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Hyponatremia as the Initial Presentation of Cryptococcal Meningitis After Liver Transplantation

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Introduction: Meningoencephalitis is the most common clinical manifestation of cryptococcal infection, as the organism has a propensity to invade the CNS. Patients often present with elevated intracranial pressure, focal motor deficits, altered mentation and internal hydrocephalus. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been reported as a notable cause of euvolemic hyponatremia in immunocompromised patients.

Case Presentation: A 67-year-old male with liver transplantation due to hepatitis C (HCV) related liver cirrhosis developed severe hyponatremia four months after liver transplantation, which was discovered during routine clinic visit. Patient was referred to the emergency department, treated and discharged with normal serum sodium level. Few days later, he presented with dizziness, confusion, ataxia, abnormal muscle movements and leg pain. Laboratory investigations were consistent with SIADH and revealed a sodium level of 115 mmol/L. Brain MRI showed a leptomeningeal enhancement in the superior cerebellar sulci suspicious for infection. Lumbar puncture was performed and consistent with *Cryptococcus neoformans* infection; therefore, cryptococcal meningitis was diagnosed. Amphotericin B was started for the patient for six weeks followed by fluconazole for one year. His level of consciousness improved significantly, and his serum sodium level slowly returned to its normal baseline over three weeks after starting amphotericin B.

Conclusions: Symptomatic hyponatremia secondary to SIADH remains a rare complication of cryptococcal meningitis.

Keywords: Hyponatremia; Meningitis; Cryptococcal; Liver Transplantation; Syndrome of Inappropriate ADH (SIADH) Secretion

1. Introduction

Diagnosis of hyponatremia is established when serum sodium level falls below 135 mEq/L. Acute hyponatremia is associated with altered mentation, seizures or unconsciousness and death in less than 48 hours due to cerebral edema. On the contrary, patients with chronic hyponatremia may develop gastrointestinal, mild neurological symptoms or no symptoms at all. True hyponatremia can be either hypovolemic, euvolemic, or hypervolemic. Syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been reported as a notable cause of euvolemic hyponatremia in human immunodeficiency virus (HIV) infection, central nervous system diseases (1), malignancies and respiratory diseases. Moreover, SIADH is the most notable cause of hyponatremia in admitted patients (1). Criteria for diagnosis of SIADH include euvolemic, eucortisolemic and euthyroid status, high urine sodium of more than 20 mEq/L, high urine osmolality of more than 100 mOsm/kg, low plasma osmolality of less than 275 mOsm/kg and disuse of diuretics (1). The mentioned criteria must be met in the presence of normal thyroid, cardiac, hepatic, renal, and adrenal functions (1).

Herein, we report a case of a 67-year-old male status post liver transplantation due to hepatitis C (HCV) related liver cirrhosis who developed hyponatremia secondary to syndrome of inappropriate antidiuretic hormone (SIADH) as a first presentation of cryptococcal meningitis. Up to our knowledge, this is the second case with such presentation reported in the literature and the only case after liver transplantation (2).

2. Case Presentation

A 67-year-old man status post liver transplantation three months ago was found to have severe hyponatremia with sodium of 119 mmol/L during routine follow-up and was referred to emergency department on 7th of August, 2014 with constipation, fatigue and tremor. Patient had no history of fever, nausea, vomiting, and

abdominal pain. Patient's medical history was significant for uncontrolled type 2 diabetes mellitus and liver cirrhosis secondary to HCV, which he underwent liver transplantation for on 7th of May, 2014. Post transplant medications included prednisone, cyclosporine, Septra, magnesium oxide, omeprazole, amlodipine, and insulin mixtard. On examination, the patient was afebrile with a blood pressure of 118/58 mmHg and heart rate of 115 beats per minute. Laboratory investigations revealed hyponatremia (115 mmol/L), hyperkalemia (6.9 mmol/L), serum osmolarity of 254 mOsmol/L (275 - 295 mOsmol/L), elevated urine sodium (70 mmol/L) and urine osmolarity of 503 mOsmol/L (50 - 1400 mOsmol/L), suggestive of SIADH. Intravenous normal saline was started in the emergency department, but sodium levels dropped further to 113 mmol/L with worsening of his presenting symptoms. Sodium was then corrected to 125 mmol/L during two days using hypertonic saline (NaCl 3%) at a rate of 30 mL hourly, and then, patient was discharged home.

Four weeks later, the patient referred again to the emergency department complaining of dizziness, confusion, ataxia, abnormal muscle movements, and leg pain. Patient denied any history of fever, nausea, vomiting, abdominal pain, weight loss, decreased appetite, sweating, travel or raw milk ingestion. On examination, he was euvolemic with altered sensorium.

Laboratory investigations revealed hyponatremia (122 mmol/L), despite correcting sodium levels to 130 mmol/L over 72 hours. His level of consciousness temporary improved but worsened again. He developed fever (39˚C) became drowsy, and was unable to follow commands with altered mental status (the Glasgow coma scale: 9) and positive meningeal signs.

Chest X-ray and ultrasound of abdomen were unremarkable. Magnetic resonance imaging (MRI) of the brain showed leptomeningeal enhancement in the superior cerebellar sulci suspicious for infection. Lumbar puncture was consistent with *Cryptococcus neoformans* infection: high white blood cell count (250×10^6/L; 43% neutrophils, 37% monocytes and 8% lymphocytes), high protein (1326 mg/L), low glucose (0.97 mmol/L), and positive cryptococcal antigen and India Ink stain. The patient's hyponatremia was due to syndrome of inappropriate antidiuretic hormone (SIADH) secondary to cryptococcal meningitis.

Amphotericin B was administered for six weeks followed by fluconazole for one year. His level of consciousness improved significantly, and his serum sodium level slowly returned to its normal baseline over three weeks after starting amphotericin B.

He underwent Roux-en-Y hepaticojejunostomy for biliary stricture after failed percutaneous transhepatic cholangioplasty. He also, achieved sustained virologic response to 6-month therapy with Sofosbuvir plus ribavirin for treatment of HCV.

3. Discussion

Meningoencephalitis is the most common clinical manifestation of cryptococcal infection (3). The organism has a propensity for the central nervous system and is found in 40% - 86% of cases (4). Following inhalation, *C. neoformans* causes an infection, which disseminates hematogenously after an observed or asymptomatic pulmonary infection (5, 6). It is critical to investigate for cryptococcal meningitis in immunocompromised patients with cryptococcal infection affecting other body systems (3). The commonest strain of *Cryptococcus neoformans* found in immunocompromised patients is *C. neoformans* var. *neoformans* (5). Organ transplant, lymphomas, glucocorticoid therapy, HIV infection and other states of immunodeficiency are predisposing factors for cryptococcal infection (5).

Cryptococcus preferably invades the meninges due to lack of cell mediated immunity (5) and factors that inhibit its growth, which are often found in the serum (7). Patients often present with typical meningeal signs, which are nonspecific for cryptococcal infection (2, 5), making the diagnosis difficult (2). A lumbar puncture and cryptococcal antigen detection following CSF culture are essential for the diagnosis of cryptococcal meningoencephalitis. Typical findings of a potential cryptococcal meningoencephalitis include high opening pressure > 200 mmH_2O (especially in AIDS patients), high protein levels, low glucose levels and high lymphocytic count. As a consequence of cryptococcal meningitis, patients develop elevated intracranial pressure, focal motor deficits, altered mentation and internal hydrocephalus (5).

SIADH was a complication of cryptococcal meningitis in our patient, resulting in severe hyponatremia. SIADH arises most frequently secondary to small cell lung cancer and CNS disturbance (8, 9). The most common cause of CNS disturbance is meningitis caused by tuberculosis and other bacteria (2). Fungal meningitis is uncommon (2). X-ray and CT of chest had normal findings in our patient, which excluded lung cancer. Moreover, we hypothesized that our patient developed SIADH secondary to CNS disturbance caused by infection.

Up to our knowledge, only one case of SIADH secondary to cryptococcal meningitis was reported in the literature; the patient was receiving immunosuppressive treatment (prednisone and azathioprine) for ulcerative colitis (2). Cerebral salt wasting syndrome (CSWS) is another condition, which may present similarly to SIADH in a patient with cryptococcal meningitis, but usually the patient is hypovolemic (10). Laboratory findings such as high urine osmolality, high urine sodium concentration, low serum uric acid, and low serum osmolality are found in both conditions (10). SIADH is a result of increased levels of antidiuretic hormone, which leads to water retention and hyponatremia. The higher the plasma ADH is, the more concentrated the urine is. Fluid resuscitation does not suppress ADH release, and urine remains concentrated. This leads to water retention, which increases total body

water. CSWS involves salt loss from the kidneys due to decreased reabsorption of sodium. Moreover, treatment of CSWS varies from that of SIADH (10). Before managing SIADH, duration of hyponatremia and the underlying disorder must be identified. The treatment of choice in SIADH is fluid restriction, preferably lower than 800 mg/day (1). Hence, it is very important to rule out CSWS in a patient with hyponatremia because fluid restriction would result in cerebral infarction. In CSWS, fluid resuscitation is the mainstay of therapy and is performed using normal saline (1). Our patient was not persistently hypovolemic, as inferred from the signs and symptoms that ruled out CSWS.

Positive India ink staining, low glucose and WBC in CSF (< 20 cells/mL), high CSF opening pressure, extraneural dissemination, treatment with glucocorticoids, hyponatremia, malignancy, high antigen to antibody ratio and visual abnormalities are indicators of unfavorable outcome in cryptococcal meningitis (5).

In conclusion, symptomatic hyponatremia secondary to SIADH remains a rare complication of cryptococcal meningitis. Patient's medical and surgical history is important to identify the cause of immunosuppression status leading to cryptococcal infection. CSWS must be ruled out before treating SIADH. To our knowledge, this is the first reported case of hyponatremia secondary to cryptococcal meningitis in a patient who underwent liver transplantation.

Authors' Contributions

1- Study concept and design: Hussien Elsiesy, Faisal Abaalkhail, Wael Al-Kattan, Mohamed Alsebayel, and Waleed Al hamoudi, 2- acquisition of data: Hussien Elsiesy, Asma Alnajjar, Saad Mansoor, and Hamzah Juhardeen, 3- analysis and interpretation of data: Hussien Elsiesy, Asma Alnajjar, Saad Mansoor, and Hamzah Juhardeen, 4- drafting of the manuscript: Hussien, Elsiesy, Asma Alnajjar, Saad Mansoor, and Hamzah Juhardeen, 5- critical revision of the manuscript for important intellectual content: Hussien Elsiesy, Faisal Abaalkhail, Wael Al-Kattan, Mohamed Alsebayel, and Waleed Al hamoudi, 6- administrative, technical and material supports: Hussien Elsiesy and Asma Alnajjar, 7- study supervision: Hussien Elsiesy.

References

1. Pillai BP, Unnikrishnan AG, Pavithran PV. Syndrome of inappropriate antidiuretic hormone secretion: Revisiting a classical endocrine disorder. *Indian J Endocrinol Metab.* 2011;**15 Suppl 3**:S208–15.
2. Shahani L. Hyponatraemia masking the diagnosis of cryptococcal meningitis. *BMJ Case Rep.* 2012;**2012**.
3. Gal AA, Koss MN, Hawkins J, Evans S, Einstein H. The pathology of pulmonary cryptococcal infections in the acquired immunodeficiency syndrome. *Arch Pathol Lab Med.* 1986;**110**(6):502–7.
4. Sabetta JR, Andriole VT. Cryptococcal infection of the central nervous system. *Med Clin North Am.* 1985;**69**(2):333–44.
5. Subramanian S, Mathai D. Clinical manifestations and management of cryptococcal infection. *J Postgrad Med.* 2005;**51 Suppl 1**:S21–6.
6. Tripathi K, Mor V, Bairwa NK, Del Poeta M, Mohanty BK. Hydroxyurea treatment inhibits proliferation of Cryptococcus neoformans in mice. *Front Microbiol.* 2012;**3**:187.
7. Igel HJ, Bolande RP. Humoral defense mechanisms in cryptococcosis: substances in normal human serum, saliva, and cerebrospinal fluid affecting the growth of Cryptococcus neoformans. *J Infect Dis.* 1966;**116**(1):75–83.
8. Moses AM, Miller M, Streeten DH. Pathophysiologic and pharmacologic alterations in the release and action of ADH. *Metabolism.* 1976;**25**(6):697–721.
9. De Troyer A, Demanet JC. Clinical, biological and pathogenic features of the syndrome of inappropriate secretion of antidiuretic hormone. A review of 26 cases with marked hyponatraemia. *Q J Med.* 1976;**45**(180):521–31.
10. Lee S, Collado A, Singla M, Carbajal R, Chaudhari A, Baumstein D. Diagnosis and Treatment of Cerebral Salt Wasting Syndrome With Cryptococcal Meningitis in HIV Patient. *Am J Ther.* 2015.