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Out of the Fry Pan into the Fire: Pyrexia of Unknown Origin

Nawaz Qabulio S[1], Fahad Zakir M[1], Sohail F[1], Jahangir U[1] and Tanwir F[2*]

[1]Department of Medicine, Dr. Ziauddin Hospital, Karachi, Pakistan

[2]Matrix Dynamics Group, Faculty of Dentistry, University of Toronto, Canada

[*]**Corresponding author:** Tanwir F, Matrix Dynamics Group, Faculty of Dentistry, University of Toronto, Canada, Tel: 011-6472816064; E-mail: Farzeen_tanwir@yahoo.com.

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Abstract

Fortunately, we were designed with a complex mechanism for our own immune system called pyrexia. Pyrexia is a rise in the body's core temperature, otherwise known as a fever. Fever is generally a medical condition characterized by an elevation of body temperature above the normal range of 36.5 to 37.5°C due to an increase in the temperature regulatory set-point. When body temperature increases, there is a feeling of cold despite an increasing body of temperature. It is a mechanism developed by the immune system to reduce the severity of illness by preventing bacteria and viruses from multiplying. This activation of the immune system has worked for centuries before medicine was invented. Most individuals view a fever as something that is bad or harmful, but it is a sign that our body is working in our favor to fight disease. Fever is generally the result of an immune response by your body to a foreign invader. These foreign invaders may include viruses, bacteria, fungi, drugs, or other toxins. Here we discuss the case of a 29-year-old male patient who is suffering with pyrexia of unknown origin.

Keywords: High grade fever; Endocarditis; Pyrexia; Hepatosplenomegaly; Sepsis

Introduction

This is a case of a 29-year-old male patient married for eight years, with no known co-morbidity, resident of Balochistan admitted via outpatient department with chief complaints of fever for two years on and off and dry cough for 15 days. According to the patient he was in his usual state of health when he developed fever 2 years ago, for which he visited a local doctor who treated him initially as viral fever but later as enteric fever. Soon after that he started having on and off fever that progressively increased from low grade to high grade documented as 102F to 103F for the last four months. He was prescribed first with inject able ceftriaxone for three days and then cap cefixime 400 mg for five days and later on tab ciprofloxacin 500 mg for few days (exact duration not known) but fever remains the culprit, for which he got anxious and visited our medical outpatient department where he was advised for further workup and management.

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Past history was insignificant with no surgical interventions, no history of blood transfusion as well. He has positive sexual history multiple times 8 years back with similar women for which he used condom as contraceptive measure. Personal history positive for weight loss (10-12 kg), decrease appetite and no addictions. Socio-economic history was satisfactory.

Case Report

On examination, the patient is ill looking anxious emaciated, jaundiced well oriented with time place and person *CNS*: Grossly intact, *CVS:* S1+S2 audible, *Chest:* B/L equal air entry. *Abdomen:* Soft non tender liver palpable 2 fingers below costal margins spleen tip palpable, *Gut:* sound is audible, no fluid thrill and no shifting dullness. *Throat:* Hyperemic, our initial impression was respiratory tract infection/acute hepatitis/infective endocarditis/enteric fever/tuberculosis.

Laboratory investigations are ordered for CBC, Urea, Creatinine and electrolytes in urine, D/R, ECG, Chest x-ray. Blood C/S three samples, viral profile (A, B, C, D, and E) and Liver function test.

CBC: HB 11 gm/dl, Tlc 2.8 *Platelet:s* 105, *LFT:* Total *Bili:* 4.4 *Direct Bili:* 2.8 *SGPT* 1435, *Alkpo4:* 155, *GGT:* 190. Viral profile (negative for HepA B C D E), *Malarial parasites: e* ICT-ve.

Initial treatment started with injection ceftriaxone 2 g bid, Injection, paracetamol 1 g thrice daily, syp terbutaline 1 tsp thrice daily, niflam gargles and I/V hydration continues. Patient conditioned remains same not touching fever to baseline further appeared pallor and jaundiced with static condition so LFTS were repeated and Blood C/S plus, MPICT and Dengue serology were send all turn out to be negative, Blood c/s also negative (for initial bacterial growth).

Infectious disease team and Gastro team were took onboard and was advised for HIV serology and Echo to rule out infective endocarditis, *ANA* profile for vasculitis, S. *LDH,* Reticulo count for hemolyisis plus repeat of Chest X-ray plus Cytomegalovirus and *Eibstein barr* viru.

ECho: Normal LVF, No Vegetation EF 60%. ANA negative, Retic count 1.5 not increased, LDH high 3154, Pt: patient and controlled 30/12, INR>4.5, CXR shows Effusion this time, effusion was aspirated and report was LDH 556 Protein 1.70 serum protein 4.49 (exudative) case was discussed in grand round and input was for syphilis serology, bone marrow biopsy, MRCP liver biopsy and change of antibiotic to Tanzo and azithromycin.

Patient started on Tanzo and his fever got better for few days, however, syphilis serology was negative. *Brucella* turned out to be negative. HIV is negative. We planned for CT scan of abdomen with contrast which showed hepatosplenomegally with sub-centeric mesenteric nodes, MRCP turned out to be normal, CBC were repeated which showed pancytopenia with deranged LFTS, patient now was in sepsis and Meropenum 1 g bid with Tanzobactum 4.5 g was adviced thrice daily.

On the10^{th} day of admission case discussed with family with multidisciplinary to the family for bone marrow biopsy (which turned out to be negative. On 12^{th} day of admission patient become drowsy Rbs was checked which turn out to be low that is 50 mg/dl, 25% D/W ampoule were given with close monitoring of Rbs, pt had recurrent low Rbs, he was started on infusion D/S, with shifting to ICU for close monitoring, which was done), Liver biopsy (hold as patient get seriously ill) and critical

condition of patient. We did not come to the conclusion, all department involved including infectious control team involved. This case is really tricky and could not come to the diagnosis. 18th day of admission of shifting to Icu.pt suddenly have fit which was generalized type and pt was not maintaining So2, with chest was clear. Abgs were orders which shows severe Acidosis and hypoxia, pt placed on Vent, after an hour of placing, he started bleeding from gums, eye and mouth, and collapsed within few hours secondary to DIC/SEPSIS, and patient expired without being diagnosis with pending labs of Bone marrow biopsy and *Brucella* antibodies which later turn out to be Negative, Plan was for liver biopsy but un fortunately pt expired before the proper treatment could have been started.

Results and Discussion

Peters Dorf and Beeson characterized pyrexia as a fever of unexplained origin [1]. According to that we can deduce the following points:

1. A temperature more prominent than 38.3°C on a few events.
2. Accompanied by over three weeks of disease.
3. Failure to achieve a determination following one week of inpatient examination.
4. This planning permitted rejection of patients with extended however self-constrained viral diseases, giving time for studies to be finished. This has now been changed to incorporate patients who are analyzed after two outpatient visits or three days in healing facility. PUO is utilized all through this article for consistency. Extra classifications have now been included, including [2,3]. Nosocomial PUO in healing facility patients with fever of 38.3°C on a few events, brought on by a procedure not present or brooding on confirmation, where starting cultures are negative and analysis obscure following three days of examination. Neutropenic PUO, which incorporates patients with fever as above with $<1 \times 10^9$ neutrophils, with introductory negative cultures and conclusion questionable following three days [4].
5. HIV-related PUO, which incorporates HIV-positive patients with fever as above for four weeks as outpatients or three days as inpatients, with a dubious conclusion following three days of examination, where no less than two days have been considered societies to brood. Normal reasons for pyrexia of obscure origin [3-6]. Most cases are abnormal introductions of basic sicknesses-e.g., tuberculosis, endocarditis, gallbladder ailment and HIV contamination, as opposed to uncommon or intriguing diseases [7].
6. In grown-ups, contaminations and tumor (25% to 40% of cases each) represent generally PUOs [8]. Immune system issue represents 10% to 20% of cases [9].
7. In kids, a methodical audit found that irresistible infection (37.6%) was the primary driver of PUO, trailed by danger (17.2%), incidental sickness (16.1%) and collagen vascular malady (14.0%) [5].

Bacterial abscesses

There might be no confining side effects. Previous stomach or pelvic surgery, injury or history of diverticulitis or peritonitis improves the probability of a mysterious intra-abdominal ulcer. They are most generally in the subphrenic space, liver, right lower quadrant, retroperitoneal space or the pelvis in ladies. Tuberculosis-when spread has happened (e.g., in patients who are immuno-compromised) the underlying introduction will probably comprise of protected indications than confining signs. CXR might be ordinary. Urinary tract contaminations (UTIs)-these are uncommon causes. Peri-nephric abscesses incidentally neglect to speak with the urinary framework, bringing about an ordinary urinalysis.

Endocarditis

Endocarditis (This is an uncommon reason for PUO). Culture-negative endocarditis is accounted for in 5% to 10% of endocarditis cases. The HACEK gathering is in charge of 5% to 10% of instances of infective endocarditis and is the most well-known reason for Gram-antagonistic endocarditis among individuals who don't manhandle intravenous medications: This is a gathering of Gram-negative bacilli-*Haemophilus* spp., (*H. parainfluenzae*, *H. aphrophilus* and *H. paraphrophilus*), *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis, Eikenella corrodens* and *Kingella* spp. They are a piece of the ordinary oropharyngeal greenery, are moderate cultivators and incline toward a carbon dioxide-advanced environment. Because of their demanding development necessities, they have been a continuous reason for culture-negative endocarditis.

Previous anti-microbial treatment is the most incessant purpose behind negative blood cultures. Hepatobiliary contaminations (e.g., cholangitis)-these can happen without nearby signs and with just somewhat lifted or ordinary LFTs, particularly in the elderly. Osteomyelitis-this for the most part causes restricted agony or uneasiness at any rate sporadically.

Brucellosis

This ought to be considered in patients with steady fever and a background marked by contact with cows, swine, goats or sheep, or in patients who expend crude drain items. *Borrelia recurrentis*-this is transmitted by ticks. It is in charge of creating backsliding fever. Other spirochetal maladies that can bring about PUO-these incorporate *Spirillum* minor (rodent nibble fever), *Borrelia burgdorferi* (Lyme illness) and *Treponema pallidum* (syphilis) and other viral infections. Herpes infections, (for example, cytomegalovirus (CMV) and Epstein-Barr infection (EBV)-these can bring about delayed febrile ailments with established indications and no noticeable organ signs, especially in the elderly.

HIV

Prolonged febrile scenes are visit in patients with cutting edge HIV disease. Approximately 60% of the cases are irresistible in nature. The rest of them are for the most part because of lymphomas and a little portion of them are because of HIV itself [7]. Patients with AIDS and lymphoma regularly have extra-nodal contribution, especially CNS, gastrointestinal tract, liver and bone marrow [10].

By microorganisms

Immunosuppression, the utilization of expansive range anti-infection agents, the nearness of intravascular gadgets and aggregate parenteral sustenance all incline individuals to spread contagious diseases.

By parasites

Toxoplasmosis: This ought to be considered in patients who are febrile with lymph hub extension.

- *Trypanosoma, Leishmania* and one-celled critter animal types-these may once in a while cause PUO.
- Rickettsial life forms.
- *Coxiella burnetii* may bring about interminable diseases, perpetual Q fever or Q fever endocarditis might be distinguished in patients with a PUO.
- Psittacosis [11].

- Contamination by the causative living being, *Chlamydophila psittaci* ought to be considered in a patient with PUO who has a background marked by contact with feathered creatures.
- *Lympogranuloma venereum* [12].
- This ought to likewise be considered however is uncommon.
- Neoplasm Hodgin's lymphoma and non-Hodgkin's lymphoma-these may bring about PUO. Leukaemias-these may likewise be dependable. Among strong tumors-renal cell carcinoma is most generally connected with PUO. Solid tumors, (for example, adenocarcinomas of the bosom, liver, colon or pancreas) and liver metastases from any essential site-these may give fever.

Malignant histiocytosis: This is an uncommon, quickly dynamic and dangerous.

Tranquilize fever

A wide assortment of medications can bring about medication fever. The most basic are beta-lactam anti-toxins, procainamide (now stopped) and isoniazid. Ceasing the medication by and large prompts recuperation inside two days. It is normally joined by a rash. Collagen vascular and immune system maladies. Systemic-onset adolescent idiopathic joint pain. High-spiking fevers, non-pruritic rashes, arthralgias and myalgias, pharyngitis and lymphadenopathy ordinarily are available [13]. Here are the other possible causes and symptoms given below:

1. ***Polyarteritis nodosa* (PAN):** Rheumatoid joint pain and blended connective tissue maladies ought to be considered. Granulomatous maladies, Sarcoidosis, Crohn's malady (the most widely recognized gastrointestinal cause), Granulomatous hepatitis and Vasculitides, Giant cell arteritis and furthermore the related polymyalgia rheumatica [14], *Polyarteritis nodosa etc., and* Behçet's ailment has additionally been reported [15].
2. **Fringe aspiratory emboli:** Fringe aspiratory emboli and mysterious thrombophlebitis can bring about PUO.
3. Acquired maladies: Familial Mediterranean fever.
4. Hyperthyroidism and sub-acute thyroiditis.
5. These are the most widely recognized endocrine reasons for PUO.
6. Adrenal deficiency is an uncommon however possibly lethal reason for PUO.
7. **Kikuchi's sickness:** Kikuchi's sickness is a self-restricting necrotizing lymphadenitis. It has been accounted for as a reason for PUO [16].
8. **Undiscovered:** 10% to 15% of patients stay undiscovered regardless of broad examinations and, in 75% of these, the fever settle suddenly. In the rest of, signs and indications make the conclusion clear [17].

Epidemiology

This is a typical issue. In western nations, connective tissue illnesses, vasculitis disorders and granulomatous maladies are the most widely recognized non-irresistible causes. Among these conditions, mammoth cell arteritis and polymyalgia rheumatica are the most successive particular determination in the elderly. In more youthful patients, the most regular finding is grown-up onset Still's illness [18].

Diagnosis

The initial step is to affirm temperature by taking it yourself [19]. Search for signs normally going with fever-eg, tachycardia, chills [4,5]. It is imperative to take an exhaustive history:

1. Inquire about side effects from every significant framework. Incorporate general grievances-e.g., fever, weight reduction, night sweats, migraines and rashes.
2. Record all grumblings, regardless of the possibility that not as of now present. Past ailments, including surgery and psychiatric issues, are imperative.
3. Discuss nourishment, including utilization of dairy items and the wellspring of these items.
4. Drug history ought to be recorded, to incorporate over-the-counter medicines, doctor prescribed pharmaceuticals and any illegal substances.
5. Immunization status ought to be archived.
6. Enquire about family history of disease.
7. Occupational history ought to incorporate presentation to chemicals/creatures.
8. Take a background marked by travel and recreational propensities-including conceivable presentation to ticks and different vectors.
9. Sexual history ought to be recorded.

Examination of the patient ought to include the following:

1. Documentation of fever and rejection of factitious fever (might be up to 10% of cases), which are basic early strides in the physical examination.
2. Measuring the fever more than once and within the sight of another. Electronic thermometers offer access to fast and unequivocal documentation of fever.
3. Diseases, for example, brucellosis, berylliosis and Hodgkin's infection tend to bring about repetitive scenes of fever.
4. Physical examination ought to be rehashed every day while the patient is in healing facility. Especially, look for: Rashes, Lymph hub amplification, Signs of joint pain, New/changing heart mumbles.

Abdominal tenderness

In an HIV-positive patient-bone marrow aspiration or biopsy. Abnormal LFTs should prompt a liver biopsy (even if normal size).

Conclusion

We did not come to the conclusion, all department involved including infectious control team involved. This case is really tricky and could not come to the diagnosis.

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