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Fever of Unknown Origin Remains a Mystery in the Modern Era: An Exhaustive and Challenging Case of a Young Woman and Mini Review

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ABSTRACT

Background: Fever of unknown origin occurs when a person's body temperature surpasses 38.3°C many times and symptoms last at least three weeks without a diagnosis after rigorous inpatient or outpatient testing. A complete medical history, physical exam, blood tests, and imaging studies may assist in identifying the causes. **Case presentation:** This case had multiple recurring fever episodes. A 27-year-old woman was taken to the emergency department after a couple of days of fever and coughing. She had no noteworthy medical history, but all of a sudden, she had a high temperature and sporadic coughing. Both eyes were sensitive to light, and she had vaginal and aphthous ulcers. All vital signs were normal throughout the episodes, with the exception of a slight increase in the WBC count and some fluctuations in complete blood count (hemogram). No notable abnormalities were detected in any of the serological blood test reports. CRP and ESR were elevated, but liver and kidney functions were normal. All imaging tests showed no noteworthy findings, except the ^{18}F-FDG-PET/CT scan showed a few minor FDG avid right paratracheal, AP window, and subcarinal lymph nodes. **Discussion and conclusion:** The patient had ulcers in her mouth and vagina, high levels of C-reactive protein and ESR, low levels of vitamin B12, a normal level of procalcitonin, and a high temperature accompanied by light-sensitive eyes. No other major problems were discovered. However, symptoms resembled Behçet disease. The patient has not complained since the last episode of fever.

Keywords: Fever of unknown origin, 27-year-old woman, aphthous-ulcers, lymph nodes inflammation, Behçet disease.

1. INTRODUCTION

Fever of unknown origin (FUO) and inflammation of unclear cause are diagnostic conditions that present major difficulties. Fever of unknown cause is characterized by a body temperature beyond 38.3°C on many occasions, accompanied by symptoms persisting for no fewer than three weeks, without a conclusive diagnosis following extensive inpatient or outpatient evaluations [1]. A comprehensive history and physical examination are the first steps in the diagnostic process, which includes a methodical assessment that is followed by standard laboratory testing. If the results of the first tests are not unequivocal, further sophisticated imaging and laboratory testing could be necessary. There are four types of diagnoses: infectious, inflammatory processes that are not infectious (NIID), malignancies, and undiagnosed instances [2,3].

FUO lacks generally recognized guidelines that all individuals with this medical condition must comply with. The first official diagnostic criteria, known as the "classic" FUO criteria, were created by Petersdorf and Beeson [1]. They used a three-week fever duration and a one-week hospital-based examination. Durack and Street suggested in 1991 that the assessment duration be extended from one week to three days of inpatient study or three outpatient visits [4,5]. In 1997, De Kleijn et al. recommended replacing the quantitative criteria (i.e., time-dependent) with a qualitative condition to eliminate bias during selection in series caused by investigators' differing experiences and variances in diagnostic resources across hospitals and nations [6].

Because its differential diagnosis includes a wider range of possibilities than any other medical condition, covering both very rare and fairly common issues in four main groups—FUO remains a major clinical challenge (Figure 4) [3]. The distribution of causes has been steadily shifting towards more NIID and fewer infections and tumors. Furthermore, the percentage of unidentified cases in the most recent published series ranges from 15 to 50%, despite the advancement of quick laboratory testing and effective

diagnostic tools [7,8]. The various physical examination findings suggest a potential reason for the unidentified fever (Figure 5) [9,10].

2. CASE PRESENTATION

This particular instance, characterized by a recurring fever, was the culmination of many episodes.

2.1. Episode one.

In March 2024, the emergency department admitted a 27-year-old woman who had been exhibiting a fever and persistent cough for nine days. She was entirely healthy with no medical history until nine days before, when she developed an atypically high fever and a persistent cough that occurred intermittently. The temperature rises progressively, diminishes with the administration of 650 mg of paracetamol at six-hour intervals, and then increases again after a certain time frame. Following the spike of fever, coughing also occurred simultaneously. The patient underwent laboratory tests, as per the physician's recommendation, in the final week of February 2024, prior to hospitalization. The results indicate a hemoglobin level of 13.5 g/dL, packed cell volume of 40.20%, platelet count of 322,000/mm³, neutrophil percentage of 68.60, lymphocyte percentage of 27.60, total white blood cell count of 9500/mm³, red blood cell count of 5.05 mill/mm³, AST (SGOT) level of 21.0 U/L, ALT (SGPT) level of 15.9 U/L, GGTP level of 20.0 U/L, alkaline phosphatase level of 74.00 U/L, total bilirubin of 1.48 mg/dL, total protein of 7.54 g/dL, and albumin of 4.62 g/dL.

Shortly after arrival, the patient's temperature ranged from 39.44 to 40°C, the pulse rate was 96 beats per minute, and the blood pressure was 140/90 mmHg, raising primary suspicion of a respiratory or urinary tract infection.

Upon examination, no chest rales or heart murmurs were detected. Her ECG was normal, she had no chest discomfort, and a chest radiograph revealed a slight dilatation of the mediastinum (Figure 2). Laboratory test results showed a normal white blood cell count (9,500/mm³), high concentration of C-reactive protein (CRP) (105.37 mg/dL), hemoglobin level of 11.70 g/dL, packed cell volume of 35.70%, platelet count of 335,000/mm³, neutrophil percentage of 68.9, lymphocyte percentage of 25.20, red blood cell (RBC) count of 4.43 mill/mm³, mean corpuscular volume (MCV) of 81 fL, which is slightly lower than the normal range (83 to 92 fL), and mean corpuscular hemoglobin (MCH) of 26.50 pg, which was again a little lower than normal (27 to 32 pg). The procalcitonin level was also in the normal range. Alkaline phosphatase level (serum) was 61 U/L, bilirubin (direct) was 0.18 mg/dL, total protein was 7.4 g/dL, serum albumin was 3.6 g/dL, serum globulin was 3.8 g/dL, Na^+ concentration was 136 mmol/L, K^+ concentration was 3.8 mmol/L, blood urea concentration was 19 mg/dL, blood creatinine level was 0.52 mg/dL, and the liver and kidney functions were normal. Overall, the results indicate that while some values, such as MCH, are slightly below normal limits and the CRP value was very high (Figure 1 and Table 1), the liver and kidney functions remain within a healthy range.

Serological blood tests were also performed, and all these tests showed negative results at all dilutions. The consistent negative or non-reactive results from these tests strongly indicate that the patient does not currently have any of the assessed illnesses.

The results of the specialized tests (triiodothyronine [T3], thyroxine [T4], and thyroid-stimulating hormone [TSH]) used to assess thyroid function were all within normal limits, indicating that the thyroid function itself was also normal.

A few specialized tests were conducted to look for infections caused by TB in the body, such as a cartridge-based nucleic acid amplification test (CBNAAT sputum); however, these tests also came up negative. The negative outcome was followed by a TB platinum interferon gamma release assay (IGRA), which yielded a positive result this time (IFN-γ antigen tube: 249.05 pg/mL and IFN-γ nil tube: 13.99 pg/mL). Although it does not prove an ongoing infection, this positive IGRA test indicates that the patient has been exposed to the TB bacteria at some time.

The anti-nuclear antibody/factor (ANA/ANF) values were significantly lower than the threshold, suggesting that there is no associated danger. We also did an ultrasound scan of the patient's whole abdomen, which revealed nothing out of the ordinary.

The patient received Ringer's lactate solution (RLS) and normal saline (NS) alternately throughout the duration of her hospitalization at a 2:1 ratio. Additionally, intravenous paracetamol 650 mg was also administered four times a day, maintaining the gap of six hours, along with omeprazole 40 mg (as per protocol; once daily). Since the patient reports experiencing nausea and vomiting, the medical team advises administering intravenous ondansetron at a dosage of 4 mg every eight hours daily. As the fever cycle persisted without interruption, antibiotics (100 mg of doxycycline every 12 h and 1 g of meropenem trihydrate every eight hours in 100 mL of NS) were prescribed as per protocol. Additionally, taking montelukast (10 mg) and levocetirizine (5 mg) tablets together once a day at bedtime along with acetylcysteine (600 mg) helps reduce mucus secretion, runny nose, stuffy nose, sneezing, itching, and airway swelling, which improves breathing.

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The patient remained hospitalized for 12 days. Following the 10th day, there was a slow and systemic drop in the fever cycle, which followed the same pattern as its peaks. The patient was instructed to take a capsule containing 10 mg of vitamin B1 (thiamine mononitrate), 10 mg of vitamin B2 (riboflavin), 100 mg of vitamin B3 (niacinamide), 3 mg of vitamin B6 (pyridoxine hydrochloride), 100 mcg of vitamin B7 (biotin), 1.5 mg of vitamin B9 (folic acid), 15 mcg of vitamin B12 (cobalamin), 50 mg of vitamin B5 (calcium pantothenate), and 150 mg of vitamin C (ascorbic acid) once daily at bedtime for the next 30 days, along with two days of complete bed rest following hospital discharge.

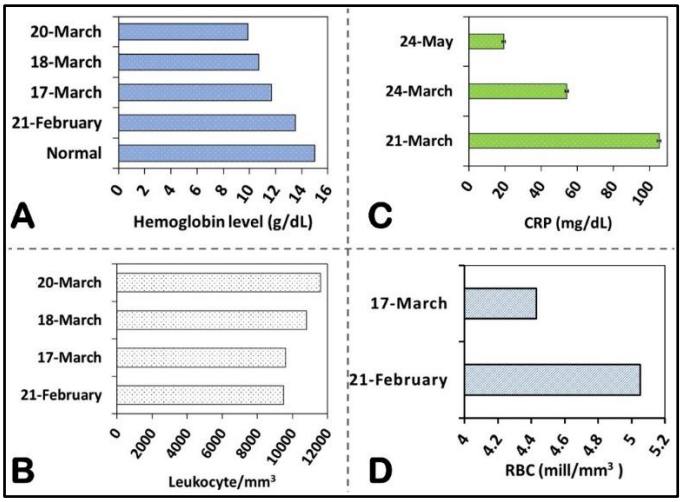

Figure 1: Fluctuations in the patient's hemoglobin (A), leucocyte (B), CRP (C), and red blood cell (D) levels during episode one. Data are expressed as mean ± SD of triplicate measurements.

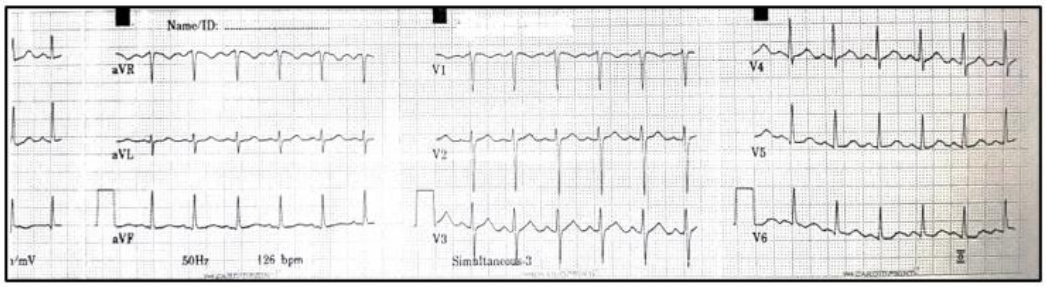

Figure 2: Electrocardiogram (ECG) of the patient. ECG was normal (Sinus tachycardia, Vent. Rate: 126 bpm, QRS duration: 68 ms, QT/QTc: 1310/448 ms, PR interval: 136 ms, P duration: 104 ms, RR interval: 476 ms, P-R-T axes: 22 63 23).

2.2. Episode two.

Two months later, in the first week of May 2024, this lady returned to our hospital's outpatient department (OPD) with the same situation (elevated temperature). The temperature of the patient was 40°C, the pulse rate was 95 beats per min, and the blood pressure was 130/90 mm Hg. She did not report any chest discomfort, and the ECG data revealed no abnormalities (Figure 2). Upon inspection, there was once again no indication of a cardiac murmur or chest rales. The findings of every laboratory test were almost identical to those of episode one, with just minor variations. Once again, the CRP level was elevated (98.23 mg/dL) in comparison to normal.

The patient was instructed to take 650 mg of paracetamol four times a day along with doxycycline twice a day for five days. She was moreover encouraged to consume plenty water beside suitable homemade meals. After five days, the frequency of the fever cycle significantly decreased, and by the 7th day, the fever had completely disappeared. Hospitalization was not necessary at this time.

2.3. Episode three.

This lady returned to our hospital's emergency department on May 2024, in the same condition as she had in episodes one and two. The patient had a five-day history of fever, with temperatures recorded at 38.33°C in the morning, 39.44°C in the afternoon and

evening, and 40°C at night, indicating a progressive rise in fever severity throughout the day. Fever was linked to many additional distressing symptoms, including diaphoresis, arthralgia, myalgia, thoracic constriction, and a moderate cough.

As the patient was being admitted, vital signs such as temperature (37.28°C), pulse rate (128 beats/min), blood pressure (120/80 mmHg), saturation of peripheral oxygen (SpO2; 100%), capillary blood glucose (154 mg/dL), and respiration rate (18 breaths/min) were recorded.

The patient underwent a blood test (a complete hemogram/C.B.C.), which revealed concerning results: the concentration of hemoglobin in the blood was 10.2 g/dL, whereas the normal range is between 11.5 and 16.5 g/dL, RBC count was 4.83 million/mm³ (normal range: 3.8-4.8 million/mm³), mean corpuscular volume (MCV) was 79.3 fl (normal range: 83-92 fl), mean corpuscular hemoglobin (MCH) was 24.2 pg (normal range: 27-32 pg), mean corpuscular hemoglobin concentration (MCHC) was 30.6 g/dL (normal range: 32-35 g/dL), and ESR value was 90 mm/h (normal range: 0-20 mm/h). The total WBC count was 14,210/mm³ (normal range: 4,000-10,000/mm³), and the platelet count was elevated at 599,000/mm³ (normal range: 150,000-450,000/mm³).

In addition to the aforementioned tests, a smear for the identification of malarial parasites (MP) was performed, and the results were satisfactory with a negative outcome.

The postprandial (PP) blood glucose level was normal at 105 mg/dL; however, the fasting blood glucose level was increased at 115 mg/dL (normal range: 74-106 mg/dL). The blood ferritin level was assessed and found to be normal at 128.8 ng/mL.

The results of all laboratory tests were also within normal limits, with the exception of two that were somewhat below average: urea and creatinine. The chemiluminescence immunoassay measured NT-pro BNP at 164 pg/mL and vitamin B12 at 138 pg/mL (normal levels are between 211 and 946 pg/mL). The blood level of 25(OH) vitamin D was 11 ng/mL, and the levels of T3, T4, and TSH were all within normal ranges. The patient also underwent a routine urine test, which produced satisfactory results. Serological blood tests were also performed, and all these tests showed negative results at all dilutions, just like in episode one.

She also had a full abdominal ultrasonography (USG), which revealed no abnormalities. Additionally, neither the X-ray image of the paranasal sinuses obtained in the occipitomental view (PNS OM) nor the chest PA (posteroanterior) X-ray showed any abnormalities. Furthermore, patient underwent M-mode 2D echocardiography and found no issues.

Finally, ^{18}F-Fluorodeoxyglucose whole-body PET/CT (Positron Emission Tomography/Computed Tomography) was conducted following the established procedure, with 13.2 mCi of ^{18}F-fluorodeoxyglucose injected intravenously. To facilitate the diffusion and absorption of the radiotracer, the patient was allowed to rest calmly for 60 minutes in a protected environment. Imaging was conducted using a PET/CT scanner (GE Discovery, USA). CT scans were taken to correct attenuation and localize anatomical structures, and then PET scans were taken from the skull to the middle of the thigh. Initially, normalized the maximal standardized uptake value (SUVmax) with lean body mass (LBM) to achieve more precise and consistent measurements. Prior to the scan, the patient's serum creatinine and blood glucose levels were 0.59 mg/dL and 115 mg/dL, respectively. CT scanning was conducted with non-ionic intravenous and oral contrast agents. No negative reactions were noted during the scan. The ^{18}F-FDG-PET/CT scan shows no indication of metabolically active illness anywhere else in the body, despite the presence of a few minor FDG avid right paratracheal, AP window, and subcarinal lymph nodes (Figure 3).

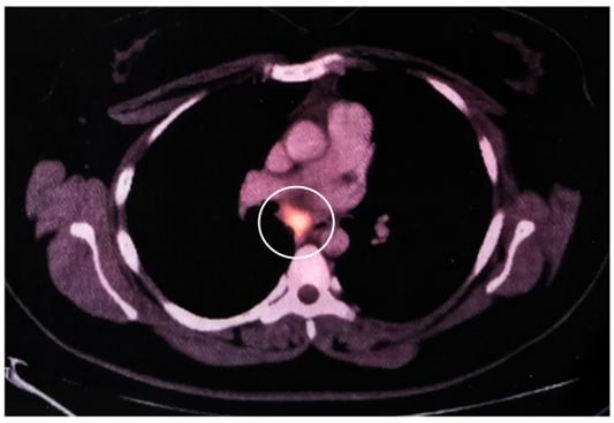

Figure 3: ^{18}F-FDG-PET/CT scan shows minor FDG avid right paratracheal, AP window, and subcarinal lymph nodes (mark by white circles).

The patient received RLS and NS alternately in a 2:1 ratio throughout her hospitalization, consistent with episode one. In addition, the patient received 650 mg of intravenous paracetamol four times a day at a six-hour interval, along with 40 mg of omeprazole (per protocol, once daily). She remained hospitalized for 10 days. Following the 8th day, there was a slow and systemic drop in the fever cycle, which followed the same pattern as its peaks. At the time of hospital discharge, the patient was in hemodynamically stable condition and was prescribed certain medications, including one tablet of paracetamol (650 mg) in case of fever, one tablet of pantoprazole (40 mg) before breakfast for seven days, one capsule of B-Complex and vitamin C (3 mg) for fifteen days. Additionally, the patient was told to follow a regular diet.

Table 1: Patients' laboratory tests. Some of important laboratory tests results with their corresponding normal ranges of episode one and three.

Laboratory tests	Patients' laboratory results	Reference ranges
EPISODE ONE		
Hemoglobin	11.70 g/dL	11.5 and 16.5 g/dL
Red blood cell (RBC)	4.43 mill/mm³	3.8-4.8 million/mm³
Mean corpuscular volume (MCV)	81 fL	83 to 92 fL
Mean corpuscular hemoglobin (MCH)	26.50 pg	27 to 32 pg
C-reactive protein (CRP)	105.37 mg/dL	0.8-1 mg/dL
ESR	70 mm/h	0-20 mm/h
Platelet count	335,000/mm³	150,000-450,000/mm³
Episode three		
Hemoglobin	10.2 g/dL	11.5 and 16.5 g/dL
Red blood cell (RBC)	4.83 million/mm³	3.8-4.8 million/mm³
Mean corpuscular volume (MCV)	79.3 fl	83-92 fl
Mean corpuscular hemoglobin (MCH)	24.2 pg	27-32 pg
Mean corpuscular hemoglobin concentration (MCHC)	30.6 g/dL	32-35 g/dL
C-reactive protein (CRP)	100.33 mg/dL	0.8-1 mg/dL
ESR	90 mm/h	0-20 mm/h
Platelet count	599,000/mm³	150,000-450,000/mm³
WBC count	14,210/mm³	4,000-10,000/mm³
Vitamin B12	138 pg/mL	211 and 946 pg/mL

3. DISCUSSION

FUO continue to be considered among the most challenging medical diagnostic problems (Figure 4) [3]. Doctors often ask for imaging and special tests early in the investigation of fevers with no known cause, but these tests might not help or could even give wrong information because these fevers can be caused by many different serious illnesses (Figure 5).

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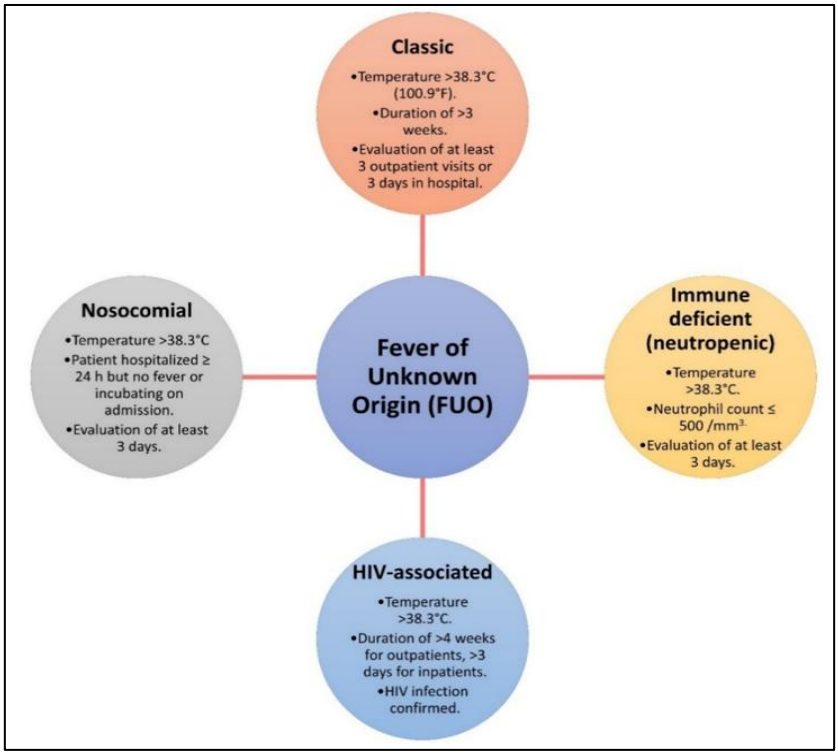

Figure 4: Typical subclass-related causes of Unknown-Origin Fever. In this picture delineate four main groups (classic, nosocomial, immune deficient, and HIV-associated) of FUO.

Irregularities in blood pressure and/or pulse between the extremities.	Takayasu arteritis.
Nodule in the epididymis	Extrapulmonary tuberculosis, Periarteritis nodosa, Sarcoidosis, Systemic lupus erythematosus.
The fever reaches its zenith in the morning.	Polyarteritis nodosa, Typhoid fever, Whipple disease.
Bradycardia, accompanied by a fever (facet sign)	Central nervous system malignancy, Lymphoma, Typhoid fever, Yellow fever.
Isolated hepatomegaly	Hepatic neoplasia, Metastatic carcinoma, Q fever, Renal neoplasia.
Lymphadenopathy	Rheumatoid arthritis, Sarcoidosis, Systemic lupus erythematosus.
New heart murmur	Atrial myxoma, Infective endocarditis.
Aphthous and/or genital ulcers	Behçet disease, Systemic lupus erythematosus.
Rash appears	Infective endocarditis.
Roth spots	Infective endocarditis.
Spinal tenderness along with back pain	Vertebral osteomyelitis.
Splenomegaly occurs	Cirrhosis, Crohn disease, Cytomegalovirus, Epstein-Barr virus, Miliary tuberculosis.
Fever rising twice a day in a systematic manner.	Malaria, Miliary tuberculosis, Still disease, Visceral leishmaniasis.

Figure 5: Physical exam results point to possible causes of unknown fever.

No standard protocol exists for the management of FUO due to the diverse potential etiologies. The primary objective is to investigate and exclude all possible diagnoses. Specific treatment should commence upon establishing a diagnosis. It is important to note that empiric antibiotics are not recommended unless the FUO patient is neutropenic, as they may obscure the diagnosis of certain hidden infections [7]. Similarly, empiric glucocorticoids are unwarranted unless there is a strong clinical suspicion of a specific rheumatologic condition. However, empirical therapy trials of antibiotics, steroids, or antituberculosis drugs may be considered in individuals who are exhibiting clinical deterioration.

In this instance, the patient remained stable until the abrupt beginning of repeated fever episodes during the previous several months and had no notable medical history, either genetically or physically. All vital signs are essentially normal during episodes one through three, with the exception of minor variations brought on by an elevated heartbeat during the fever and light sensitivity in both eyes. She also suffered from vaginal and aphthous ulcers. Additionally, she experienced joint discomfort, neck pain, and lower back pain. During those periods of fever, this patient also developed an upper respiratory tract infection. RBC, WBC, and platelets fluctuated throughout those all-fever bouts, and CRP was also quite high. Ferritin was normal; however, the ESR was increased (90 mm/h). Serological testing (bacterial and viral tests), entire abdominal ultrasonography, and 2D echocardiography did not reveal anything important. Thyroid function, chest CT scan, and ECG were all normal. There was no evidence of arthritis or autoimmune illness. The patient's appetite was completely normal both throughout and outside of these fever bouts. Although there are a few small FDG avid lymph nodes in the right paratracheal, AP window, and subcarinal regions, the FDG-PET-CT scan reveals no signs of metabolically active disease anyplace else in the body. No significant anomalies were discovered that would have enabled us to draw a specific diagnosis. However, the symptoms were somewhat comparable to those of Behçet disease [11].

4. CONCLUSION

In addition to light sensitivity and a high temperature, the patient's medical conditions included oral and vaginal ulcers, elevated C-reactive protein and ESR levels, decreased vitamin B levels, and normal procalcitonin levels. Finally, we come to the conclusion that there were some similarities between the symptoms and those of Behçet's illness. Thankfully, after the third bout of fever, the patient was released from the hospital in a hemodynamically stable state. The patient has not complained since the 3rd fever episode. In the future, the patient will be recommended to take specific medications, such as corticosteroids and anti-inflammatory drugs, to achieve near-complete resolution of the symptoms in similar circumstances. Subsequently, it is imperative to conduct ongoing monitoring. Additional study is required to enhance the comprehension of disease pathophysiology and to augment the literature for the treatment of these disorders.

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AUTHORS' CONTRIBUTIONS

Dr. Tithi Ghosh: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Visualization, Writing - original draft, Writing - review & editing; **Mr. Soumyadeep Ghosh:** Data curation, Investigation, Software, Visualization, Writing - original draft, Writing - review & editing; **Dr. Saru Kumar Debbarma:** Resources, Writing - review & editing.

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AVAILABILITY OF DATA AND MATERIALS

Due to the sensitive nature of the research supporting data is not available.

DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethics committee clearance was not needed for this case report.

CONSENT FOR PUBLICATION

The patient gave written informed permission for this case report along with any related photos to be published.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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Conflict of Interest Statement: All authors have nothing else to disclose.

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