A Case of Fever of Unknown Origin "The Clinical Case Series of Cerrahpaşa"

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Case Presentation

Dr. Fansa: A 37-year-old woman from Iran sought outpatient care with a 2-week history of fever, chills, abdominal pain, dry cough, and night sweats following her return from a 20-day trip to Iran. The patient had been admitted to several hospitals with these complaints. Initial assessments included suspected diagnoses such as acute bronchitis, asthma, peptic ulcer, and renal colic. The patient was prescribed a range of antibiotics, including cefuroxime axetil and dirithromycin during the pre-evaluation process. Laboratory analyses revealed a total white blood cell count of 17 400/mm^3, with 83% neutrophils, a hemoglobin level of 9.4 g/dL, a platelet count of 749 000/mm^3, and elevated inflammatory markers, including a C-reactive protein (CRP) level of 145 mg/L (normal range: 0-5) and an erythrocyte sedimentation rate of 59 mm/h. Additional findings included a ferritin level of 503 ng/mL, alkaline phosphatase at 390 IU/L, and gamma-glutamyl transferase at 197 IU/L. Further details of the laboratory results can be found in Table 1. Her chest x-ray was normal and no acid-fast bacilli were observed in her sputum. Interferon gamma release assay test for tuberculosis was also negative. Thyroid hormone levels were in the normal range, and tumor markers such as CEA, CA19-9, and rheumatoid factor were all negative. Serologies for syphilis, brucellosis, hepatitis B virus, human immunodeficiency virus, Epstein-Barr virus, toxoplasmosis, and cytomegalovirus were unremarkable.

An abdominal magnetic resonance imaging revealed 4 complex cystic lesions with slightly irregular wall contrast. Despite a negative result for hydatid disease in the Indirect Hemagglutination test, the patient received ceftriaxone for a preliminary diagnosis of cholangitis. Blood and urine cultures were sterile. In the second month of persistent fever, a peripheral blood smear was conducted due to a significant drop in hemoglobin levels. The Giemsa staining revealed chromatin-like structures in the erythrocytes, prompting the administration of artemisinin based on suspicion of malaria. On the third day of antimalarial treatment, and the 65th day of fever, the patient was referred to the department for further investigation. Upon admission, the patient presented with confusion, agitation, and blurred vision, alongside complaints of weight loss (8 kg), nausea, and vomiting. On examination, vital signs were stable with a temperature of 36.6°C, heart rate of 72 beats per minute, blood pressure of 100/62 mm Hg, respiratory rate of 18 breaths per minute, and oxygen saturation of 98% on room air. Systemic examinations revealed no notable findings. Cranial imaging and fundoscopic examination showed no pathological signs. The patient continued to exhibit neutrophilic leukocytosis (white blood cell count: 19 300/mm^3, neutrophils: 83%), thrombocytosis (606 000/mm^3), and normochromic microcytic anemia (hemoglobin: 9.4 g/dL). However, due to a sudden increase in acute phase reactants, including elevated CRP (237 mg/L) and ferritin (1319 ng/mL) levels, empirical treatment with piperacillin-tazobactam was initiated. Although the malaria treatment was completed during the follow-up, malaria was excluded by blood smear microscopic examinations and malaria rapid diagnostic tests, which yielded negative results.

The patient was categorized as a case of fever of unknown origin (FUO), with normal complement levels. A thoraco-abdominal computed tomography (CT) scan revealed no significant abnormalities. Ultimately, a positron emission tomography (PET)-CT scan demonstrated heightened fluorine-18 fluorodeoxyglucose (FDG) uptake in the aortic arch, ascending and descending aorta, and the abdominal aorta, as well as in the proximal segments of the right brachiocephalic, bilateral common carotid, and left subclavian arteries, indicative of vasculitis. Subsequent to these findings, a diagnosis was established, and management decisions were implemented.

Pulse methylprednisolone was administered. Echocardiography, carotid ultrasonography (USG), cranial magnetic resonance angiography (MRA), and renal Doppler USG were scheduled and were found to be normal. Following the initiation of glucocorticoid therapy, the patient experienced resolution of fever by the second day, and by the seventh day, there was a significant decrease in leukocyte count and acute phase reactants (CRP and ESR). Subsequently,

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Table 1. Laboratory Data

Variable	Reference Range	First Evaluation, Previous Hospital	At Admission in the Clinic	In the First Week of Treatment
White blood cells (per mm^3)	4.300-10.300	17.400	19.300	12.600
Neutrophils (%)	41-73	83.6	83	67.5
Hemoglobin (g/dL)	12-16	9.4	9.4	11.6
Hematocrit (%)	36-48	29.4	28.7	33.9
Mean corpuscular volume (fL)	80-99	80	79.2	77.6
Mean corpuscular hemoglobin (pg)	27.2-33.5	25	25.9	26.6
Mean corpuscular hemoglobin concentration (gr/dL)	32-36	32	32.7	34.3
Red cell distribution width (%)	12-15	13.9	15.6	17.2
Platelet (per mm^3)	156.000-373.000	749.000	606.000	1.065.000
C-reactive protein (mg/L)	<5	145	237	7
Ferritin (ng/mL)	15-160	-	1319	-
Erythrocyte sedimentation rate (mm/hr)	0-20	59	112	50
Urea (mg/dL)	17-49	54	29	60
Creatinine (mg/dL)	0.5-0.9	0.53	0.44	0.44
Alanine aminotransferase (U/L)	<32	64	10	26
Aspartate aminotransferase (U/L)	<32	38	11	12
Total/direct bilirubin (mg/dL)	<0.3/<0.3	0.5/0.3	0.36/0.31	-/0.25
Alkaline phosphatase (U/L)	35-105	390	159	-
Gamma glutamyl transferase (U/L)	<40	197	62	252
Thyroid stimulating hormone (μIU/mL)	0.27-4.2	1.15	0.88	-
Free T3 (pg/mL)	2-4.4	2.6	2.08	-
Free T4 (ng/dL)	0.93-1.7	1.2	1.42	-
Rheumatoid factor		Negative		
Rose bengal		Negative		
Brucella IgM		Negative		
Brucella IgG		Negative		
Anti HIV		Negative		
Anti HCV		Negative		
HBs Ag		Negative		
Anti HBs		Negative		
Anti HBc IgG		Negative		
Anti HBc IgM		Negative		
EBV VCA IgM		Negative		
EBV VCA IgG		Positive		
Anti CMV IgM		Negative		
Anti HAV IgM		Negative		
Anti HAV IgG		Positive		
Anti Toxo IgM		Negative		
VDRL-RPR		Negative		

the patient was discharged with a prescription for oral prednisolone and scheduled for monthly intravenous cyclophosphamide as part of the follow-up plan in the rheumatology clinic.

Radiological Discussion

Dr. Asa: Fluorine-18 fluorodeoxyglucose is a radiopharmaceutical widely used as a glucose analogue in PET imaging. Since malignant cells use glucose more than normal cells, imaging tumors with rapid glucose metabolism is performed with FDG. In addition, glucose metabolism increases in associated cells during infection or inflammation. Infectious or non-infectious inflammatory conditions can, therefore, also be visualized with FDG.[1]

To clarify the etiology of FUO and to determine the contribution of a diagnostic test to patient management, it is useful to know the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the imaging test.[2]

In Takeuchi et al's[3] meta-analysis comparing the efficacy of FDG PET/CT and FDG PET in FUO, FDG PET/CT had superior sensitivity (86% vs. 76%). However, both modalities showed similar specificity in this analysis (52% vs. 50%). Furthermore, in a study by Bleeker-Rovers et al[4] using FDG-PET, the PPV and NPV were 85% and 95%, respectively.

In a prospective study of 72 patients diagnosed with FUO by Schönau et al,[5] the contribution of FDG-PET/CT to the diagnosis was found to be 66% independent of CRP levels in patients older than 50 years. While the contribution was 42.1% in patients younger than 50 years with CRP >30 mg/L, it was only 8.3% in the group younger than 50 years with CRP <30 mg/L. In a study , in which patients were grouped according to final diagnosis, FDG-PET had the highest sensitivity (100%) in the tumor and granuloma groups. In addition, the sensitivity was 89% and 65% in the infectious diseases and autoimmune diseases/vasculitis groups, respectively.[5] In addition to these, there are also cases of false-negative FDG PET in systemic lupus erythematosus, cytomegalovirus infection, urinary tract infection, and Crohn's disease.[6-8] A recent study on cost-effectiveness highlighted that employing FDG PET/CT early on in FUO patients could potentially decrease hospital stays and medical expenses.[9]

In the meta-analysis by Soussan et al[10] evaluating the efficacy of FDG PET/CT in vasculitis, the sensitivity and specificity for detecting large vessel inflammation in patients with giant cell arteritis (GCA) were found to be 90% and 98%, respectively. Furthermore, the findings revealed a sensitivity and specificity of 87% and 73%, respectively, for the assessment of disease activity in Takayasu's arteritis. It has been reported that vascular activity on PET images is equal to or greater than liver activity, which is a valuable criterion for the diagnosis of vasculitis. It is recommended that FDG-PET imaging should be planned as soon as possible (within 1-3 days) after starting steroids in patients with suspected vasculitis who urgently need to start steroids. In addition, intravenous contrast can be used during imaging to better evaluate the vascular structures of FUO patients with suspected vasculitis if there is no contraindication.[11]

In contrast-enhanced FDG PET/CT imaging of the patient (Figure 1), increased FDG uptake was detected in the arcus aorta and thoracic aortic walls in thorax axial PET/CT fusion and PET sections (A, C, and B, D; arrows). In addition, increased activity uptake was observed in the walls of the ascending aorta in PET sections with thorax coronal PET/CT fusion (E and F; arrows). Apart from these, increased activity uptake was also observed in the bilateral carotid, right brachiocephalic, and left subclavian artery walls in the whole body maximum intensity projection images (G; arrowheads). The observed increased activity uptake in the vascular walls was considered indicative of vasculitis.

Radiological Diagnosis

Vasculitis

Differential Diagnosis

Dr. Seyahi and Ozdede: Fever of unknown origin is defined as a condition in which the fever exceeds 38.3°C, lasts at least 3 weeks, and the underlying cause cannot be determined. The underlying etiologies include infection, malignancy, and noninfectious inflammatory diseases.[12-14]

Since there may be nonspecific constitutional symptoms at the beginning of the disease, vasculitides should also be considered in long-term fever periods in rheumatology practice.[15,16] One of them, Takayasu, is a large vessel vasculitis in which the aorta and its branches are affected, leading to narrowing, occlusion or aneurysm. Depending on the involvement of the aorta and its branches, patients could suffer from a spectrum of clinical findings, including claudication in the extremities, resistant hypertension, and angina; however, constitutional symptoms including fatigue, weight loss, and fever have also been reported in the early stages of the disease.[16,17] The non-infectious inflammatory diseases that should be considered in those presenting with FUO before the age of 40 are summarized in general terms.

Atherosclerosis: In Takayasu's arteritis, the progression to premature atherosclerosis is accelerated by the structural defect in the vessel after initiated inflammation in the adventitia layer of the vessel. It is crucial to differentiate between atherosclerosis and vasculitis that cause vessel damage for proper treatment and follow-up. Atherosclerosis is characterized by an irregular vessel wall, an increase in nonhomogeneous intima-media thickness, and the presence of atherosclerotic plaques. In contrast, there is diffuse homogeneous wall thickness in Takayasu's arteritis. In the later stages of vasculitis, peripheral wall calcifications and atherosclerosis can be observed in the affected areas.[18]

Fibromuscular dysplasia: It is a non-inflammatory and non-atherosclerotic disease of unknown etiology and is often observed in young women and is included in the differential diagnosis of vasculitis due to the arterial structural damage it causes.[19]

Giant cell arteritis: It is a large vessel vasculitis seen in the elderly population, especially with the involvement of extracranial branches such as the temporal arteries. They may present with a wide spectrum of clinical findings such as headache, weight loss, myalgia, fever, fatigue, and loss of vision. Early diagnosis and treatment of GCA are crucial in elderly patients with fever of unknown etiology for timely medical management.[20,21]

Behçet's disease: It is an inflammatory condition in which other systems such as ophthalmic, neurologic, vascular, and gastrointestinal systems can be affected in addition to mucocutaneous involvement.[22] Among the systemic involvements, vascular involvement is the most significant in terms of morbidity and mortality. Especially in the presence of long-term refractory fever, Behçet's should be evaluated in terms of vascular involvement.[23-26] Notably, there have been cases of Behçet's disease patients with involvement of the pulmonary artery[26] and intracardiac thrombus with refractory fever.[26,27]

Buerger's disease: It is included in the differential diagnosis when the upper extremity arteries cannot be palpated unilaterally or bilaterally in a young patient. It has been revealed to have a strong association with smoking. Although it is not an inflammatory disease, it is reported that there are quite dense cellular and inflammatory thrombi in pathology studies.[28]

Retroperitoneal fibrosis, sclerosing retroperitoneal granuloma, or chronic periaortitis: It is characterized by the presence of mass-like fibrosis around the inferior vena cava and ureters

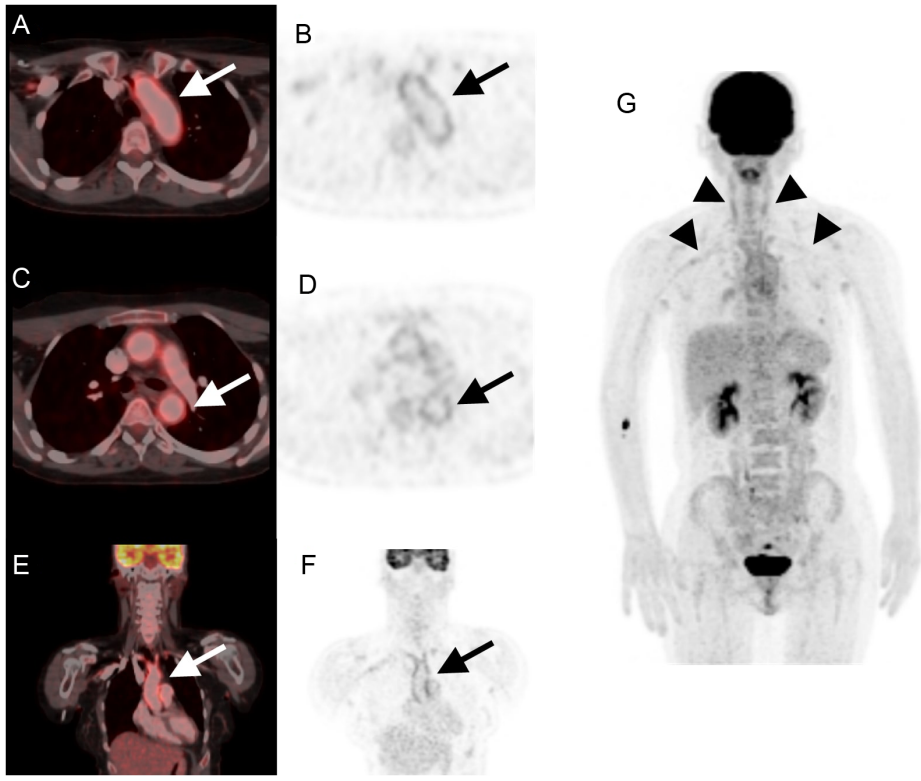

Figure 1. Contrast-enhanced FDG PET/CT imaging of the patient.

in the retroperitoneal region. Abdominal and back pain, commonly observed in patients, should be considered in the differential diagnosis for vasculitis with prominence in the abdominal aorta.[29]

Mycotic aneurysm: This may be the differential diagnosis in thoracic or abdominal aneurysms. The majority of infective aneurysms, which are called mycotic because the vessel wall changes resemble fungi, are developed by bacteria. The symptoms at the time of presentation are mostly non-specific and can range from constitutional findings such as fatigue, weight loss, and fever to severe uncontrolled sepsis.[30]

Systemic lupus erythematosus: It is a multisystem-involved autoimmune disease. Non-specific symptoms such as fever and malaise have been reported at the time of diagnosis or during attacks.[30] Particularly, major organ involvements of lupus, such as renal, cardiac, and serosal involvement, should be considered in the differential diagnosis of febrile patients reported to be refractory to treatment.[31-33]

Adult-onset Still's disease: It is one of the diseases that should be considered in terms of differential diagnosis in patients presenting with fever. It is characterized by daily fever, transient rashes, and inflammatory polyarthritis, and it can lead to serious life-threatening complications such as macrophage activation syndrome.[34,35]

Laboratory: There is no specific marker for Takayasu's arteritis. Laboratory data are needed to exclude infection, malignancy, and autoimmune diseases in the differential diagnosis when FUO is taken into account at the age of 40 years and earlier.

Echocardiography: Echocardiography is used to demonstrate or rule out the possibility of infective endocarditis and intracardiac thrombus in patients with unexplained fever. It is useful for detecting ascending aortic width and aortic insufficiency and identifying increased pulmonary artery pressure due to involvement of the pulmonary artery.[36]

Imaging modalities: To diagnose Takayasu's arteritis, identify the involved vessels, and monitor disease progression, imaging modalities are required. The aim is to detect structural disorders such as thickening, narrowing, occlusion or aneurysm in the wall of the vessel secondary to the inflammation. The main ones are Doppler USG, computed tomographic angiography (CTA), MRA, and PET/CT.[37]

Doppler ultrasonography: It is a noninvasive method used to show the vessel wall structure and pathologies in the vessel lumen. User dependency and the inability to show the branches of the aorta in the thoracic regions also limit its use.[37]

Computed tomographic angiography: It is a high-resolution imaging modality useful for detecting structural lesions and wall inflammation in the vessel. Compared to MRA, it is a shorter-term method but involves radiation, which restricts its use in circumstances where a contrast agent is contraindicated.[37]

Magnetic resonance angiography: It detects edema and vascularization on the vessel wall more effectively than other images. However, it does not depict small blood vessels well; imaging of the extremities is inadequate. There is no use of radiation and contrast material complications are minimal.[37]

Positron emission tomography/computed tomography: It is a nuclear imaging technique based on the metabolically active cells' uptake of FDG. Positron emission tomography is utilized to detect potential malignancy or inflammatory processes in the etiology of FUO based on the uptake of FDG by malignant and inflammatory cells. It is useful for the early diagnosis of vasculitis because it displays inflammation in the vessel wall prior to vascular structural damage.[37-39]

Discussion of Management

Dr. Fansa: During outpatient follow-up, the patient was initially treated with oral prednisolone combined with monthly intravenous cyclophosphamide. This regimen initially relieved her

symptoms. However, towards the end of the 3-month treatment period, when the steroid dose was tapered, the patient's symptoms relapsed, and tocilizumab treatment was initiated. Since switching to tocilizumab, the patient's disease has been successfully managed for a prolonged period.

Dr. Seyahi: Takayasu arteritis, a type of vasculitis affecting large blood vessels, should be diagnosed and treated promptly due to the mortality and morbidity it may cause. Takayasu arteritis can be associated with unexplained prolonged fever and should be part of the FUO evaluation.[40] In the active phase, it is recommended to start treatment with high-dose oral glucocorticoids; when organ involvement causes a life-threatening risk, intravenous pulse glucocorticoids should be considered. To reduce the glucocorticoid dose and control the disease, non-glucocorticoid immunosuppressive therapies should be added to the treatment. Non-biological immunosuppressives used as initial therapy are methotrexate, azathioprine, and cyclophosphamide, and the use of cyclophosphamide is recommended, especially in life-threatening organ involvement or in resistant patients. Among the immunosuppressive drugs, some data have proven to be biologically effective in anti-TNF (tumor necrosis factor) drugs.[41]

Tocilizumab, an IL-6 blocker, has been shown to be effective in GCA,[42] whereas the primary efficacy endpoint was not met in the randomized controlled trial in Takayasu arteritis.[43] It has been noted that tocilizumab may be considered in patients with inadequate responses to other immunosuppressive treatments.[41,44]

Final Diagnosis

Takayasu Arteritis.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

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