A Case with Fever of Unknown Origin Diagnosed as Wegener
Granulomatosis

Wegener Granülomatozis Tanı Konulan Bir Nedeni Bilinmeyen Ateş Olgusu

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Abstract
Fever of unknown origin (FUO) was described in 1961 by Petersdorf and Beeson as a fever above 38.3°C that lasts more than three weeks and cannot be diagnosed despite a one-week hospitalized examination. In 1991, Durack and Street made a different FUO description for patients with nosocomial infections, human immunodeficiency virus (HIV) and neutropenia. Along with this reconsideration, the investigation period was limited to one week of investigation, three days of hospitalization or three clinical visits. In the literature, the most frequent cause of FUO is infections followed by neoplasms and connective vascular diseases, respectively. The etiology in 5-15% of patients cannot be diagnosed despite detailed examination. Here, we present a 75-year-old patient admitted to the hospital with a two-week history of fever, fatigue and lack of appetite. He had been examined in the infection and lung diseases clinics over a three-month period without diagnosis. In our internal medicine clinic, we diagnosed the patient as Wegener granulomatosis and a satisfactory response to the therapy was observed.

Key words: Fever, proteinuria, wegener granulomatosis

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Introduction
Fever of unknown origin (FUO) was described in 1961 by Petersdorf and Beeson with the criteria of fever above 38.3°C lasting more than three weeks without a diagnosis despite a one-week hospitalized examination (1). With a re-evaluation of Durack and Street in 1991, the one-week examination period for FUO inquiry was limited to three days of hospitalization or three clinical visits, and FUO was separately redefined for four different patient groups (2).

Among the various causes of FUO, the majority are attributed to bacterial infections. Tuberculosis is generally considered among FUO diagnoses. Herpes viruses, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) may cause fever with non-specific symptoms. Immunosuppression, medication with broad-spectrum antibiotics, intravascular devices, and total parental nutrition may specifically cause disseminated fungal infection with Candida albicans.

Connective tissue diseases may frequently cause fever with specific symptoms like skin eruption and arthritis and other symptoms like pulmonary involvement. These connective tissue diseases such as systemic lupus erythematosus (SLE), adult Still’s disease, polyarteritis nodosa, rheumatoid arthritis (RA), mixed connective tissue disease, temporal arteritis, and polymyalgia

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rheumatisma may be determined in FUO etiology due to their non-specific presentations.

To continue, neoplastic diseases like Hodgkin’s and non-Hodgkin’s lymphomas or leukemia may cause FUO. Specifically, peripheral blood during preleukemia phase, bone marrow aspiration and biopsy may not be sufficient for diagnosis. Solid tumors in general and renal cell carcinoma in particular may cause FUO.

Endocrine diseases like hyperthyroidism and subacute thyroiditis are among the major causes of fever as well. Acute adrenal insufficiency may rarely be a cause of FUO. In addition, rarely observed fatal acute adrenal crisis can also cause FUO. Lastly, FUO can also be encountered with pulmonary embolism and thrombophlebitis.

Case Presentation

A 75-year-old male involved with animal husbandry first consulted a physician with complaints of continuous fever, respiratory disorder, fatigue, and lack of appetite. The patient had a history of tuberculosis diagnosed around 30 years ago and an inguinal hernia operation three years ago. He had no other history of a chronic disease. It had been determined that his complaints had started with a fever and continued with respiratory disorder and fatigue. After a treatment with broad-spectrum antibiotics for five days with a prognosis of pneumonia, the patient was referred to the state hospital without any success in controlling the fever. During this period, the patient also complained of dyspepsia. With an early diagnosis of peptic ulcer and stomach carcinoma at the state hospital, the medical staff had planned an endoscopy for the patient, who had also experienced weight loss since his early complaints. However, because of dyspepsia and generalized poor condition, the patient was referred to the sanatorium hospital.

Laboratory findings of the patient under monitoring at the sanatorium hospital included hemoglobin (Hb) 12 g/dl, WBC 13x10⁹/l, and sedimentation 85 mm/s, with normal chest X-ray and normal values of complete urine analysis. During his hospital stay, there was no growth in urine and blood cultures. The albumin level of the patient was 1.8 g/dl and other biochemical parameters were normal. After detecting the D-dimer level of 4872 μg/L (N: 0-250 μg/L), a computerized tomography (CT) angiography was performed. Patches of millimetric filling defects in pulmonary artery branches in segmental and sub-segmental levels on the right lower lung zone, focal nodular infiltrative densities and focal bronchial spread on posterior segments of the right upper lobe, and linear and peripheral atelectasis in the right middle lobe, in the medial segment of the right lower lobe and in the left lower zone were reported. A pulmonary thromboembolism (PTE) was considered and the patient was administered coumadin.

During the full abdominal ultrasound performed at the sanatorium, a cystic form measuring 1 cm had been observed on the sub-diaphragmatic sphere of the right lobe anterior segment, with the right lobe of the liver greater than normal size (19 cm). A grade 1 increase in parenchyma in both kidneys and an increase in prostate size were also identified. After a full abdominal CT, nodular calcification and mesenteric densities in millimeters were reported on the dome of the liver. Contour and size of kidneys were normal, parenchyma was homogeneous and collecting system was normal in size. Acid-fast bacilli (AFB) culture was consistently negative in four different tests. No response of fever was observed during a 10-day treatment with 1g 4x1 intravenous (i.v.) empiric ampicillin/sulbactam (Ampeesid). After an Escherichia coli growth in urine culture and a increase in WBC to 23x10⁹/l, levofloxacin (Tavanic) flacon i.v. was given for 3 days. As the high fever continued, moxifloxacin (Avelox) i.v. for 8 days, cefepime (Maxipim) 1g + amikacin (Amikin) 500 mg for 9 days and thienamycin (Tienam) 500 mg flacon i.v. for 7 days were administered respectively.

During his stay in the chest diseases clinic in the sanatorium, the etiology of the fever could not be identified and the patient was referred to the Ministry of Health Ankara Hospital Infectious Diseases Clinic. Here, early laboratory findings of the patient were: Hb 9.3 g/dl (N: 12.6-17.4 g/dl); WBC 24x10⁹/l (N: 4.5-11 x10⁹/l) (80% neutrophil); thrombocyte 413x10⁹/l (N: 150-450 x10⁹/l); sedimentation 120 mm/s; blood urea nitrogen (BUN) 81 mg/dl; creatinine 2.1 mg/dl; albumin 2.7 g/dl; calcium (Ca) 7.9 mg/dl; sodium (Na) 130; potassium (K) 3.3 mmol/L; and procalcitonin 0.8 ng/ml (N: 0-0.5 ng/ml). Other than a 1+ erythrocyte in full urine test, no pathological result was detected. During the clinical stay, the blood, urine and sputum cultures were reevaluated and no specific growth was detected. In three different tests, AFB culture was always negative and C-reactive protein (CRP) level was 17.1. Fecal occult blood result was negative in three different stool tests and brucella Rose Bengal, tube agglutination and salmonella agglutination were all negative. IgG level was 2450 (N: 751-1560); other immunoglobulin levels were normal; β2 microglobulin level was 20.4 (N: 1.42-3.21); and CMV, EBV, hepatitis serologies and tumor indicators were all detected as negative. Due to the high level of BUN and creatinine, a 24-hour urine test was performed and a proteinuria of 797 mg/day was detected. Because of continuing anemia, a multiple myeloma was suspected, but his protein electrophoresis was detected as normal. After a hematologic consultation, bone marrow aspiration and biopsy were recommended. At this point, the patient was accepted by our clinic from the Infectious Diseases Clinic of Ankara Hospital with all his findings.

In our clinic, all treatments performed since the early complaints of the patient were reviewed. During this period, the general condition of the patient was poor and his cooperation was poor. Basals of both lungs had rules with a bilateral 3+ pretilial edema and the patient complained of distinct non-purulent cough, which we also observed. We identified a progressive increase in
infectious diseases accounted for 36.6% followed by non-
leukemia cases were identified. vasculitis (14%). In addition, of 126 cases of malignant
35.7% or 49 cases, followed by SLE (16.7%) and systemic Still’s was the most frequent disease, with a frequency of
Among the group of connective tissue diseases, adult
infectious endocarditis (9.6%, 39 cases), respectively.
36.4% of the patient, experience of the physician and technical
capabilities.
25.6% of the cases with unidentified fever etiology.
conflict of interest is declared by authors.
No conflict of interest is declared by authors.
References

Discussion
Diseases causing FUO vary according to the socioeconomic status, personal characteristics, geographic region of residence, and age of the patients. We see an advance in discovering the causes of FUO due to the increasing utilization of high quality laboratory tests, imaging technologies and the increasing number of initiative inspections. There is a variation in the frequency of detecting FUO causes according to the characteristics of the patient, experience of the physician and technical capabilities.

In their study on a series of 857 FUO cases between 1990 and 2006, Sipahi et al. (3) reported the causes of FUO as infectious diseases (47%, 403 cases), connective tissue diseases (15.9%, 137 cases) and neoplasms (14.7%, 126 cases), while the etiology could not be identified in 16.1% or 138 cases. In the same study, tuberculosis was the primary infectious disease, with a frequency of 36.4% (147 cases) followed by brucellosis (12.6%, 51 cases) and systemic Still’s was the most frequent disease, with a frequency of
among 11 different case series, infectious diseases accounted for 36.6% followed by non-infectious inflammatory diseases (15.9%) and malignancies (11.2%), respectively. The study reported 25.6% of the cases with unidentified fever etiology.

In the literature, we identified only nine studies mentioning Wegener’s granulomatosis and FUO together (5-13). In the study of Sipahi et al. (3), this disease was identified in only 3 cases out of a total of 857.

In view of the extent of the spectrum for diagnosis of patients with FUO, a multidisciplinary approach is essential.

Conflict of interest
No conflict of interest is declared by authors.

BUN and creatinine, which were within normal limits in the early observation. The increase continued during his stay at our clinic. During this period, immunological indicators were rheumatoid factor (RF) <20 IU/ml; ANA (-); anti-dsDNA (-); c-ANCA 437.4 IU/ml (N: <5 IU/ml); and p-ANCA 4.2 IU/ml (N: <5 IU/ml). Pathologists reported crescentic, focal necrotizing glomerulonephritis and vasculitis after the kidney biopsy, which was performed because of the high level of c-ANCA. We later diagnosed the patient as Wegener granulomatosis and started a treatment of pulse steroid together with a planned i.v. cyclophosphamide treatment of one dose for three weeks. After the diagnosis, we applied 10 treatments of plasmapheresis in total. After the third day of treatment, the patient’s fever decreased and no increase was observed. While the patient referred to our clinic with a creatinine level of 2.8 mg/dl, during the diagnosis this level increased to 6.4 mg/dl, and in the second week of the steroid and cyclophosphamide treatments, it decreased to 4.7 mg/dl. The patient was discharged with a creatinine level of 2.8 mg/dl. CRP level of 17.1 at the sanatorium hospital was 0.8 at the time of our discharge. Similarly, 3+ pretibial edema, rales and cough complaints were totally resolved.

In another study on FUO prepared by Gaeta et al. (4), of 1458 FUO cases, 36.6% followed by non-