Ad-din Medical Journal
July 2024, 2(2):41-44

Case report

Pyrexia of Unknown Origin in a Bangladeshi Citizen

Received: 02.03.2024 Accepted: 28.06.2024.

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Abstract

The term pyrexia of unknown origin refers to a condition in which the patient has an elevated temperature (fever) but, despite investigations by one or more qualified physicians, no explanation is found. It was introduced by Petersdorf and Beeson in 1961. A 36-year-old male patient, attended in Bashundhara Ad-din Medical College Hospital (BAMCH), presented with a two-months' history of fever. Notably, his fever was unaccompanied by other symptoms such as cough, runny nose, changes in appetite, chills, abdominal pain, urinary issues, diarrhea, weight loss, chest pain, dyspnea, or palpitations. Over this period, he underwent treatment with multiple antibiotics including Azithromycin, Ceftriaxone, Meropenem, Vancomycin, Gentamycin, and Doxycycline. While empirical antibiotic therapy can be life-saving in certain situations, it may also impede accurate diagnosis. Typically, drug-induced fever manifests within 7–10 days, though this timeframe can vary considerably from hours to several months. This case describes that while medicine is often viewed as a remedy for illnesses, it can inadvertently contribute to their onset. In spite of the fact that medicine is sometimes thought of as a cure for ailments, this case illustrates how it might unintentionally hasten their development.

Key word: Pyrexia of unknown origin, Drug fever, Quantiferon TB Gold Test.

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How to cite this article: Sarker MI, Islam MM, Afroz R, Rupom AJ. Case report: Pyrexia of Unknown Origin in a Bangladeshi Citizen. Ad-din Med J. 2024 Jul;2(2):41-44

Introduction

Pyrexia of unknown origin (PUO) refers to fever that is not resolved spontaneously, while its etiology cannot be determined despite extensive diagnostic workup.[1] The term PUO was first introduced by Petersdorf and Beeson in 1961. It is characterized by a fever exceeding 38.3 °C (> 101 °F) on multiple occasions, lasting for over three weeks, and the inability to diagnose specifically after one week of hospital investigations.[2] There are many causes of PUO like Malignant: lymphoma, renal cell carcinoma, Infectious diseases: milliary TB, brucellosis, Q fever, Inflammatory disorders: Adult still's disease, juvenile rheumatoid arthritis, and Giant cell arteritis. Miscellaneous disorders: drug fever, cirrhosis, and Idiopathic.

Case Summary

Mr. Nazrul (pseudonym), a 36-year-old male patient, presented in the outpatient department of BAMCH with a two-month history of fever, which was not associated with cough, runny nose, changes in appetite, chills, rigor, abdominal pain, burning sensation during micturition, diarrhea, or weight loss, chest pain, dyspnea, palpitation, orthopnea, and any urinary symptoms. He had been admitted to various hospitals in different locations, including Chittagong, Khulna, Barishal, and Cumilla, for approximately 32 days. During this period, he received several antibiotics, including Azithromycin, Ceftriaxone, Meropenem, Vancomycin, Gentamycin, and Doxycycline.

Mr. Nazrul revealed no known drug allergies or any other comorbidities. He lived in the Middle East for around 12 years and had a family history of pulmonary tuberculosis. He also reported a previous episode of enteric fever two months back. Apart from the raised temperature, his blood pressure was 110/70 mmHg, and his pulse rate was 76 beats/min. All other physical and systemic examinations revealed no abnormalities.

Past investigations reveal persistently raised Erythrocyte sedimentation rate, C reactive protein. Other investigations, including Serum electrolyte, Serum creatinine, Routine microscopic examination of Urine, Dengue Antibody, Urine culture & and sensitivity, Blood culture & and sensitivity, ICT for malaria-kala azar, Triple antigen, Chest X-ray P/A view, reveal no significant abnormalities (Appendix 1). We have advised for HIV screening, Bone marrow study, and QuantiFERON TB Gold test, where QuantiFERON TB Gold test was positive.

As there were no compelling indications, and for observation purpose, we had decided to stop all drugs. The fever was subsided within the next three days. As no sign of active TB, instead of starting Anti TB drugs, we put the patient on observation. Then we made a follow-up visit after 15 days with CBC, CRP (6 mg/l), Serum creatinine, Peripheral blood film, Urine R/M/E, CXR P/A view, and acute phase reactants like ESR become normal.
The patient was apyretic for 14 days and all other investigations with ESR became almost normal

Discussion

Evaluation of a patient with PUO is difficult. Initial assessment involves a thorough history covering occupation, travel, animal exposure, family diseases, and past illnesses. Misdiagnosis often stems from inadequate evaluation, by delayed testing and inappropriate investigations. Repeated interviews and file reviews can reveal crucial diagnostic clues.[1] A fever of unknown origin without any identifiable source of infection was observed in our patient, Mr. Nazrul.

While initiating empirical antibiotics might be life-saving in some circumstances, it might also pose a barrier to confirming a diagnosis. Typically, the onset of drug-induced fever occurs within 7–10 days, but this timeframe can vary from hours to several months.[3] Upon discontinuation of the responsible drugs, fever resolution usually takes around 2–3 days. However, if other hypersensitivity symptoms like a widespread rash accompany the fever or if a particular agent is slow to be eliminated, the fever may persist for additional days or even weeks. Our patient used a variety of antibiotics, including beta-lactamase, over an extended period and the cessation of all antibiotics resulted in the resolution of fever within 72 hours of hospitalization. The possibility of drug fever could be considered in this case due to several factors, such as Mr. Nazrul has been treated with various antibiotics over a significant period without resolution of his fever, which could suggest an underlying cause other than infection. The absence of symptoms commonly associated with infections, such as cough, runny nose, diarrhea, or urinary symptoms, despite the prolonged fever, may raise suspicion for an alternative diagnosis like drug fever. Despite extensive investigations, including blood and urine cultures, dengue antibody test, and chest X-ray, HIV screening, Bone marrow study no significant abnormalities were found, which could indicate that the fever is not due to an infectious process. Positive QuantiFERON TB Gold test is suggestive of latent tuberculosis infection, it is not conclusive evidence of active tuberculosis. Therefore, other potential causes for the fever, such as drug reactions, should still be considered.

The following reasons suggest that this may not be a case of drug fever, such as despite discontinuation of various antibiotics, the fever persisted, which is not typical for drug fever. Drug fever usually resolves once the causative medication is stopped. Normal findings on HIV screening and bone marrow studies suggest that infectious and hematologic causes for the fever are less likely, which could potentially rule out drug-induced reactions as well. Positive QuantiFERON TB Gold test indicates latent tuberculosis infection. However, it does provide another potential explanation for the fever. Our patient demonstrated a positive QuantiFERON TB Gold test result. It is a simple blood test that aids in the detection of Mycobacterium Tuberculosis. QFT is an interferon¬ Gamma (IFN¬Y) release assay, commonly known as an IGRA, and is a modern alternative to the Tuberculin skin test (TST, PPD, or Mantoux). A positive QFT can't distinguish between active TB disease and latent TB infection and is intended for use with risk assessment, radiography, and other medical and diagnostic evaluations. Like any diagnostic aid, QFT can't replace clinical judgment.[4] QFT is more sensitive and specific than TST.[5,6] QFT Gold test is 94.1% sensitive and 97.3% specific, on the other hand, TST is 68.9% sensitive and 59% specific. QFT TB Gold test may result in a false positive in Previous TB vaccination with BCG and Infection with non-tuberculosis mycobacteria.

The diagnosis of TB relies on a combination of clinical evaluation, radiological findings, and other laboratory investigations, including the QFT Gold test. A positive result indicates exposure to Mycobacterium tuberculosis but does not necessarily mean active disease. In our case Mr. Nazrul, while the QFT is positive, it's crucial to consider the absence of clinical symptoms suggestive of active TB, along with normal findings on other investigations such as chest X-ray and bone marrow study.

Given the absence of symptoms consistent with active TB and normal findings with other tests, the decision is not to initiate anti-TB treatment. However, regular monitoring and follow-up may be necessary to ensure early detection and management or development of active TB in the future, especially considering his history of living in a high TB burden area and family history of pulmonary TB.

Conclusion

Our case highlights the paradox that while medicine is often seen as the solution to diseases, it can also inadvertently invite and contribute to their occurrence. This emphasizes the importance of careful consideration in medical decisions to ensure optimal patient outcomes.

Conflict of interest

The authors hereby declare that no conflict of interest exists.

Acknowledgement

We are thankful to Prof. Dr. Tarek Mahmood, Department of Medicine, BAMCH, Dhaka. for his kind cooperation in preparing this report.

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Appendix 1: Investigations and their reports

Date	Test Name	Findings
30/12/23	QuantiFERON-TB Gold test	Positive
30/12/23	Bone marrow Study	Normal
30/12/23	HIV Screening	Negative
26/12/23	Complete blood count with Erythrocyte sedimentation rate	Hemoglobin 8.4 gm/dl, White cell count 15100/µL , Neutrophil 82.8%, Erythrocyte sedimentation rate 100mm/hour, Platelet count 768000/µL
26/12/23	Serum creatinine	0.7mg/dl
26/12/23	Routine microscopic examination of Urine	Normal
25/12/23	Chest Xray P/A view	Normal
17/12/23	Serum electrolytes	Normal
10/12/23	Urine culture & sensitivity	Normal
10/12/23	Blood culture & sensitivity	Normal
09/12/23	Reticulocyte	1.5%
07/12/23	Serum lactate dehydrogenase	437.6U/L
07/12/23	Complete blood count with Erythrocyte sedimentation rate	Hemoglobin 10.2 gm/dl, White cell count 21500/µL , Neutrophil 79%, Erythrocyte sedimentation rate 100mm/hour, Platelet count 470000/µL
06/12/23	Complete blood count with Erythrocyte sedimentation rate	Hemoglobin 11.4 gm/dl, White cell count 17689/µL , Neutrophil 77%, Erythrocyte sedimentation rate 120mm/hour, Platelet count 420000/µL
05/12/23	MRI of Lumbo sacral spine	Disc Bulge at L4-L5 level abutting the L5 transversing nerve root on both side straightening of lumber lordotic curve. Hypo intense marrow singnal intensity in both T1-T2
04/12/23	ICT for malaria-kala azar	Negative
02/12/23	Tripple antigen	Normal
20/11/23	Dengue Antibody	Negative
19/11/23	Duplex scan of left lower limb	Suggestive of incompetence of sapheno popliteal valve of left lower limb. No DVT or Varicosity of superficial vein present
14/11/23	Ultrasonography of whole abdomen	Mild hepatomegaly
(follow up inv.) 15/01/24	CBC, Serum creatinine, Peripheral blood film, Urine r/m/e, CXR P/A view,CRP	Normal
	ESR	22 mm in first Hour