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Severe toxoplastic hepatitis in an immunocompetent patient

Running title: Toxoplastic hepatitis

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Abstract

Acute *Toxoplasma gondii* infection causes different clinical courses in 10-20% of cases. In immunocompetent patients, toxoplasmosis most often presents as asymptomatic cervical lymphadenopathy. Clinical manifestations such as pneumonia, myocarditis, hepatitis and encephalitis are rarely reported. We present an immunocompetent patient with toxoplasmic hepatitis of serious complicated clinical course in whom maculopapular rash was present. Diagnosis was confirmed by serology, and presence of bradyzoites in liver biopsy.

Toxoplasmosis is caused by infection with the obligate intracellular parasite *Toxoplasma gondii*. Primary infection is usually subclinical but in some patients cervical lymphadenopathy or ocular disease can be present. Infection acquired during pregnancy may cause severe damage to the fetus (1). Some patients develop severe symptoms, including high fever (39–40°C), myalgias, arthralgias, fatigue, dry cough, dyspnoea, generalised lymphadenopathy, hepatosplenomegaly and maculopapular rash (2). Clinical manifestations such as pneumonia, myocarditis, hepatitis and encephalitis are rarely reported (3).

On the contrary, toxoplasmosis can also be fatal in immunodeficiency or immunocompromised patients. Immunocompromised hosts often experience a life-threatening involvement of one or more organs during primary infections or can suffer reactivation of pre-existing tissue cysts, due to deficiency of the immune system (3). We here wish to inform on a case of toxoplasmic hepatitis in an immunocompetent female thereby implicating that awareness of the etiology needs to be kept in mind in severe unclear conditions in spite of a presumed relative rarity.

A female patient of 46 years admitted with the complaints of fever, nausea, vomiting, fatigue, loss of appetite and myalgias for 2 days. She revealed eating raw meat since her
childhood. She used paracetamol for high fever. Physical examination showed as fever 39.5 °C, pulse 102/min, blood pressure 120/70 mmHg. There were no neck stiffness and abnormalities on auscultation of respiration and heart. There was no adenopathy. Disseminated maculopapular rashes, hepatomegaly and pain on the right upper abdominal quadrant with palpation were noted. Laboratory analysis showed hemoglobin (Hb): 13.4 g/d, hematocrit: 41.1%, platelet count (Plt): 218x10^3/µL, white blood count (Wbc): 13.94x10^3/µL (granulocytes 36%, lymphocytes 40%, eosinophiles 16%), aspartate transaminase (AST): 633 U/L (normal: 0-38 U/L), alanine transaminase (ALT): 698 U/L (normal: 0-49 U/L), alcaline phosphatase: 260 U/L (normal: 45-129 U/L), lactate dehydrogenase: 848 U/L (normal: 120-246 U/L), gamma glutamyl transpeptidase: 140 U/L (normal: 0-38 U/L), albumin: 3.0 g/dl (normal: 3.2-4.8 g/dl), total serum protein: 5.6 g/dL, IgE: 1050 IU/mL (normal: ≤ 100), rheumatoid factor: 15.7 IU/mL (normal: ≤ 15), ferritin: 210 ng/mL (13-150 ng/mL), C-reactive protein: 124 mg/L (normal: 0-5 mg/L). Electrolytes, blood urea nitrogen, creatinine, calcium phosphate, bilirubine and sedimentation rate were within normal limits. In abdominal ultrasonography, hepatomegaly (195 mm) was present. Steatosis and dilatation of biliary canals and lymphadenopathy were not observed. Skin lesions were accepted as drug eruptions due to paracetamol use. Methylprednisolone 60 mg/daily was initiated. High fever (39-40°C), maculopapular rashes and itching persisted even under methylprednisolone treatment.

Wbc: 30.98x10^3/µL, Hb: 13.2 g/dL, and Plt were 160x10^3/µL. Bilirubine levels raised, total bilirubine (TB) reached 3.1 mg/dL and direct bilirubine (DB) 2.6 mg/dL. Considering high fever, leucocytosis, TB: 3.1 mg/dL, DB: 2.6 mg/dL and pain on right upper quadrant, piperasillin tazobactam 3x4.5 gr was started with the preliminary diagnosis of acute cholangitis. The following tests obtained in order to investigate fever and hepatitis etiology: hepatitis B, hepatitis C, hepatitis E, Human Immunodeficiency Virus, Cytomegalovirus, Epstein-Barr Virus, Rubella, Herpes Simplex virus, and Brucella, Antinuclear antibody
(ANA), antimitocondrial antibody (AMA), anti-dsDNA, perinuclear anti neutrophil cytoplasmic antibody (P-ANCA), anti-smooth muscle antibody (ASMA), liver-kidney microsomes antibody (LKM) were negative. Besides, chest X-ray, cranial magnetic resonance imaging, ophthalmic examination and echocardiography were normal.

*T. gondii* serology results revealed Anti Toxoplasma IgM (result:2, cut off:0.9), and anti Toxoplasma Ig G positivity (result:83.4, cut off:8) (Capture ELISA system, Chorus). Therefore, in addition with these laboratory findings, a history of eating raw meat led to the diagnosis of toxoplasmosis and clindamycin 4x600mg was started. Two weeks later, there was four-fold increase in anti Toxoplasma IgG titers (result: 464).

Liver and skin biopsies were performed because of the persistence of increase in liver enzymes and itchy maculopapular rashes. Liver biopsy revealed mixed inflammatory cell infiltration with fewer eosinophil leucocytes in the sinusoids and portal regions. Focal necrosis, cholestasis in periportal regions and cloudy swellings along with widening in sinusoids were noted. Pathological examination with haemotoxylin eosine, giemsa and Periodic Acid Schiff (PAS) stains showed *T. gondii* bradyzoites and hepatitis (Figure). Skin biopsy was reported as chronic vasculitis. Piperacillin/tazobactam treatment discontinued on the day 14. AST and ALT decreased to 44 U/L and 141 U/L respectively on the 8th day of clindamycin treatment. Patient was discharged with clindamycin 4x600mg in a good general health condition. On follow up, clinical and laboratory findings ameliorated. Treatment was discontinued on the day 21.

Toxoplasmosis is mainly acquired by ingestion of food or water that is contaminated with oocysts shed by cats or by eating undercooked or raw meat containing tissue cysts (1). Our patient revealed eating raw meat. Acute *T. gondii* infection causes different clinical courses in 10-20% of cases. In immunocompetent patients, most often toxoplasmosis presents as asymptomatic cervical lymphadenopathy (3). However, pneumonitis, myocarditis and
myositis may occur. Rarely, hepatitis has been reported in immunocompetent and immunodeficient patients (4-8). Vischer TL et al. reported two cases of hepatitis due to toxoplasma gondii in 1967 (9).

Severe cases of toxoplasmosis have been previously reported in French Guiana, Suriname and Brazil (10-12). Patients commonly develop a generalized infectious syndrome with visceral involvement such as mild hepatitis, jaundice, atypical pneumonia, enlarged lymph nodes and less frequently, myositis and chorioretinitis (8,10). Patient admitted with fever, rashes and clinical picture of hepatitis.

The diagnosis of toxoplasmosis in acute phase depends on amplification of parasite DNA from blood and body fluids, revealing and isolating *T. gondii* bradyzoites in histopathological examination of biopsy materials (direct) or detection of antibodies against parasites in blood (indirect). Bradyzoites are rarely seen in stained tissue sections during histopathological examination. Bradyzoites are present in primary and reactive infections and indicate active infection (3). We detected bradyzoites in liver tissue of our patient. Therefore, diagnosis was confirmed by histopathologic and serologic means.

The standard treatment for acquired toxoplasmosis in both immunocompetent and immunodeficient patients is the synergistic combination of pyrimethamine and sulphonamides. However, because of toxicity, the therapeutic efficacy of pyrimethamine-sulphonamide combinations may be limited. Alternatively, newer macrolides and clindamycin may be used (3). Due to severe clinical signs and visceral involvement in our patient (maculopapular rash and hepatitis), we initiated clindamycin treatment, although such a therapy is rarely indicated in immunocompetent patients. We preferred clindamycin due to being easier to reach and because the lack of pyrimethamine and sulfadiazine combination in our regional market. A total of 21 day treatment managed the disease and resulted in cure.
In conclusion, in patients with hepatitis, especially along with fever and rashes, Toxoplasmosis must be kept in mind to provide efficient cure.

Conflict of Interest: The authors declare no conflict of interest.

References

**Figure Legend:** Toxoplasma gondii bradyzoites seen in hepatocyte stained by PAS