth considering a rapid access clinic in secondary care setting to ensure timely investigations such as appropriate blood culture at appropriate intervals.

ACKNOWLEDGEMENTS

Authors would like to thank the research committee, PHCC Qatar for their input and advise on this case report.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Ali M, Mahmood S, Rashid RA. A case report of pyrexia of unknown origin in a 15-year-old boy. Int J Res Med Sci 2023;11:1047-9.