The causes of fever of unknown origin (FUO) mainly include infections, malignancies and collagenous vascular diseases. Large panarteritis nodosa (PAN) is a systemic vasculitis which affects small and medium-sized arteries. The disease mainly affects skin, joints, kidneys, peripheral nerves and gastrointestinal system. In the clinical picture of the disease, in addition to non-specific symptoms including fever, malaise, weight loss and loss of appetite, symptoms related to the affected organ may be seen. Laboratory findings are not diagnostic, but may reflect a systemic inflammatory pathology. It may rarely be manifested as fever of unknown origin. In this case, a patient with FUO diagnosed with PAN after examination and follow-up which lasted for one month is presented.
CASE REPORT

A 44-year-old male patient was admitted to our clinic with complaints of rash and fever which had been lasting for 10 days. He had used moxifloxacin for diagnosis of pneumonia following the complaint of fever before he was referred to our hospital. Since his body temperature did not come to normal limits, ceftriaxone treatment had been started after hospitalization and rash occurred at the end of the third day. Because no focus for fever could be found with the investigations performed, the patient was referred to our hospital. In his medical history, he was on medication for arterial hypertension. On the admission, the patient had malaise and extensive muscle pain, cough, nausea, and vomiting. On physical examination, his temperature was 39°C and his blood pressure was 160/100 mmHg. He had extensive erythema on the back and anterior chest wall which blanched when pressed upon, and eruptions on the extremities which showed dermographism which were more prominent on the arms. The muscles in the arms and legs were tender with palpation. Laboratory tests were as follows: Hemoglobin: 14.3 gr/dl, WBC: 10 600/mm³, Platelets: 12 000 000/mm³. No atypical cells were observed in the blood film. Biochemical analysis revealed: Urea: 25 mg/dl, creatinine: 1 mg/dl, aspartate aminotransferase (AST): 146 IU/L, alanine aminotransferase (ALT): 40 IU/L, total protein: 6.6 gr/dl, albumin: 3.8 gr/dl, creatinine kinase (CK): 343 IU/L, lactate dehydrogenase (LDH): 881 IU/L. Serum bilirubin levels were found to be normal. There was no electrolyte imbalance. C-reactive protein (CRP): 204 mg/L, erythrocyte sedimentation rate (ESH): 29 mm/hour, ferritin: >2000 ng/ml. Urinalysis revealed hemoglobinuria (3+) and erythrocyturia. Thyroid function tests were within the normal limits. There was no consolidation on chest X-ray. On abdominal ultrasonography, a grade II increase in hepatic echogenicity (hepatosteatosis) and ectasis in the upper calix of the left kidney was observed. Blood, urine and bone marrow cultures were negative. Rheumatology consultation was requested considering adult Still’s disease (ASD). However, it was stated earlier that diagnosis of ASD and other viral diseases should be excluded. Rheumatoid factor, antinuclear antibody (ANA), anti-dsDNA, c-ANCA and p-ANCA were found to be negative. On the fifth day of hospitalization, the following laboratory tests were obtained: WBC: 15 000/mm³, plt: 44 000/mm³, CK: 1713 IU/L, AST: 363 IU/L, ALT: 62 IU/L, LDH: 3282 IU/L, ESR: 43 mm/h. PCR for Crimean Congo hemorrhagic fever (CCHF) and MAT (microagglutination test) for leptospira were investigated, and found to be negative. No finding in favor of vegetation was found on transthoracic echocardiogram performed in terms of infective endocarditis. The patient could not tolerate transesophageal echocardiography. Bone marrow aspiration and biopsy revealed no atypical findings. Bone marrow tuberculosis PCR was found to be negative. ELISA tests performed for Ebstein Barr Virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV), human immunodeficiency virus (HIV), rubella, measles and toxoplasma were found to be negative. Brucella tube agglutination tests which were performed for two times with an interval of one week found to be negative. Screening test for syphilis was negative. Anti HAV IgG and anti-HBs were positive (it was learned from his past medical history that he had been vaccinated against hepatitis B) and anti-HCV was found negative. Mantoux tuberculin skin test was anergic. Chest tomography showed infiltrates in the basal segments of the left lung. We started levofloxacin treatment for his pneumonia owing to the fact that the patient had beta-lactam allergy which had been detected during the use of ceftriaxone. The patient still had fever, ranging between 38.0°C and 39.8°C, which responded to antipyretic medication. His eruptions persisted to the 8th day of hospitalization. Empirical doxycycline treatment was started after sending Weil-felix test considering rickettsiosis, because of rash and fever. Antibiotic treatment for pneumonia was completed to 14 days. The patient was seen by an otolaryngologist for further investigation on the focus of fever. No focus of active infection was found. Weil-felix test was found to be negative. In the follow-up, his platelet count increased to 227 000/mm³ and CRP was still high (176 mg/dl). His creatinine level increased to 1.6 mg/dL. On the 20th day of hospitalization, his fever.
persisted. The patient lost 14 kg since the beginning of the disease. In the meantime, rheumatology consultation was requested again to exclude collagenous diseases and vasculitis while planning to start treatment for tuberculosis and to go from treatment to diagnosis. A computerized tomography angiography was performed because of the suspicion of classical PAN. No pathology was found except for atherosclerotic plaques in the distal abdominal aorta which did not disrupt hemodynamics. However, the patient was diagnosed as having classical PAN because he met five of the American College of Rheumatology (ACR) criteria (weight loss, diastolic hypertension or worsening of the present diastolic hypertension, diffuse myalgia-malaise, increased blood urea nitrogen/creatinine not related with dehydration or obstruction, livedo reticularis), and almost all other causes of fever were ruled out. Intravenous pulse methylprednisolone treatment at a dose of 1 g/day for three days was started. On the second day of treatment, his body temperature was normal and did not increase again. Subsequently, 1 g intravenous pulse cyclophosphamide was administered to the patient. The treatment was continued with 1 mg/kg (maximum 60 mg) oral prednisolone. The patient’s general status improved, and his muscle weakness regressed. On the 5th day of treatment, CRP became negative. His other laboratory values were as follows: WBC: 5 300/mm³, platelets: 240 000/mm³, urea: 22 mg/dl, creatinine: 0.7 mg/dl, AST: 31 U/L, ALT: 35 U/L, CK. 22 IU/L. Monthly pulse cyclophosphamide was administered for 6 times. The dose of oral steroid was gradually tapered to 5 mg/day by the 6th month of treatment.

**DISCUSSION**

Fever of unknown origin is defined as fever higher than 38.3°C which lasts longer than three weeks, and the cause of which cannot be explained by investigations performed in hospital for one week. The most common reason of FUO is infections. The third most common reason after malignancies is inflammatory rheumatological diseases. Therefore, the etiology is generally investigated in the department of infectious diseases in cases of FUO. In recent years, infectious disease is diagnosed in a shorter time with development of radiological imaging methods and microbiological diagnostic methods (serology, blood culture systems which give results in a short time), and this leads to a relative increase in the number of patients who have an inflammatory rheumatological disease and can not be diagnosed.³

PAN is a necrotizing vasculitis which affects small and medium arteries and is seen rarely. Its incidence is 2-9/one million in Europe and USA, while it is 77/one million in the Alaska population in whom hepatitis B (HBV) virus is endemic. Although it may express itself at any age, it is more common between the ages of 40 and 60 years.² In a study conducted in France, the prevalence of PAN was reported to be 30.7/one million, most of the patients were at the age of 47.7±14.7 years, and the male/female ratio was reported to be 15/8.⁴ In terms of age and gender, our patient was in the group in which PAN occurs commonly. In the same study, it was reported that microscopic polyangiitis (MPA) and Wegener granulomatosis (WG) started at younger ages.

In the etiology of classical PAN, many factors including mainly HBV, varicella zoster virus, parvovirus B-19, CMV, EBV, hepatitis A virus, human T-cell leukemia virus, and recently HIV have been blamed. Our patient was vaccinated against hepatitis B, and had had hepatitis A before. All other causes which could be tested were excluded in our patient.

The diagnostic criteria which were published by ACR in 1990 are used in the diagnosis of PAN (Table1).⁵ Presence of at least three of these criteria is accepted as PAN with a sensitivity of 82% and a specificity of 86%. Our patient had the criteria numbers 1,2,4,6 and 7.

In cases of polyarteritis nodosa, nonspecific symptoms including fever, weight loss, malaise, muscle and joint pain and skin eruption are seen with a rate of 65-80% as initial symptoms.²,⁶ Our patient had these symptoms. Ischemic heart pain and testicular pain, renal findings including hematuria, proteinuria and hypertension and neurolog-
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...ical findings constitute the other symptoms. Skin findings including livedo reticularis, palpable purpura, ulcerations and ischemic changes in the ends of the extremities may be observed. One of the initial complaints of our patient was skin eruptions.

Renal involvement may be seen in 11-66% of the patients, but renal failure which would cause to problems is rare. Absence of significant renal failure is an important criterion in the differential diagnosis with other vasculitis syndromes. Erythrocyturia and proteinuria are present in 70% of the patients. Hypertension is observed with a rate of 21-33%, and is especially common in PAN related with HBsAg. Our patient had worsening in hypertension which was diagnosed before in addition to erythrocyturia and proteinuria. In the follow-up, creatinine level also increased. The laboratory findings which supported PAN included increased CRP and ESR, anemia, abnormal AST-ALT levels, HBs Ag positivity and increased CK. All these laboratory findings except for HBs Ag positivity were present in our patient.

Tuberculosis was also considered because of presence of fever which had been lasting for a few weeks, malaise and weight loss, though miliary pattern was not seen on lung X-ray. In our country, the most common reason of fever of unknown origin is miliary tuberculosis. At least three weeks should pass after initiation of fever for the lesions to be visualized radiologically. In these patients, tuberculosis granulomas is diagnostic. Bone marrow biopsy was given priority, since the risk of intervention was lower in the patient.

In our country, brucellosis should be definitely considered in the etiology of FUO. The tests should be repeated at certain intervals because of difficulties including long incubation periods of blood cultures, and initially negative serological tests and bone marrow culture should be done. In our patient, brucella tube agglutination tests which were repeated with an interval of one week were found to be negative, and brucellosis was also excluded with bone marrow culture.

Another important cause which should be considered in patients presenting with fever and skin eruption in whom no infectious etiology could be found is adult Still’s disease. In our patient, this diagnosis was considered primarily. However, Still’s disease is a diagnosis of exclusion, it has no specific diagnostic tests. In our patient, skin eruptions were constant and livedoid rather than being typical Still eruptions. Fever was persistent, and reduced only with antipyretic medication. When the transaminase levels were measured, it was found that increased AST was in the forefront and this indicated muscle destruction rather than liver damage. Our patient never had arthritis picture. It is known that increased ferritin and WBC are non-specific markers of inflammation and may be observed in any inflammatory and infectious condition. Therefore, they are not sufficient for the diagnosis of Still’s disease.

The recommendation of PAN European vasculitis study group is a combination treatment glucocorticoids and cyclophosphamide. While glucocorticoids are given at a maximum dose of 1 mg/kg (maximum 60 mg/day) as oral prednisolone, cyclophosphamide may be administered orally at a dose of 2 mg/kg/day (maximum 1.2 g/month) or at a dose of 15 mg/kg as monthly intravenous administration. We treated our patient according to

<table>
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<th>TABLE 1: American College of Rheumatology 1990 polyarteritis nodosa diagnostic criteria.</th>
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<td>1  Weight loss of more than 4 kg which is not related with diet or other factors from the beginning of the disease.</td>
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<td>2  Livedo reticularis.</td>
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<td>3  Testicle pain or tenderness</td>
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<td>4  Muscle pain, pain and weakness in the muscles of the legs</td>
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<td>5  Mono- or polyneuropathy</td>
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<td>6  Diastolic blood pressure &gt; 90 mmHg</td>
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<td>7  Increase in blood urea or creatinine level which is not related with dehydration or obstruction</td>
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<td>8  Presence of Hepatitis B surface antigen or antibody</td>
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<td>9  Abnormal celiac or renal angiography</td>
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<td>10 Findings including polymorphonuclear leukocytes in the medium-small arteries on tissue biopsy.</td>
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the recommendation of the European vasculitis study group.

In conclusion, this case was presented to remind classical PAN as a rare cause among the etiologies of fever of unknown origin. Cases of PAN can manifest with non-specific signs and symptoms. Especially extensive myalgia and fever can easily be confused with a viral infection. According to the ACR diagnostic criteria, tissue biopsy or organ damage is not imperative for a diagnosis of PAN. It should be kept in mind that especially vasculitis may have a role in the etiology of fever, and weight loss in patients in whom a diagnosis can not be made as a result of detailed investigations for the etiology of fever.

REFERENCES


