

Toxoplasmic Hepatitis in an Immunocompetent Patient

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SUMMARY: Acquired toxoplasmosis is more frequently an unrecognized disease. Immunocompetent adults and adolescents with primary infection are generally asymptomatic, or symptoms observed may include malaise, fever, and lymphadenopathy. In contrast, immunocompromized patients may experience severe manifestation including encephalitis and multi system organ failure. We report a case of toxoplasmic hepatitis presenting with hepatomegaly in an immunocompetent patient.

Key Words: Toxoplasmic hepatitis, hepatomegaly, histopathologic and serologic diagnosis

Bağışıklık Sistemi Normal Bir Hastada Toksoplasmik Hepatit

ÖZET: Edinsel toxoplasmosis sıklıkla tanı konulamayan bir hastalıktır. Primer enfeksiyonu olan bağışıklık sistemi normal erişkin ve gençlerde enfeksiyon genellikle asemptomatiktir ya da halsizlik, ateş ve lenfadenopati gibi belirtiler görülebilir. Bunun aksine, bağışıklık sistemi baskılanmış hastalarda ensefalit ve pek çok organda şiddetli harabiyet görülebilmektedir. Bu olgud sunumunda, bağışıklık sistemi normal bir hastada hepatomegali ile seyreden toxoplasmik hepatit tanımlanmıştır.

Anahtar Sözcükler: Toksoplasmik hepatit, hepatomegali, histopatolojik ve serolojik tanı

GİRİŞ

Toxoplasma gondii is the most common cause of protozoan infections in humans that infects 35-40% of the adult population in the world and demonstrates various clinical manifestations. It is possible for tissue parasitism to emerge without any signs of symptoms during the proliferative phase in man. It may lead to a transient disease characterized by lymphadenopathy, fever and fatigue, or a really severe disease. Severe manifestations of the disease most commonly occur in patients with impaired immunity (4, 9, 10). The clinical spectrum of *Toxoplasma gondii* infection ranges from no symptoms to a syndrome of fever and lymphadenopathy and diffuse multi system organ involvement. The disease's picture may simulate infectious mononucleosis, with chills, fever, headache, myalgia, lymphadenitis, and extreme fatigue. A chronic toxoplasmic lymphadenitis has been described. Infection may be severe on rare occasions accompanied by a maculopapular rash apart from the above mentioned symptoms, and occasionally hepatitis, encephalomyelitis, or myocarditis can be seen (4, 17). Lymphadenopathy occurs in 10% to 20% of acute cases and may be accompanied by

constitutional symptoms. The differential diagnosis is broad, considering the diverse presentation. Ingestion of the agent by non-feline host leads to formation of tachyzoites and further dissemination with the formation of cysts in skeletal muscle and central nervous system (CNS). In many different tissues, especially lung, heart, lymphoid organs, and the cells of CNS, parasites may be present. Multiplication of the parasites within an infected cell usually leads to death and rupture of the cell, releasing the parasites to spread the infection to new cells, or it may lead to formation of a cyst (4, 5).

Primary infection may be promoted by immunosuppression. Reactivation of toxoplasmosis is also seen in medically immunosuppressed or otherwise compromised hosts. Most of the remainder had some type of malignancy, collagen vascular diseases and organ transplants.

Acute *Toxoplasma gondii* infection causes different clinical course in 10-20% of cases. In immunocompetent patients, most often toxoplasmosis presents as a symptomatic cervical lymphadenopathy (2, 3, 13, 15, 16). However, pneumonitis, myocarditis, myositis can occur from time to time. Rarely, hepatitis has been reported in immunocompetent and immunodeficient patients (2, 3, 13-15, 17, 19).

Here, we reported a case of hepatitis due to *Toxoplasma gondii*.

CASE REPORT

A 61 years old female patient presented with a 5-6 weeks history of lost of appetite, lack of energy and abdominal pain on right hypocondrium. Our patient who had been suffering from diabetes mellitus for ten years, was treated with insulin. There were no history of alcohol addiction, blood transfusion or another drug use.

Physical examination revealed the following: temperature, 37.3°C, blood pressure 140/80 mmHg, pulse 86 bpm. Pulmonary and cardiac examinations were normal. Abdominal examination revealed tender and rounded edged liver of 7 cm span in the right mid-clavicular line. Lymphadenopathy was not observed. The results obtained from her laboratory examination were like the following: Hb: 12gr/dl, white blood count: 9800/mm (in microscopic examination: 6% atypical lymphocyte was observed), platelet count: 240000/mm³, sedimentation rate: 70 mm/h, glucose: 160mg/dl, aspartate transaminase (AST): 90 U/L, alanine transaminase (ALT): 110 U/L (normal 0-41 U/L), alkaline phosphatase (ALP): 495 U/L (normal 98-270 U/L), gamma glutamyl transpeptidase (GGT): 190 U/L (normal 8-50 U/L), cholesterol: 260 mg/dl, trigliseride: 225 mg/dl, total serum protein: 6.7 g/dl, albumin: 2.9 g/dl. Electrolytes, blood urea nitrogen, creatinine, calcium phosphate and bilirubine were within normal limits. In abdominal ultrasonography, hepatomegaly was present. Steatosis and dilatation of biliary canals and lymphadenopathy were not observed. Serologic studies for hepatitis B, hepatitis C, Human Immunodeficiency Virus, Cytomegalovirus and Epstein-Barr Virus and Brucella were negative. Antinuclear antibody and antimitocondrial antibody were negative. Anti toxo IgM Enzyme Immuno Assay (ELISA) was negative (cut off: 0.403, patient sample; 0.245), anti toxo IgG ELISA was positive (cut off: 0.380, patient sample; 0.964) (Toxonostica IgM and IgG micro ELISA system, 80343 Organon Technica). Her chest X-ray and electrocardiography were normal.

Liver biopsy was performed for the purpose of diagnosis. Microscopic examination of liver biopsy revealed features of mild to moderate hepatocellular injury. Liver cell plates were irregular because of cell swelling and loss. Also, there were small foci of necrosis. Glycogenated nuclei were observed in some hepatocytes. Kupffer cells were prominent and mild infiltrate of lymphocytes were seen in sinusoid. Mild infiltrate of mononuclear cells that were not associated with piece meal necrosis were observed in portal tracts. The high power microscopic examination revealed *Toxoplasma gondii* tachyzoites both in the liver cells and sinusoids. (Fig 1-2) Immunohistochemical staining by toxoplasma antibody (monoclonal, prediluted; NeoMarkers, San Fransisco, CA, USA) without dilution also confirmed histopathological diagnosis. Because of histopathological findings, *Toxoplasma gondii* serological tests were repeated after 8 days. Anti toxo IgM ELISA titer was negative (Cut off: 0.402, patient sample; 0.398), anti toxo IgG ELISA titer was positive (Cut off: 0.342, patient sample; 1.457). Serum IgA ELISA titer was positive (Cut off: 0.336, patient sample; 1.1 capture units) (Cat.code 4022, Version:TOXA003; Meddens Diagnostics B.V). Avidity of toxoplasma specific IgG was low avidity (*Toxoplasma gondii* IgG Avidity EIA test, Cat.K1TGA Radim). The lymphocyte CD4 to CD8 ratio was in normal range, and in ocular examination toxoplasmic chorioretinitis was not observed. As a result, the patient was diagnosed as having acute toxoplasmic hepatitis.

DISCUSSION

Toxoplasmic hepatitis is rarely reported in immunocompetent patients, but the use of immunosuppressive therapy and the increasing incidence of acquired immunodeficiency syndrome in some parts of the world may increase the frequency. In a previous study, Kabukcuoglu *et al.* had shown histopathologic features of *Toxoplasma gondii* infection in different organs taken by biopsy or autopsy of 19 cases without immunosup-

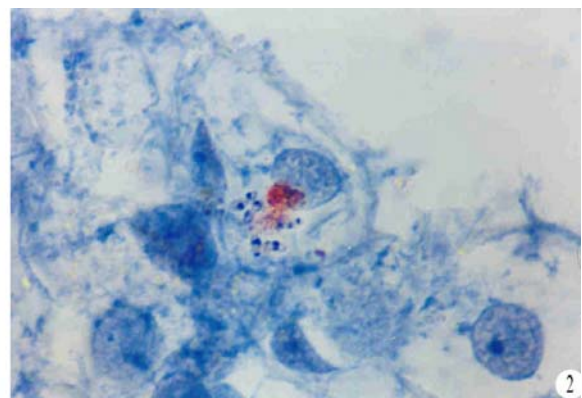
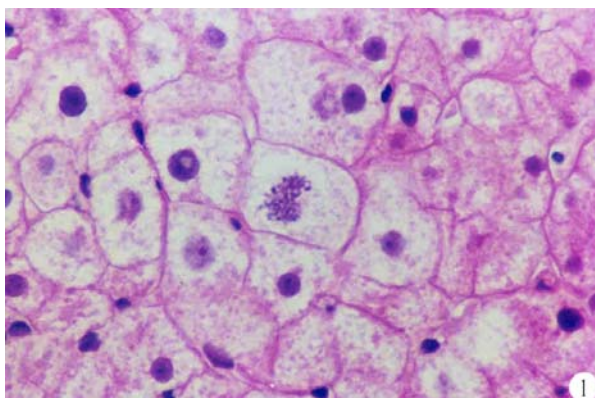


Figure 1. *Toxoplasma gondii* tachyzoites seen in hepatocyte stained by Haematoxylin eosine (X800); **2.** *Toxoplasma gondii* tachyzoites seen in hepatocyte stained by toxoplasma specific immunohistochemical stain (X2000)

ression which were prospectively investigated between 1999-2001. Serologic studies were performed with specific *Toxoplasma gondii* antibodies including IgG, IgM, IgA, Avidity by ELISA. In this study, correlation between histopathologic diagnosis and serologic tests were studied (1, 11). This is a case report of one patient with acute toxoplasmic hepatitis seen in this study in Departments of Pathology and Microbiology of Eskisehir Osmangazi University Hospital.

Tutkun *et al.* described the clinical characteristics of active ocular toxoplasmosis in a large population of Turkish patients. In this retrospective study, 109 consecutive patients with active ocular toxoplasmosis were seen at Department of Ophthalmology in Istanbul University Faculty of Medicine, from 1995 to 2005. All patients had positive serum anti-*Toxoplasma* IgG antibodies, but negative IgM antibodies. Preexisting retinochoroidal scars were found in 90 (83%) patients. The most common accompanying signs were vitritis (100%), anterior uveitis (49.5%), and periphlebitis (33%). All patients received antiparasitic treatment. Systemic corticosteroids were used in 86% of the patients (18). A study of Zhu *et al.* showed that the prevalence of antibodies against *Toxoplasma gondii* in psychotic patients was much higher than in normal persons in different areas in China; and the difference was statistically significant (20).

Toxoplasma gondii should be considered in the differential diagnosis of hepatitis when the aetiology is not clear. Diagnosis can be achieved through liver biopsy. In the differential diagnosis of this patient with non-specific symptoms and high levels of amino transferases and alkaline phosphatase, viral hepatitis, hepatic granulomas, intrahepatic cholestasis and space occupying lesions of liver were considered. However, in our patient there was no evidence of drug-induced, viral, bacterial or autoimmune aetiology.

Toxoplasmic hepatitis is rare and usually a primary manifestation of acute, acquired toxoplasmosis without adenopathy (19). None of the signs or symptoms from involvement of liver is specific for infection with *Toxoplasma gondii*. Our patient presented with a disease simulating the flu, with her liver involved and having no lymphadenopathy. Diagnosis is usually made by various serologic procedures, and histological microscopic examination of tissue impression smears is very helpful (3, 4, 6, 9, 14). Serologic tests for detection of IgG and IgM antibodies are used for initial investigation of acute acquired toxoplasmosis in the immunocompetent patients. The presence of *Toxoplasma gondii* specific IgM is the hallmark of a recently acquired infection (4, 9, 10). Commercial kits for detection of *Toxoplasma gondii* IgM antibodies are being increasingly used. However, false positive and false negative results have been reported by using these kits for parasite-specific IgM detection. The main reason for false-negative result is being saturation of IgM binding sites by IgG antibodies. In order to

avoid this problem, additional serologic test are required for sufficient accuracy (4, 6, 7). Therefore, in our patient, IgA and avidity of IgG antibodies were performed. IgA antibodies and low avidity antibodies indicate recent infections (4). Consequently, clinical, histopathologic and serologic results were correlated with acute acquired toxoplasmosis infection.

Histology of toxoplasmic infection varies with the infected organs. Characteristic histologic criteria alone are probably sufficient to establish the diagnosis of toxoplasmic lymphadenitis.

It is difficult to demonstrate parasites on biopsy specimens, and while some authorities believe that histologic appearance is very characteristic, some others consider histologic changes to be non-specific. Although, many individuals have been exposed to *Toxoplasma gondii* and may have cysts within the tissues, recovery of organisms from tissue culture or animal inoculation may be misleading, since the organisms may be isolated but may not be the aetiological agent of disease. For this reason, serologic tests are often recommended as the diagnostic approach of choice (4). Hepatic histopathology is not specific to toxoplasma infection. In previous studies, swelling of cells, focal hepatocellular necrosis, mononuclear infiltration in sinusoids and portal areas, and granulomas have been described (3, 9, 11, 14, 17, 19). In our patient, liver histology revealed cell swelling, focal necrosis and mild infiltrate of mononuclear cells and parasites both in hepatocytes and sinusoids even by hematoxylen-eosin staining. Demonstration of tachyzoites in tissue sections establishes diagnosis of acute toxoplasmosis. Although it is difficult to see the tachyzoite with ordinary stains, immunohistochemical staining technique has been successful (6, 14, 17).

Immunity is crucial for controlling acute infection with *Toxoplasma gondii* (17, 19). Our patient's lymphocyte CD4 to CD8 ratio was within the normal range, showing no functional loss in the cellular immune system. Acute toxoplasma infection is usually self-limited in the patients with no cellular immunodeficiency and there is no need for treatment unless the hepatitis continues to progress after several weeks (17, 19). Therefore, the patient was discharged from the hospital without treatment. She did not come up for further examination because she felt good. Two months later, a local practitioner in her town informed us that her liver function tests were normal. For this reason, we could not repeat her serologic tests.

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