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Resolution of Hepatic Encephalopathy Following Hepatic Artery Embolization in a Patient with Well-Differentiated Neuroendocrine Tumor Metastatic To Liver

Joseph P Erinjeri, MD, PhD, Ajita Deodhar, MD, Raymond H Thornton, MD, Peter J Allen, MD, George I Getrajdman, MD, Karen T Brown, MD, Constantinos T Sofocleous, MD, PhD, and Diane L Reidy, MD

Departments of Radiology (JPE, AD, RHT, GIG, KTB, CTS), Surgery (PJA) and Medicine (DLR), Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10021, Phone: 212-639-6610, Fax: 212-717-3325

Abstract

Hepatic encephalopathy is considered a contraindication to hepatic artery embolization. We describe a patient with well-differentiated neuroendocrine tumor metastatic to liver with refractory hepatic encephalopathy and normal liver function tests. The encephalopathy was refractory to standard medical therapy with lactulose. The patient's mental status returned to baseline after 3 hepatic artery embolization procedures. Arteriography and ultrasound imaging before and after embolization suggest that the encephalopathy was due to arteriportal shunting causing hepatofugal portal venous flow and portosystemic shunting. In patients with primary or metastatic well-differentiated neuroendocrine tumor whose refractory hepatic encephalopathy is due to portosystemic shunting (rather than global hepatic dysfunction secondary to tumor burden), hepatic artery embolization can be performed safely and effectively.

Keywords

Hepatic encephalopathy; hepatic artery embolization; neuroendocrine tumor

INTRODUCTION

Hepatic encephalopathy refers to a syndrome of neuropsychiatric symptoms which occur due to acute or chronic hepatocellular failure, portosystemic shunting, or both (1). Symptoms can range from mild alterations in consciousness or behavior to coma (2). In cancer patients, hepatic encephalopathy is usually the result of abnormality of the portal venous system (3) such as thrombosis (4) or hypertension (5) causing portosystemic shunting, or massive hepatic tumor burden causing global hepatocellular insufficiency (6, 7). These changes may result in the inability of the liver to metabolize many substances including ammonia (8). One hypothesis regarding the etiology of the symptoms of hepatic

Address for correspondence: Joseph P Erinjeri, MD, PhD, Interventional Radiology Service, Department of Radiology Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021, Phone 212-639-6610, Fax 212-717-3325.

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encephalopathy is that increased ammonia levels alter neurotransmitter events in the brain, leading to neuronal dysfunction (9).

Curative therapies for primary (10) and metastatic hepatic malignancy (11), including resection, transplantation, and ablative therapies, are only possible in a minority of patients (10–40%), making local or regional therapies and palliative treatments a major focus of clinical care. In nonsurgical candidates, hepatic artery embolization (HAE) (12) and transarterial chemoembolization (TACE) (13) have become standard palliative treatments for certain tumor types. Because hepatic artery embolotherapy is often targeted to diseased segments, sectors, or lobes of the liver rather than to single tumors, hepatic encephalopathy may be worsened by embolization of non-tumor bearing liver parenchyma. Thus, hepatic encephalopathy is considered a contraindication to hepatic artery chemoembolization (14). In this report we describe a case of successful treatment of severe hepatic encephalopathy by hepatic artery embolization in a patient with well-differentiated neuroendocrine tumor (NET) metastatic to liver.

CASE REPORT

A 63-year-old male with past medical history of hyperlipidemia and hypertension presented to his primary care physician in January 2008 with fatigue, elevated alkaline phosphatase and gamma-glutamyl transpeptidase (GGT) levels. The patient had a history of minimal alcohol consumption. His computed tomographic examination at the time of presentation demonstrated an arterially-enhancing mass in the tail of the pancreas with punctate calcifications, as well as multiple arterially-enhancing, centrally necrotic masses within both lobes of the liver (Figure 1a). Retroperitoneal and porta hepatis lymphadenopathy, as well as multiple subcentimeter lung nodules, were identified. The patient underwent whole body Indium-111 octreotide imaging at 4 and 24 hours which revealed marked uptake of tracer by the pancreatic and liver lesions (Figure 1b). All hormone markers were within normal limits suggesting a non-functional islet cell tumor.

The patient was evaluated at our institution one month later. On physical examination, the patient was alert and oriented to person, place and time. Reflexes and motor function were intact. The liver was enlarged, with no shifting dullness identified. No scleral icterus was noted. Laboratory studies showed normal aspartate aminotransferase (AST) 34 units/L, alanine aminotransferase (ALT) 28 units/L, albumin 5.9 g/dL, international normalized ratio (INR) 1.1, and total bilirubin 0.9 mg/dL. Biopsy of the liver tumor was performed, resulting in a diagnosis of well-differentiated NET, islet cell type. Given the extensive tumor burden, it was recommended that the patient be started on octreotide therapy in an attempt to arrest disease progression. The patient received the first test dose of long acting octreotide in clinic (Sandostatin LAR, Novartis Pharmaceuticals Corporation, East Hanover, NJ) without complication.

One month after his initial consultation at our institution, and four days after receiving 20 mg long acting octreotide therapy, the patient presented to an outside hospital with tremors, followed by lethargy and malaise. His serum ammonia level was elevated (131 mcM/L). A computed tomography of the head demonstrated no acute changes and no brain

metastases. He was started on lactulose, improved and was discharged home on Rifaximin (Xifaxan, Salix Pharmaceuticals, Morrisville, NC). Four days later, the patient presented to our institution with increasing confusion and disorientation. Neurological examination revealed that the patient was disoriented to time, with decreased comprehension and concentration. Asterixis was present. Laboratory work demonstrated an elevated ammonia level of 326 mcM/l (normal range 0–50) and alkaline phosphatase of 473 units/L; other liver function tests were normal (albumin 4.0; INR 1.1, AST 48 units/L, ALT 33 units/L, total bilirubin 0.7 mg/dL). All other laboratory studies were normal. His hepatic encephalopathy was initially treated with lactulose. There was no substantial response in ammonia levels or clinical status. His ammonia level rose to 482 mcM/L and his mental status deteriorated to a point where the patient was responsive only to pain.

Because of the lack of response to standard medical therapy for hepatic encephalopathy and the continuing rise in ammonia level, other causes for the patient's diminished mental status were considered. Because liver synthetic function was preserved in the face of the hepatic tumor burden, a paraneoplastic syndrome secondary to the NET was considered in the differential diagnosis. We decided to attempt hepatic artery embolization, with the hope of decreasing tumor burden, thereby mitigating any potential paraneoplastic effect. Prior to the planned procedure, Doppler imaging was performed, showing hepatofugal flow in the main, right and left portal veins.

On arrival to the angiography suite, the patient was obtunded and consent for the procedure was obtained from his wife. Cefazolin (Ancef, GlaxoSmithKline, Research Triangle Park, NC) 1gm intravenously, octreotide (Sandostatin, Novartis Pharmaceuticals Corporation, East Hanover, NJ) 250 mcg subcutaneously, and ondansetron (Zofran, GlaxoSmithKline, Research Triangle Park, NC) 4mg intravenously were administered prior to the procedure. Diagnostic arteriography of the hepatic arteries was performed, demonstrating multiple bilobar hypervascular tumors. Morphologic findings of portal hypertension were present, with hepatofugal flow in the portal vein, and enlarged coronary vein (Figure 1c,d). We decided to make an initial attempt at a limited embolization because of the patient's poor clinical condition, and superselective particle embolization of the segment IV hepatic artery was performed with trisacryl microspheres (Embosphere, size range 40–120 microns; Biosphere Medical Rockland, MA) (Figure 1f).

Post embolization, the patient's liver function tests rose: AST 234 units/L, ALT 53 units/L, alkaline phosphatase 487 units/L, total bilirubin 1.3 mg/dL. However, the patient's ammonia level dropped to 228 mcM/L and mental status subsequently improved. At 48 hours the patient showed spontaneous eye opening. By 72 hours post embolization, he was awake and responsive to verbal commands, but remained disoriented.

On post embolization procedure day #4, the patient underwent hepatic angiography, which showed arteriportal shunting with retrograde flow in the intrahepatic and extrahepatic portal vein (Figure 2a,b,c,d). Particle embolization of the anterior division of the right hepatic artery with 40–120 microns Embospheres was performed. 24 hours later, the patient was awake, alert and oriented to place and person, and his ammonia level dropped to 83 mcM/L. Subsequent abdominal ultrasound showed normal hepatopetal flow in the main and

right portal vein, with persistent hepatofugal flow in the left portal vein. His liver function tests normalized and he was discharged home alert and oriented to place, person and time 14 days after admission, and 7 days after the first embolization.

One month post embolization, the patient's ammonia level had normalized (49 mcM/L), with normal AST, ALT and total bilirubin levels. No asterixis was seen. The patient was oriented to place, time and person. His concentration had returned to baseline. Ultrasound imaging showed hepatopetal flow in the main, right and left portal veins. At this time, the patient underwent a third HAE, of the posterior division of the right hepatic artery with 100–300 micron Embospheres. Hepatic angiography immediately prior to this embolization demonstrated an arterial-to-portal vein shunt (Figure 2e,f,g). He tolerated the third procedure well and remains clinically well with normal mental status and working 8 months after the last embolization. Followup contrast enhanced CT 8 months after the initial embolization shows no arterial enhancing lesions within the liver.

DISCUSSION

Hepatic encephalopathy can occur in patients with hepatic malignancy for a variety of reasons. First, overwhelming tumor burden replacing normal parenchyma can cause poor hepatic function (15), resulting in an inability of the liver to clear ammonia (produced by the gut from protein metabolism via the urea cycle). Second, vascular abnormalities of the portal venous system, which disrupt delivery of the blood to the liver, can limit ammonia metabolism. Intratumoral (16) or extratumoral (17) portosystemic shunting, as well as portal vein thrombosis (18), can all result in hepatic encephalopathy. Metabolic derangement can cause encephalopathy, especially in carcinoid patients (19). Peripheral overproduction of serotonin can deplete the body's supply of tryptophan, the precursor of serotonin. Tryptophan, which is able to cross the blood-brain barrier, also becomes reduced in the central nervous system, leading to decreased production of serotonin in the brain. Since the blood-brain barrier prevents peripherally produced serotonin from entering the central nervous system, the brain becomes serotonin depleted, resulting in neuronal dysfunction (20). Finally, metastases to the brain or meninges (21) and paraneoplastic syndromes caused by malignancy can cause an encephalopathic picture in patients with hepatic malignancy. Stojadinovic and Allen (22) reported a case of carcinoid syndrome and encephalopathy in a patient with neuroendocrine tumor metastatic to liver which resolved promptly after surgical resection.

In our patient with well-differentiated NET metastatic to liver, the patient's normal transaminases, albumin, bilirubin, and INR argue convincingly against hepatic failure as a cause of his hepatic encephalopathy. No metastases were seen on head CT. The patient had no symptoms of carcinoid syndrome, making central serotonin depletion unlikely. Given the hepatofugal flow seen on both delayed arteriography and ultrasound imaging, and the patency of the main, left and right portal veins, the most likely cause of the encephalopathy in the patient was portal hypertension caused by transtumoral arteriportal venous shunting causing portal venous hypertension and hepatofugal flow. This high portal venous flow state is termed hyperdynamic portal hypertension (23), and can initiate a cascade of neurohormonal effects which act to exacerbate portal hypertension (24). While mass effect

on the central portal venous structures by tumor could also cause an obstruction to hepatopedal flow, the promptness of the clinical response argues against this mechanism of action in this case. Since reduction of tumor burden by surgical resection can improve the paraneoplastic encephalopathy (22), by analogy we reasoned that reduction of tumor burden by HAE would decrease the transtumoral arterioportal shunting, improve hepatopetal flow, and restore normal ammonia metabolism by the liver. Arterial demand by hypervascular liver metastases creates an extremely high flow state which can make such shunts difficult to image using typical injection and filming rates. We believe this explains why arterioportal shunting was only appreciated on the third angiogram, reflecting the altered flow-dynamics resulting from the prior embolizations. Although there was a close temporal relationship between the initiation of octreotide therapy and the development of initial hepatic encephalopathy, we feel that it is unlikely that there is a causal relationship between the events. Octreotide, an somatostatin analog has a cytostatic effect on neuroendocrine tumors by mimicking the endogenous inhibitory effect of somatostatin on neuroendocrine cells (25). Octreotide can also lead to vasoconstriction of the splanchnic circulation (26), which would tend to result in decreased blood flow through the portal venous circulation, reducing portal hypertension.

In conclusion, we report the case of a patient with diffuse hepatic malignancy, normal liver function, and portosystemic shunting whose hepatic encephalopathy improved after HAE. Improvement in encephalopathy after embolization was most likely due to improvement in portal hypertension and normalization hepatofugal flow by embolization of transtumoral arterioportal shunts. Although hepatic encephalopathy due to global hepatic dysfunction is considered a contraindication to HAE, it may be a useful therapy to improve encephalopathy in patients with neuroendocrine tumor metastatic to liver who have preserved synthetic liver function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Images from a 63-year-old with hepatic encephalopathy, metastatic well-differentiated neuroendocrine tumor and normal liver function testing. **(a)** Arterial phase CT demonstrates innumerable enhancing lesions within the liver. **(b)** Indium-111 octreotide whole body scintigraphy at 4 hours and 24 hours demonstrate marked uptake of tracer by the pancreatic and hepatic lesions. **(c)** Early digital subtraction angiography following selective injection of the superior mesenteric artery demonstrates retrograde filling of the gastroduodenal artery and reflux into the proper hepatic artery. **(d)** Delayed digital subtraction angiography following selective injection of the superior mesenteric artery demonstrates retrograde flow

in an enlarged coronary vein, consistent with portal hypertension. (e) Selective injection of the common hepatic artery demonstrates the anatomy of hepatic arterial system. (f) Following embolization of the segment IV branch of the hepatic artery, non-contrast CT demonstrates high attenuation contrast and particles within segment IV of the liver.

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Figure 2.

Images from a 63-year-old with hepatic encephalopathy, metastatic neuroendocrine tumor and normal liver function testing following embolization. **(a,b,c)** After embolization of the segment IV hepatic artery 4 days prior, digital subtraction angiography of the common hepatic artery demonstrates tumor blush throughout the liver. **(d)** 6 seconds after injection of the common hepatic artery, retrograde flow is seen in the intrahepatic (white arrow) and extrahepatic portal (black arrow) vein, consistent with arteriportal shunting and portal hypertension. **(e,f,g)** After embolization of the anterior division of the right hepatic artery 26 days prior, digital subtraction angiography of the right hepatic artery imaged at 2, 2.5, and 3

seconds demonstrates rapid retrograde filling of the right portal vein due to marked intratumoral arteriportal shunting.

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