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Case Report

Successful management of refractory hyperammonemia in metastatic neuroendocrine tumor

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ABSTRACT

Neuroendocrine tumors (NETs) form a heterogeneous group of neoplasms composed of pancreatic NETs and carcinoid tumors. Refractory hyper-ammonemia related encephalopathy is a condition seen rarely with metabolic liver disease and commonly with intra-abdominal shunts in the presence or absence of cirrhosis. We present here, a rare cause of medically refractory hyperammonemia, secondary to metastatic neuroendocrine tumor which was managed through interventional radiology measures. Apart from other causes of central nervous system involvement in metastatic neuroendocrine tumors, intratumoral microportovenous shunting and its management drastically improves outcomes and quality of life when diagnosed early.

Keywords: Hyperammonemia, Neuroendocrine tumor, Hepatic encephalopathy, TACE, Liver tumor

INTRODUCTION

Neuroendocrine tumors (NETs) form a heterogeneous group of neoplasm consisting of pancreatic NETs and carcinoid tumors. The World Health Organization divides NETs into well-differentiated endocrine tumors or carcinomas, poorly differentiated endocrine tumors and mixed exocrine-endocrine tumors. The well-differentiated endocrine tumors (functional or nonfunctional) are further divided into those with benign behavior (confined to pancreas, nonaggressive, <2 cm) and those with uncertain behavior (confined to pancreas, >2 cm or with vascular invasion). NETs are also classified according to the clinical syndrome they produce depending on the secretory properties.[1,2] Hyperammonemia can be due to primary or secondary etiologies. Primary diseases are mostly due to inborn errors of metabolism and secondary causes most commonly due to liver disease, large intrabdominal venous shunts or those related to metastatic malignancy. Hyperammonemia is known to occur in NETs with hepatic metastasis and leads to persistent hepatic encephalopathy in the patients which proves quite debilitating. Literature shows evidence for the cause of hyperammonemia in this rare situation to be intra tumoral micro porto-venous shunting. In the present case, we discuss the management of medically refractive hyper-ammonemia in a patient with metastatic NET and one which improved after trans-arterial chemoembolization of the large metastatic lesions in the liver.[3,4]

CASE REPORT

A 45-year-old male, teetotaler and without known chronic diseases, diagnosed with duodenal NET with metastatic liver disease in 2004, presented to our emergency with altered behavior and excessive drowsiness. Three months' prior, his illness course was complicated with recurrent episodes of altered behavior and confusion without associated jaundice, gastrointestinal bleeds or abdominal distension. The patient had received treatment for NET in 2004 at a

tertiary care center in the form of 3 sessions of chemotherapy, followed by monthly long acting somatostatin and was asymptomatic till 2009 when serial routine abdominal imaging was suggestive of progressive increase in the metastatic liver lesions. On examination the patient was emaciated, arousable on a painful stimulus and bilateral equally reacting pupils without anisocoria and without associated focal neurological deficits. Initial laboratory investigations revealed microcytic hypochromic anemia, preserved liver and renal function tests with normal electrolytes, but with severe hyperammonemia. A review of recent magnetic resonance imaging of abdomen revealed massive hepatomegaly with multiple bilobar heterogeneous lesions, the largest largest measuring 19×24×21 cm involving predominantly segments VIII, VII, V and IV of the liver (Figure 1).

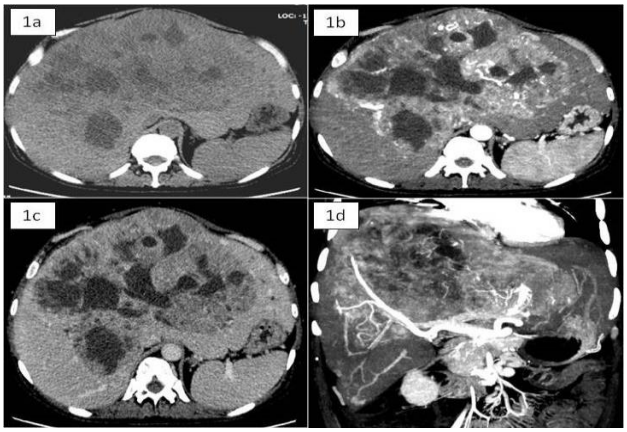

Figure 1: Axial images of triple phase computed tomograph scan of the abdomen revealing massive hepatomeagly with large hypodense; (1a) arterial enhancing hypervascular lesions with interspersed areas of necrosis involving both lobes of liver; (1b and c) Mip image; (1d) shows enlarged hepatic arteries supplying the hypervascular lesios with intense neovascularity (mip- maximum intensity projection).

In view of hyperammonemia, treatment with oral and rectal disaccharides, L-ornithine-L-aspartate, non-absorbable antibiotics and zinc supplementation was initiated. Transient clinical improvement was evident but with intermittent progression to encephalopathy. Magnetic resonance imaging of the brain and an electroencephalogram was normal. Evaluation for portal hypertension and associated chronic liver disease was negative and abdominal imaging did not show spleno-portal thrombosis or large venous shunts. Arterial blood gas analysis did not suggest respiratory alkalosis, serum amino acid assays, and plasma and urine ketone, organic acid tests were normal. After consultation with the interventional radiology team transarterial chemoembolization (TACE) was performed with continuation of anti-hyperammonemia measures (Figure 2). Post procedure in hospital observation was continued for another 15 days. The patient showed remarkable recovery from intensity and frequency of encephalopathic attacks in tandem with drastic reduction in arterial ammonia levels and improvement in performance status and quality of life. He was then discharged after a month of stay in hospital and followed up on outpatient basis. Repeat imaging of the abdomen for TACE response was undertaken on follow up and further two sessions were performed within the next 2 months of follow up (Figure 3). At time of last follow up, 4 months after the first session of TACE, the patient had rejoined his duties and were performing routine activities of daily living normally.

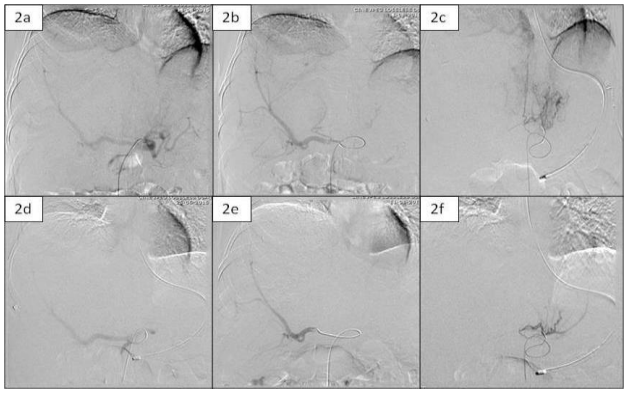

Figure 2: Digital subtraction angiogram of common hepatic; (2a) right hepatic (2b) left hepatic arteries; (2c) showing enlarged arteries feeding the large hypervascular mass lesion with neovascularisation and intense tumour blush. Post TACE completion angiogram of common hepatic; (2d) right hepatic; (2e) left hepatic; (2f) arteries revealing significant reduction of hypervascularity and tumour blush. (TACE - transarterial chemoembolization).

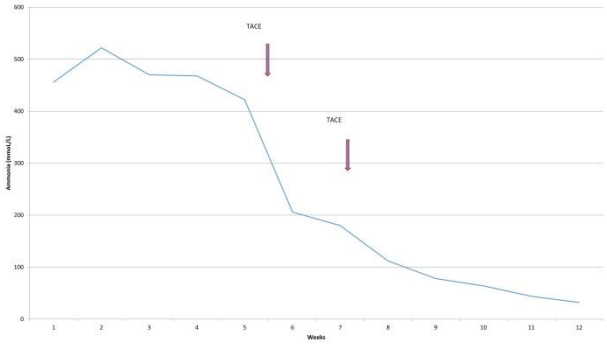

Figure 3: Serial ammonia measurement in the patient at admission, followed by during hospital course post trans-arterial chemoembolization procedure and on follow up.

DISCUSSION

NETs are often associated with symptoms that may be quite severe and significantly affect the quality of life of the patient. Liver is the most common site of metastasis in NETs as most of them arise from the pancreas and the

gastrointestinal tract. Seventy-five to 80% have liver metastases at the time of diagnosis (synchronous) while another 20–25% are found to have liver metastases during the course of treatment (metachronous). It is estimated that 80–90% of patients with liver metastases are inoperable at presentation. Neuroendocrine tumors are usually small in size and the associated liver metastasis have a much larger volume than the primary tumor. The hormones and peptides produced by NETs are metabolized by the liver and in the event of extensive liver metastasis, poor liver mass leads to spillage of metabolites directly into systemic circulation leading to new onset or worsening symptoms. Literature shows that treatment directed towards removal of the metastasis surgically or using alternative modalities has shown to improve symptoms in functional as well as non functional tumors. [5, 6] In cases where the presence of co morbidities or the general condition of the patient preclude resection alternative modalities like trans arterial chemoembolization can be done. The metastasis from the NETs derive most of their blood supply from the hepatic artery, consequently on imaging these metastases typically appear brighter than the surrounding liver during the arterial phase and during the venous phase NETs appear darker than the surrounding liver. 7 A review of literature showed 6 case reports of hyperammonemia in NET, secondary to suspected intra-tumoral micro porto-venous shunting and one which improved with TACE, leading to effective ammonia levels. 8-11 Hyperammonemic encephalopathy is most commonly seen with end stage liver disease. The mechanism in this situation is secondary to progressive hepatocellular damage and loss of hepatocyte function leading to accumulation of toxins, especially ammonia that eventually lead to central nervous system dysfunction thorugh glutamate receptor modulation. In such cases, anti ammonia lowering therapies utilizing non absorbable antibiotics, disaccharides, branched chain amino acids, sodium benzoate and zinc supplementation have been standardized as the treatments of choice. [12, 13] In some patients who do not respond adequately to this regimen, other causes for medically refractive hyperammonemia should be looked into. These include large intra-abdominal venous shunts in cirrhotics and non cirrhotics, patients with primary metabolic diseases leading to hyperammonemia or other rare causes such as severe sepsis secondary to urea splitting microbes or diversion surgeries. Published literature on hepatic encephalopathy due to liver involvement in NET is scanty, even though it can occur with progressive parenchymal extinction with large metastatic deposits. In our patient, standard ammonia lowering therapies failed to improve disease course. In such a scenario, hemodialysis could offer some benefit, if high ammonia levels are secondary to liver parenchymal disease secondary to tumoral replacement. But in the presence of extensive intra tumoral porto-venous shunting, this modality fails. Progression of NET leading to hyperammonemia can also be treated with systemic chemotherapy. But this modality is not effective in patients who have already received chemotherapy and in whom there are low grade tumors that progress slowly over time, as seen in our case.[14] This was why we decided to go for interventional radiology procedure such as TACE for management of metastatic deposits and obliteration of micro portovenous shunts. Our patient underwent 2 sessions of TACE leading to remarkable recovery from his encephalopathic symptoms and improvement in quality of life.

This case sheds light on three important aspects in metastatic NET. Firstly, large metastatic NET to the liver can present with reversible hyperammonemic encephalopathy in the indolent natural history of the disease. Secondly, in the presence of parenchymal involvement, there could be improvement in symptoms, when treated on the standard lines of hepatic encephalopathy management and thirdly, in the absence of improvement, micro porto-venous shunts in the tumorous areas need to be thought of, and timely ablative procedures such as TACE improves quality of life and performance status in this rare patient group.

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