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Cerebral Toxoplasmosis in Newly Diagnosed Cirrhosis Patient: A Case Report

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Abstract: ***Cerebral toxoplasmosis is an infection caused by the obligate intracellular parasite Toxoplasma gondii. This condition is frequently discovered in HIV/AIDS patients and is associated with high mortality and morbidity. Nevertheless, Cerebral toxoplasmosis can also be found in a patient with cancer, stem cell/organ transplantation, immunosuppressive therapy, or other immunodeficiency disorder as in this case is cirrhosis. Liver damage will lead to decreased cellular immunity mediated by T cells and macrophages, as well as decreased activity of type 1 cytokines (IL-12 and IFN-γ) which are needed to eliminate T.gondii. Several studies have reported this parasite is found in 20% - 90% of patients with cirrhosis through IgG and PCR tests. The manifestations of cerebral toxoplasmosis are decreased consciousness, headaches, cerebral dysfunction, fever, seizures, dementia, or impaired motor function. Diagnosis of cerebral toxoplasmosis is considered from clinical findings, CT scan, or MRI of the brain along with serological values. This study will discuss about cerebral toxoplasmosis in cirrhosis patients in the form of case report.***

Keywords: Encephalopathy, HIV-Negative, Immunodeficiency, Hepatitis B

1. Introduction

Toxoplasmosis is an infection of the obligate intracellular parasite *Toxoplasma gondii* which is found in 30% of the world's population.[1]*T. gondii* enters the host cell through foodborne (raw meat of infected animals), animal to human (infected cat feces in the form of oocytes), transmission (transplacental), through blood transfusions, or organ transplants from infected donors.[1–3]*T. gondii* infects the intestine in the form of tachyzoites and spread through the intestinal mucosa to the blood circulation and lymphatic system to the target organs. These parasites can evade the immune system and pass through biological barriers in the gastrointestinal tract, pancreas, liver, heart, lungs, and the most frequent organ is the brain.[3–6] In immunocompetent individuals, parasites are eliminated or converted to bradyzoite in the form of cysts resulting in chronic infection. In this stage, the immune system has an important role to control the parasites. Nonetheless, in immunodeficiency individuals, this parasite will reactivate, namely the change of bradyzoite to tachyzoite and proliferate in the target organ. In the brain, this condition will cause encephalitis (cerebral toxoplasmosis).[7]

Cerebral toxoplasmosis is frequently discovered in HIV/AIDS patients and is associated with high mortality and morbidity.[4] Nevertheless, this condition can also occur in a patient with cancer, stem cell/organ transplantation, immunosuppressive therapy, or other immunodeficiency disorder.[8] Cirrhosis is one of the diseases that causes a reduction of the immune system and is often encountered. Data from the Global Burden of Disease Study in 2017 shows that nearly 1.5 million people are diagnosed with hepatic cirrhosis with the most common causes is non-alcoholic fatty liver disease (NAFLD) (60%), hepatitis B (29%), hepatitis C (9%) and alcohol-related liver disease (ALD) (2%).[9] Liver damage will lead to decreased cellular immunity mediated by T cells and macrophages, as well as decreased activity of type 1 cytokines (IL-12 and IFN-γ) which are needed to fight parasites and prevent toxoplasmosis reactivation.[10–12] Several studies have reported this parasite is found in 20% - 90% of patients with cirrhosis through IgG and PCR tests.[3,10,13]

The manifestations of cerebral toxoplasmosis are decreased consciousness, headaches, cerebral dysfunction, fever, seizures, dementia, or impaired motor function.[4] Diagnosis of cerebral toxoplasmosis is considered from clinical findings, serological examination, and imaging such as CT scan, or MRI of the brain.[9,14] CT scan without contrast shows hypodense lesions resembling mass and edema, while on CT scan with contrast shows hypodense lesions, solitary or multiple, nodular or ring enhanced with edema. MRI examination is the best modality for cerebral toxoplasmosis, it will show a target sign consisting of three alternating zones, as well as a constellation image in the form of hypointense at the core surrounded with hyperintense lesions and edema.[6]

Cerebral toxoplasmosis often shows non-specific manifestations, making it difficult to distinguish from another encephalitis. This causes delays of the treatment resulting in high morbidity and mortality rates. For example, a post-mortem study of 233 HIV/AIDS patients in India showed that approximately 6.8% of patients died due to cerebral toxoplasmosis, which was not previously suspected clinically.[15] Similarly, a study by Ganiem et al. reported the mortality of patients with cerebral toxoplasmosis was found to be high because the infection was distracted by tuberculous meningitis, cryptococcus, or other infections.[4] This study will discuss about cerebral toxoplasmosis in cirrhosis patients in the form of case report.

2. Case Illustration

A 58 year-old man came to the emergency room with complaints of bloody vomiting about 3 hours earlier. Patient denies complaint of projectile vomiting, weakness of the limbs, decreased consciousness, or headache. Thereafter, the patient complained of abdominal distension and swelling in both legs 2 weeks before. Complaints of swelling in other body, yellowish eyes or body, stool mixed with blood, dark color urine, reduced urine frequency, pain when urinate were denied. The patient does not experience dizziness, fever, shortness of breath, or chest palpitations. Patient never complained the same problem before. Patient has tattoos on his chest and arms. Patient sometimes consumes alcohol but denies the routine consumption of painkillers or the use of intravenous drugs. Patient and his family members do not have a history of comorbidities such as hypertension, heart disease, kidney disease, diabetes, autoimmune disease, or malignancy. None of the members had a similar complaint.

Patient came with weakness appearance, compos mentis, and normal vital signs. On physical examination, there was no jaundice, the conjunctiva looked anemic, no icteric, there was no murmurs sounds in the heart and there was no rhonchi or wheezing in the lungs. Abdominal examination shows distension with positive results on the flank dullness and shifting dullness. There were no spider naevi or caput medusa. On examination of the limbs, there was pitting edema in both legs, no palmar erythema was found.

Blood tests showed Hemoglobin 7.4 g/dl (12-16 g/dL), Leukocytes 10.5 (5-10 $x10^6$/uL), Platelets 74 (140-440 $x10^3$/uL), SGOT 209 U/L (10-34 U/L), SGPT 122 U/L (10–34 U/L), Albumin 2.4 g/dl (3.5-5.0 g/dl), Urea 45 mg/dl (10–35 mg/dl), Creatinine 2.2 mg / dl (0.5-1.2 mg/dl), Natrium 132 mmol/L (136-145 mmol/L), Potassium 4.7 mmol/L (3.5-5.1 mmol/L), Chloride 101 mmol/L (97-111 mmol/L), HbsAg 5962.7 S/CO (Non-reactive <1 S/CO), Anti-HCV 0.06 S/CO (Non-reactive <1 S/CO). Abdominal ultrasound (USG) shows the presence of free fluid in the peritoneal cavity, the intensity of the hepatic echo parenchyma increases with irregular edges. Chest X-ray examination showed normal heart size, no infiltrate or consolidation in the lungs. From the recent illness history, physical examination, blood test, and abdominal USG, patient was diagnosed with cirrhosis. Patient was admitted to the ward with symptomatic, supportive, and antibiotic therapy for prophylaxis against spontaneous bacterial peritonitis (SBP).

During treatment, vital signs and clinical symptoms were monitored regularly. Patient's condition tends to be stable and shows improvement, namely complaint of bloody vomit, abdominal distension and leg swelling no longer exist. However, on the 5th day of treatment patient complained of dizziness especially if he changes position and opens his eyes, and headache. Complaints of tinnitus, spasms, and weakness of the limbs were denied. Furthermore, patient was complained of changes in behaviour, disoriented, and fell asleep easily by his wife. At the time of examination, patient was somnolent, vital signs and generalist status were within normal limits. Neurological examination did not reveal lateralization. Meningeal signs and pathological reflex were negative. Examination of nystagmus and cerebellar function cannot be performed because the patient complains of dizziness when opening the eyes.

Blood tests were performed with the results of Hemoglobin 10.4 g/dl (12-16 g/dL), Leukocytes 4.5 (5-10 $x10^6$/uL), Platelets 104 (140-440 x 10^3/uL), SGOT 154 U/L (10-34 U/L), SGPT 101 U/L (10-34 U/L), Urea 40 mg/dl (10-35 mg/dl), Creatinine 1.6 mg/dl (0.5-1.2 mg/dl), Random Blood Sugar 160 mg/dL (<200 mg/dL), Sodium 133 mmol/L (136-145 mmol/L), Potassium 4.5 mmol/L (3.5-5.1 mmol/L), Chloride 97 mmol/L (97-111 mmol/L). From the recent illness history and blood tests results in increased liver function with normal value of electrolytes , we suspect the decreased consciousness is due to metabolic processes (Hepatic Encephalopathy).

Head CT scan without contrast was performed 2 days later because the patient still had a similar complaint with the result perifocal tentacle and edema in the right frontal lobe. The CT scan results can be seen in **Figure 1**. The patient's family denies the habit of eating raw food, living with cats, use of immunosuppressive therapy, or history of organ transplants. The next tests performed were Toxoplasma serology with Anti-Toxoplasma IgM 0.15 IU/ml (Non-reactive <0.65 IU), Anti-Toxoplasma IgG> 300 IU (Non-reactive <8 IU) and Non-reactive Anti-HIV. The patient is diagnosed with Cerebral Toxoplasmosis and given the appropriate therapy.

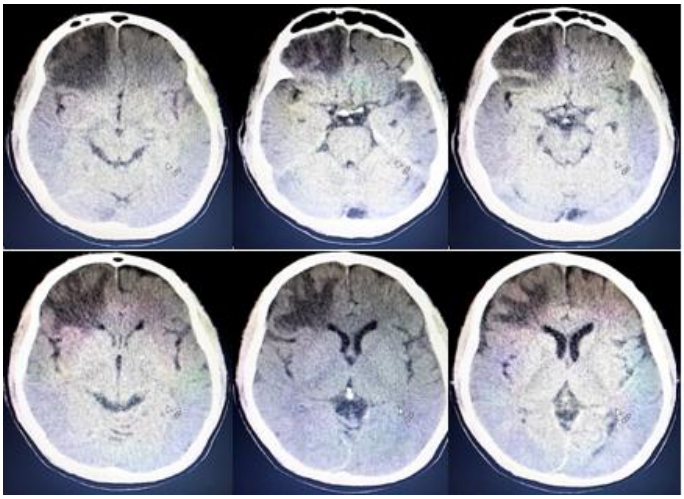

Figure 1: Head CT Scan without contrast shows perifocal tentacle and edema in the right frontal lobe

3. Discussion

Patient was diagnosed with cirrhosis at the time. Diagnosis is obtained through history taking, evaluation of risk factors, physical examination, blood tests and USG. Research by Scaglione et al. shows about 70% of patients with cirrhosis are unaware of their disease and present when complications arise such as varicose rupture, ascites, peritonitis, or even encephalopathy.[16] During treatment, patient was complaint of dizziness, headache, changes in behavior, disoriented, and easy to fall asleep. In patient with cirrhosis, altered level of consciousness is commonly caused by toxins accumulation in the brain as a result of liver failure to removed it (Hepatic Encephalopathy). Hepatic encephalopathy (HE) is a complication of hepatic cirrhosis characterized by changes in behavior, decreased consciousness, and motor or cognitive impairment. Factors that trigger HE are infection, gastrointestinal bleeding, diuretic, electrolyte disturbances, constipation, and dehydration.[17]

HE was considered from recent illness history, complaints, blood tests, imaging and clinical experience as the findings are often non-specific. A positive response to therapy can also confirm the diagnosis.[17] Blood tests were performed on patients resulting in normal values of complete blood count, random blood sugar and electrolytes, while liver enzymes were elevated. Furthermore, in patients with headache, fever, loss of consciousness accompanied by neurological deficits, CT scans or MRI are recommended.[4,17] CT scans without contrast was performed with the results of perifocal tentacle and edema in the right frontal lobe with suspicion of mass or process of toxoplasma infection. Toxoplasma serological and Anti-HIV examination was done with the results of high level of anti-Toxoplasma IgG and Negative result of Anti-HIV.

Diagnosis of cerebral toxoplasmosis is considered from clinical findings and CT scans or MRI of the brain accompanied by high serological values. In patients with negative toxoplasma serology, we can rule out the diagnosis. However, at a positive value in the absence of a CT scan or MRI, the diagnosis cannot be confirmed, although high IgG values are only found in symptomatic cerebral toxoplasmosis patients.[4,18] In immunocompetent patients, IgM tests can be used to diagnose acute Toxoplasmosis, while immunocompromised patients often get negative results because of the decreased immune response.[6]
Cerebral toxoplasmosis is frequently discovered in HIV/AIDS patients with a prevalence of about 40%.[5] Immune system deficiencies such as CD4+ T cells, NK cytotoxic cell activity, and low production of immunoregulatory lymphokines such as IFN-γ are the causes of parasite reactivation in patients with HIV/AIDS. However, these parasites can also be found in other immunocompromised conditions.[6,14,19] As in this case cirrhosis.

Decreased immunity mediated by T cells or humoral in patients with cirrhosis will cause the inability to kill pathogens.[10] This leads to a susceptibility of opportunistic infections such as viral, bacterial, or parasite infections.[3,10] In cirrhosis caused by hepatitis infection, production and response of CD4 + and CD8 + cells are decreased, while these cells are a necessary factor to fight *T.gondii*.[20–22] Research by Ustun et al. showed 68.5% of 108 cirrhosis patients had reactive results on the toxoplasma serologic tests (IgM and IgG).[23] Similarly, research by El-Sayed et al. shows toxoplasmosis occurred more frequently in patients with cirrhosis than in patients without liver disease (30% vs 6%).[10] However, no studies have reported the prevalence of cerebral toxoplasmosis in HIV-negative cirrhosis patients.

4. Conclusion

Toxoplasmosis is an infection of the obligate intracellular parasite *Toxoplasma gondii* which is found in one-third world's population. With the ability of the parasite to evade the immune system and cross the blood brain barrier, *T.gondii* will proliferate in the brain and cause inflammation (Cerebral toxoplasmosis). Although Cerebral toxoplasmosis is frequently discovered in HIV/AIDS patients, it can also be found in patients with patient with cancer, stem cell/organ transplantation, immunosuppressive therapy, or other immunodeficiency disorder as in this case is cirrhosis. Apart from hepatic encephalopathy, other diagnoses such as cerebral toxoplasmosis should be considered in cirrhosis patient with altered levels of consciousness. By diagnosed this condition earlier, therapy can be administered immediately and improve the patient's quality of life. Further studies regarding cerebral toxoplasmosis in HIV-negative cirrhosis patientsshould be done to obtain the prevalence and learn the mechanism underlying this condition.

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