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CASE REPORT

A rare cause of fever of unknown origin : Autoimmune hepatitis

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Abstract

Fever of unknown origin is difficult to diagnose, and it is seen in the course of infection, malignancy, inflammatory diseases and many other diseases. In this report, a case who presented with fever of unknown origin and was diagnosed with autoimmune hepatitis progressed to acute liver failure is presented. Our case showed a rapid and progressive clinical course, and liver biopsy performed in the early period was useful in the diagnosis. However, mortality developed on the fifteenth day of follow up.

Keywords: Biopsy; fever of unknown origin; autoimmune hepatitis

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Introduction

Fever of unknown origin (FUO) is one of the challenging conditions in terms of diagnosis in infectious diseases practice. It was first defined by Petersdorf and Beeson, and various changes were made in the definition afterwards [1,2]. The classical definition of FUO includes cases with fever above 38.3°C with multiple measurements for more than three weeks and cases in which the diagnosis could not be made despite one week of hospitalization. The etiology of FUO is classified as infections, malignancies, non-infectious inflammatory diseases, miscelleneous diseases and undiagnosed cases.

Autoimmune hepatitis is a chronic liver disease that develops with immune mechanisms and is characterized by elevated transaminases, autoantibody positivity and interface hepatitis on histopathological examination of the liver [3]. Although the etiology of the disease is unknown, genetic and environmental factors are thought to play a role. It is more common in women. The incidence of the disease peaks in two periods, the first between the ages of 10-20 and the second between the ages of 45-70. The clinical course ranges from asymptomatic disease to cirrhosis and fulminant hepatitis.

In this report, a case who presented with FUO and was evaluated as autoimmune hepatitis after liver failure is presented.

Case

A 61-year-old woman with no known disease presented with nausea and fever for two months. On admission, the temperature was 39°C and other vital signs were stable. System examination revealed no pathologic findings. Blood tests showed, white blood cell (WBC): 4050/mm^3, haemoglobin (Hgb): 7.2g/dL, platelets: 354000/mm^3, creatinine: 1.56mg/dL, aspartate transaminase (AST): 368u/L, alanine transaminase (ALT): 174u/L, total bilirubin: 0.66mg/dL, direct bilirubin: 0.45mg/dL, lactate dehydrogenaz (LDH): 429u/L, c reactive protein (CRP): 356mg/L, procalcitonin: 5.34ng/mL. Thoracic computed tomography(CT) was normal. Abdominal CT showed a 30 mm cystic lesion in the liver and increased wall thickness in the rectum. The patient was hospitalized with a preliminary of FUO. Blood and urine cultures were obtained. Empirical ceftriaxone treatment and supportive therapies were started. Transthoracic echocardiography showed no evidence of infective endocarditis. Anti nuclear antibody (ANA), anti mitochondrial antibody (AMA), anti double stranded DNA (dsDNA), anti liver kidney microsomal antibody (LKM), anti smooth muscle antibody (ASMA), c-anti-neutrophil cytoplasmic antibody (c-ANCA), p-anti-neutrophil cytoplasmic antibody (p-ANCA), anti Sm antibody, anti cyclic citrullinated peptide (anti-CCP), anti Jo-1, anti SSA, anti SSB, anti Scl-70 were negative. Tests for HBV, HCV, HAV, CMV, EBV, HSV, *Toxoplasma, Borrelia, Brucella*, Syphilis and Hydatid cyst were negative. Magnetic resonance imaging (MRI) of the abdomen showed heterogeneous signal in the liver, contour lobulation, simple cyst in segment 2, enlargement of periportal distances, complete diffusion restriction in the liver in diffusion-weighted series, and heterogeneous contrast enhancement in the arterial phase. The findings were interpreted as fulminant hepatitis secondary to infective or systemic disease. On the seventh day of follow-up, blood tests revealed WBC: 4070/mm^3, Hgb: 8.6g/dL, platelet: 83000/mm^3, creatinine: 0.45mg/dL, urea: 20mg/dL, AST: 308u/L, ALT: 79u/L, total bilirubin: 5.92mg/dL, direct bilirubin: 5.08mg/dL, albumin: 24.1g/dL, LDH: 503u/L, CRP: 251mg/L, international normalized ratio (INR): 1.58. Our case had a score of 14 according to the International Autoimmune Hepatitis Group (IAIHG) criteria and was in the probable case group (>15 definite cases). On the eighth day of hospitalization, liver biopsy was decided and the procedure was performed. Elective colonoscopy was decided after gastroenterology consultation for increased rectal wall thickness detected on imaging at admission, but this procedure could not be performed due to progressive deterioration of the patient. *Staphylococcus lugdunensis* was grown in

the blood culture, ceftriaxone was discontinued and piperacillin-tazobactam and vancomycin treatments were started. Echocardiography was planned for infective endocarditis. Echocardiography did not reveal any findings for endocarditis. AST, ALT and bilirubin levels continued to progressively increase. On the tenth day of follow-up, fever persisted, speech disorder and altered consciousness developed. Cranial imaging (CT and MRI) revealed no acute pathology. Bilirubins, INR and ammonia levels were elevated and platelet count was decreased. Acute liver failure and hepatic encephalopathy were considered in the patient, she was admitted to intensive care unit and planned to transfer to a center that can perform liver transplantation.The results of the tests related to liver function during the follow-up of the patient are shown in Table-1. On the 14th day of follow-up, the patient was intubated and had active bleeding. On the same day, the histopathology results of the liver biopsy, which had been previously examined, showed plasma cells in the immunohistochemical study with CD138, lymphoplasmacytic cell infiltration, interface hepatitis, biliary duct destruction and ductular reaction (Figure 1). These findings were interpreted in favor of autoimmune hepatitis by the pathology physician. On the 15th day of hospitalization, despite all interventions, patient died.

Discussion

While the frequency of infections has decreased in the etiology of FUO over the years, inflammatory diseases and various other causes have increased [4]. Despite advanced and up-to-date diagnostic methods, FUO still poses a challenging situation for clinicians in terms of diagnosis. It is a recommended approach to re-evaluate the patients every day with anamnesis, physical examination and from time to time by different doctors from different perspectives. There is no guideline for the diagnostic procedures that should be performed in patients with FUO. In the literature, studies on FUO mostly consist of case series. In a recently published case series including 214 FUO cases from Turkey, infections were reported 44.9%, malignancies 15.4%, inflammatory diseases 11.7%, other causes with a rate of 8.4% and the undiagnosed group with a rate of 19.6% [5].

Imaging techniques such as CT, MRI,scintigraphic imaging and positron emission tomography as well as invasive diagnostic tests such as liver biopsy, bone marrow biopsy, laparoscopy and laparotomy may be required for diagnosis. In the follow-up of patients, invasive procedures should be performed without delay when necessary while diagnostic procedures are being performed. It should be kept in mind that postponement of invasive procedures may result in delayed diagnosis and poor prognosis. In our case, liver biopsy was performed on the eighth day of hospitalization due to progressive liver failure and clinical deterioration.

There are studies reporting a 14-17% contribution of liver biopsy to the diagnosis in cases of fever of unknown cause [6,7]. Especially in autoimmune hepatitis with acute and fulminant course as in our case, autoantibodies can be found negative in 29-39% and immunoglobulin G level in 25-39% [8]. In another study, autoantibody negativity was found to be 29% in cases with fulminant course [9]. The importance of early diagnostic biopsy for the diagnosis of autoimmune hepatitis in cases with acute and fulminant course has been emphasised in the literatüre [10,11]. Our case had an acute and fulminant course. Considering that autoantibody and immunoglobulin G levels may be negative in cases with fulminant course, the importance of liver biopsy is obvious. Liver biopsy is generally a safe procedure and complications and procedure-related death are extremely rare. Considering the benefit provided by the examination, these minimal risks have been reported to be negligible [4]. In a study of 43 cases investigating the effect of liver biopsy on diagnosis in cases of FUO, patients were divided into three groups as group 1: liver biopsy was abnormal and helpful in diagnosis and treatment, group 2: liver biopsy was abnormal but not valuable for diagnosis and treatment, group 3: liver biopsy was normal.

6 (13.9%) patients in group 1, 11 (25.6%) patients in group 2 and 26 (60.5%) patients in group 3 were observed [6]. Hepatomegaly was statistically more common in group 1, which was the diagnostic group, and abnormal values in liver function tests were found more frequently in this group, emphasizing that liver biopsy may be diagnostic in a limited patient group [6].

Autoimmune hepatitis may present with various clinical forms ranging from asymptomatic to fulminant hepatitis. Autoimmune hepatitis patients present to the clinic with acute hepatitis with a rate of 10-25% [3]. It is difficult to differentiate this condition from acute hepatitis due to other causes. This acute clinical condition in the course of autoimmune hepatitis may be observed with two different mechanisms. The first is acute reactivation of undiagnosed subclinical autoimmune hepatitis and the second is acute hepatitis without chronic histologic changes [3]. Rarely, acute liver failure may occur in some of these cases as seen in our case. To prevent poor prognosis in this form of the disease, the diagnosis of autoimmune hepatitis should be kept in mind and necessary immunosuppressive treatment should be started after rapid diagnostic tests. In our case, although the necessary tests were performed for the diagnosis of the patient, mortality developed just before the initiation of treatment due to the acute and progressive course of the disease.

Conclusion

Autoimmune hepatitis should be kept in mind as a rare cause in the etiology of FUO. Considering that the mortality rate increases with delay in diagnosis, it should be kept in mind that performing the necessary diagnostic tests without delay will contribute to the diagnosis and prognosis. As in our case, especially in FUO patients with liver failure, it is important to perform liver biopsy for diagnostic purposes in the early period without losing time, taking into account the cost-benefit ratio.

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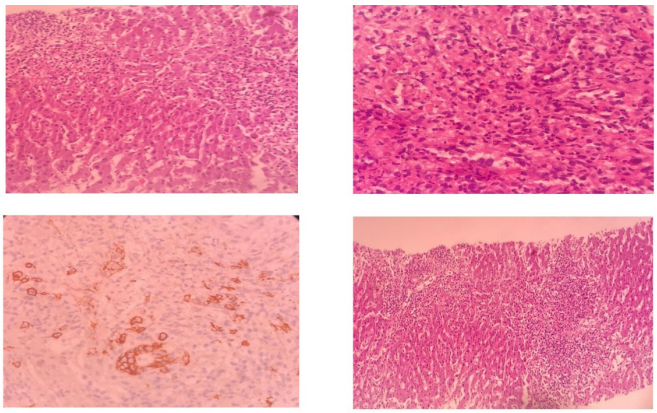

Figure 1: Plasma cells in the immunohistochemical study with CD138, lymphoplasmacytic cell infiltration, interface hepatitis, biliary duct destruction and ductular reaction

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