CASE REPORT

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A Common But Usually Overlooked Cause of Fever of Unknown Origin: Still's Disease

Nedeni Bilinmeyen Ateşin Sık Fakat Genellikle Gözden Kaçan Bir Nedeni: Still Hastalığı

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Abstract

A wide variety of causes, ranging from bacterial or viral infections to malignancies, may be responsible from the development of fever of unknown origin (FUO). However, rheumatologic disorders are usually overlooked in the differential diagnosis of FUO. The diagnosis of adult Still's disease depends on the exclusion of other possible causes, which is the main challenge. In this case report, we present a twenty-three-year-old male patient who was followed up with FUO and diagnosed with Still's disease.

Keywords: Arthritis, fever of unknown origin, Still's disease

Öz

Bakteriyel ve viral enfeksiyonlardan malignitelere varan birçok farklı faktör, nedeni bilinmeyen ateş gelişiminden (NBA) sorumlu olabilmektedir. NBA ayırıcı tanısında romatolojik hastalıklar genellikle gözden kaçırılmaktadır. Still hastalığı tanısında ana zorluk diğer hastalıkların dışlanmasıyla konulmasıdır. Bu olgu sunumunda yirmi üç yaşında, NBA ile takip edilip Still hastalığı tanısı konan bir olguyu sunmaktayız.

Anahtar kelimeler: Artrit, nedeni bilinmeyen ateş, Still hastalığı

Introduction

Fever of unknown origin (FUO was first defined by Petersdorf and Beeson (1), as fever higher than 38.3 °C on at least 3 occasions over a period of three weeks with one week of hospitalization. The term ''unknown'' is used to emphasize the difficulty in diagnosing the underlying disease. The disorder is not uncommon in internal medicine practice with an incidence of 3% of all hospital admissions and it is associated with a mortality rate of 12-35% (2).

More than 200 causes of FUO, which can be divided into 4 main categories as infections, malignancies, non-infectious inflammatory disease, and extremely rare causes, have been identified (3). Non-infectious inflammatory diseases include autoimmune and rheumatic diseases such as vasculitis, granulomatous disease and arthritis. Infections with atypic viral and bacterial agents such as parvovirus, herpesvirus, tuberculosis, toxoplasmosis, and yerisinosis may mimic the symptoms and signs of Still's disease. Moreover, cancers like lymphoid tumors or kidney and colon cancers as well as rare disorders, namely Castleman disease or Kikuchi-Fujimoto disease, may complicate the diagnosis (4). On the other hand, despite the improvements in the laboratory and radiologic techniques, a remarkable proportion of cases (10-50%) remains undiagnosed, even that some patients may undergone to surgery (5).

The main presenting feature of Still's disease is polyarthritis accompanied by fever and macular rash, which was defined by Still (6). However, patients may be admitted with a

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variety of different symptoms. Because the symptoms may mimic many infectious and rheumatologic diseases, the diagnosis may usually take weeks.

Here, we present a case of Still's disease in a young male who presented with FUO.

Case Report

A 23-year-old male with chronic hepatitis B was admitted with polyarthritis, fever, and sore throat. He had no history of chronic drug use, smoking or addiction. His polymerase chain reaction for severe acute respiratory syndrome-coronavirus-2 was negative in two occasions. On physical examination, no abnormal medical finding including lymphadenopathy, skin rash or icterus was observed. He was hospitalized to the internal medicine inpatient service.

His blood, urine and pharyngeal cultures were received at the time whenever fever exceeded 38 °C. During his follow-ups, migratory swelling in the upper and lower extremity joints was observed. His laboratory examination including TORCH panel, VDRL and TPHA for syphilis, thick-drop smear for plasmodium, brucella agglutination and PPD for tuberculosis on two occasions were negative. Except elevated serum ferritin (1614 ng/mL; normal range: 30-400 ng/mL), C-reactive protein (CRP) (241 mg/L; normal range: 0-5 mg/L) and sedimentation rate (64 mm; normal range: 0-20 mm), all biochemical, hormonal and hemogram parameters were within normal range. Furthermore, autoantibodies such as anti-nuclear antibody, anti-ds DNA, anti-CCP and also c-ANCA and p-ANCA were negative.

On ultrasonographic examination, there were two reactive right supraclavicular lymphadenopathies that were approximately 1.5x5 mm each, and hepatomegaly (160 mm) and splenomegaly (125 mm). Echocardiographic, thyroid ultrasonographic and carotid and vertebral artery Doppler ultrasonographic examinations of the patient were uneventful. Positron emission tomography-computed tomography examination performed to investigate an occult malignancy was also normal.

As his bone marrow examination and acid-resistant bacteria examination of bone marrow were found negative, he was consulted to rheumatology department. After excluding other causes of arthritis by the observation of clinical course and involvement of joints and because the autoantibodies, which are the markers of vasculitis and the other rheumatologic causes of arthritis, were negative, he was diagnosed with Still's disease. Because he had chronic hepatitis B, steroid replacement accompanied by antiviral therapy with lamivudin 100 mg/day was initiated. Subsequent to the resolution of his symptoms including fever and arthralgia and improvement in laboratory parameters such as ferritin, CRP and sedimentation rate, he was discharged with the recommendation of rheumatology outpatient visits.

Discussion

Diagnostic workup of FUO should contain the investigation of medical history, detailed physical examination and laboratory analysis including aerobic and anaerobic blood cultures. Classifying the causes into infections, malignancies, inflammatory disorders and miscellaneous causes may help to diminish the number of probable conditions. However, a remarkable proportion of the cases still remains undiagnosed. While the percentage of unresolved cases was 7% in 1961, it accounted slightly more than half of the cases in 2007 (6).

The essential presenting symptom of Still's disease is fever, which usually varies between 38'' and 40'' °C and spikes generally in the afternoon and evening, followed by resolution in the other times of the day. Sore throat is another common symptom in the early course of the disorder. However, physicians frequently fail to culture a specific pathogen, unless an overlapping bacterial infection occurs. Rash is another manifestation of the disease which usually accompanies to fever, and may disappear after the resolution of the fever. Mild arthralgia may persist for weeks and well-responds to anti-inflammatory drugs or corticosteroids. Splenomegaly may be observed between 15% and 60% of all patients (7). Other less common symptoms may range from pleuritis and myocarditis to nervous system involvement and psychiatric problems. The presenting case exhibited no radiologic or echocardiographic sign of respiratory or cardiovascular involvement.

Despite the attempts to establish a diagnosis, there is no clear and standardized laboratory test to distinguish Still's disease from other possible causes of FUO. Because Still's disease is a type of rheumatoid arthritis, patients may require synovial fluid examination which shows inflammatory synovitis (8). The arthritis may affect any joint, but most common sites are knees and wrists. Anemia and high sedimentation rate are observed during the active disease.

Early administration of steroids is not recommended due to the fact that it may camouflage signs and symptoms and may cause delay in the diagnosis as well as may complicate

the progress of the situation (9). Steroid replacement is a kind of diagnostic challenge in the differential diagnosis, especially when it indicates the probability of a rheumatologic disorder. Similarly, as the possibility of an infection was unlikely and the risk of hepatitis flare was decreased by concomitant use of antiviral therapy, our patient received steroid administration that immediately provided resolution in the symptoms.

Prognosis of Still's disease is usually well, with minor complications. Vast majority of the patients remain clinically inactive, but a negligible proportion may suffer from recurrent arthritis requiring short-term corticosteroid administration (10). However, physicians should be aware of the development of amyloidosis, which is manifested with unexplained anemia, persistent proteinuria and splenomegaly. Diagnosis of amyloidosis can be confirmed by histopathologic examination of rectal or renal biopsy (11).

In conclusion, Still's disease is a common but generally overlooked cause of FUO. Although there are published algorithms for solving FUO cases, it is reasonable to individualize the diagnostic approaches according to manifestations. With regard to Still's disease, fever, arthritis and cutaneous rash are the most common presenting symptoms. At the onset of disease, arthritis may not be evident, which may cause a delay in the diagnosis. However, because a number of disorders varying from viral infections to malignancies may mimic Still's disease, physicians should consider Still's disease in patients admitted with FUO and arthritis after excluding all other possible diagnoses.

Ethics

Informed Consent: Written informed consent received from the patient.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Follow-up of the Case: C.V., İ.S., S.Ö., Z.K., E.A., Literature Search: C.V., A.E.A., S.Ö., Z.K., E.A., Writing: C.V., A.E.A., İ.S., Z.K., Manuscript Review and Revisation: S.Ö., İ.S., E.A., A.E.A.

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