Hepatic Transcatheter Arterial Chemoembolization Complicated by Postembolization Syndrome

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ABSTRACT

Postembolization syndrome (PES) is a common complication after embolic procedures, and it is a frequent cause of extended inpatient hospital admissions. PES is a self-limited constellation of symptoms consisting of fevers, unremitting nausea, general malaise, loss of appetite, and variable abdominal pain following the procedure. Although a definite cause is unknown, this syndrome is thought to be a result of therapeutic cytotoxicity, tumor ischemia, and resulting intrahepatic and extrahepatic inflammation. The authors report a case of PES precipitated by transcatheter intraarterial chemoembolization of hepatic metastases.

KEYWORDS: Postembolization syndrome (PES), chemoembolization, hepatocellular carcinoma (HCC), transcatheter arterial chemoembolization (TACE), complications, embolization complications

CASE REPORT

A middle-aged African American man with history of hypertension, diabetes mellitus, and sickle cell trait, presented with a mass in the distal pancreas. He underwent distal pancreatectomy and splenectomy with pathology revealing a well-differentiated neuroendocrine tumor with no evidence of lymph node involvement. Several years later, he developed increasing abdominal pain and was found to have multiple arterial hyperenhancing lesions throughout his liver, consistent with metastatic disease from the pancreatic neuroendocrine primary (Fig. 1). Despite multiple treatments, including radiofrequency ablation and octreotide therapy, the patient's condition continued to worsen, and a multidisciplinary consensus-based decision was made to treat the patient with transcatheter intraarterial chemoembolization.

At the time of presentation for the procedure, the patient was in his usual state of health, only complaining of occasional sweats and loose stool, but no fevers, chills, nausea, vomiting, or new pain. The chemoembolization procedure was completed from a right transfemoral approach with a coaxially placed 3 French catheter. Four separate vessels were treated. Initially, the microcatheter was advanced into a hypertrophied branch of the replaced right hepatic artery arising from the superior mesenteric artery. Angiography demonstrated perihepatic lymph nodes and multiple hypervascular lesions in the right hepatic lobe. Lack of nontarget perfusion, specifically colonic, was confirmed with intraprocedural C-arm computed tomography (CT). This branch vessel was embolized to stasis with 40–120 micron Embospheres[®] (Biosphere Medical, Rockland, MA) and Ethiodol[®] (Savage Laboratories, Medford, NY). A

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Figure 1 (A, B) Pretreatment contrast-enhanced axial computed tomography images (arterial phase) through 2 levels of the liver, demonstrating multiple enhancing lesions within the liver, confirmed to be neuroendocrine in origin.

second, more distal branch of the right hepatic artery was then catheterized and angiography demonstrated multiple hypervascular tumors within the hepatic dome. This vessel was chemoembolized with 5 mL of a 1:1 mixture of Ethiodol[®] and chemotherapy (mitomycin, doxorubicin, and cisplatin), followed by 300–500 micron Embospheres[®]. Completion angiography demonstrated stasis of flow and lack of tumor perfusion. This procedure was repeated in a segment 6 branch of the right hepatic artery. Finally, the microcatheter was advanced into the gastrohepatic trunk and more distally into a segment 2 branch of the left hepatic artery, beyond the gastric branches. A hypervascular lesion in segment 2 was embolized with 2 mL of the Ethiodol[®]: chemotherapy emulsion, followed by 300–500 micron Embospheres[®]. The patient tolerated the procedure well, and immediate postprocedural follow-up imaging demonstrated successful embolization of multiple tumors (Fig. 2).

Following the procedure, the patient was admitted for overnight observation with a general set of prophylactic antibiotics, fluids, antiemetics, and pain relievers, in addition to his home medications. However, overnight, he developed severe nausea and diffuse abdominal pain. Despite multiple doses of intravenous

antiemetics and narcotics, he experienced three episodes of nonbilious, nonbloody emesis associated with varying degrees of abdominal pain. He also developed sinus tachycardia and significant hypertensive episodes, up to 181/107, but this lability was a chronic problem seen in multiple previous admissions and it responded quickly to antihypertensive medications. His physical exam was only significant for mild diffuse abdominal tenderness. Laboratory values over the course of his hospital stay are presented in Table 1.

The following day, he complained of drowsiness and loss of appetite, remaining nothing-by-mouth (NPO) with aggressive hydration and frequent dosing of intravenous antiemetics and analgesics with very little effect. He continued to experience several episodes of emesis, and the treatment regimen continued. On the second postprocedure day, the patient's nausea and pain began to improve but he spiked a fever with a T_{max} of 101.2°F. Due to a mild leukocytosis noted in his daily laboratories (Table 1), an infectious workup was completed, including blood cultures and urinalysis. However, both remained negative throughout his hospital stay. He continued to improve and became afebrile, tolerating a slowly advanced diet on the third day after the procedure.

Figure 2 (A, B) Posttreatment noncontrast axial computed tomography images through similar levels of Fig. 1. Hyperdensity throughout both lobes of the liver correlate with Ethiodol[®] uptake and demonstrate successful embolization of several tumors.

Table 1 Patient's Laboratory Values at Baseline and Postoperative Days (POD) 0 through 4

Type of Laboratory	Baseline	POD 0	POD 1	POD 2	POD 3	POD 4
WBC (K/mL)	4.0	2.8	5.9	11.9	11.9	9.4
HGB (M/ μ L)	13.2	13.3	13.5	13.3	12.3	12.2
ALT (U/L)	48	68	58	72	96	74
AST (U/L)	70	71	107	141	178	103
Alk Phos (U/L)	232	133	649	532	445	401
Total Bili (mg/dL)	0.8	1.4	1.7	1.1	1.9	2

The patient was discharged on POD 4.

WBC, white blood cells; HGB, hemoglobin; ALT, alanine aminotransferase; AST, aspartate transaminase; Alk Phos, alkaline phosphatase; Total Bili, total bilirubin.

He was discharged following a normal bowel movement on the fourth day. He reported in his usual state of health at a schedule 2-month outpatient follow-up.

DISCUSSION

Our case describes a patient who experienced significant nausea, vomiting, fever, and abdominal pain for 3 days following transcatheter intraarterial chemoembolization of multiple hepatic metastases. Although these symptoms are nonspecific and could be suspicious for infection, his workup was negative and a diagnosis of postembolization syndrome was made based on exclusion. Other nonspecific symptoms have also been described, such as loss of appetite and malaise, but none is required for the diagnosis of PES. Elevated serum levels of liver transaminases can also be seen in the majority of patients following transarterial chemoembolization, including our case (Table 1).¹ Currently, there are no specific laboratory values or findings to identify PES, likely due to its transient and nonspecific nature. Therefore, postembolization syndrome is a diagnosis of exclusion. The multitude of systemic symptoms usually manifests ~24–72 hours after the procedure, and the syndrome is self-limiting and resolves in approximately a week; however, it still remains the major reason for hospitalization and extended inpatient admissions after the procedure.^{2,3}

PES is extremely common and has been reported to occur in up to 90% of patients undergoing hepatic chemoembolization.² In fact, PES is so common after hepatic chemoembolization that it is sometimes considered an expected, unavoidable event in many cases. A recent retrospective study at our institution consisting of over 172 hepatic chemoembolization procedures over an 8-year period noted an incidence of PES to be 55%, consistent with other reported rates in the literature.⁴

Although the etiology of PES is unknown, the cause is thought to be multifactorial. One common hypothesis is that PES is the result of tumor ischemia and necrosis in addition to antiinflammatory responses to the actual chemotherapeutic agents. Paye et al described the occurrence of PES by the pathological status

of the nontumorous hepatocytes in addition to the extent of tumor necrosis. In this study, tumor necrosis in a retrospective review of patients who were treated with transarterial chemoembolization before undergoing surgical resection of hepatocellular carcinoma was graded in 4 categories, and the status of the remaining liver (i.e., cirrhotic or fibrotic) was also stratified. The results found no correlation with the extent of tumor necrosis, but instead, placed fibrotic livers at a significantly increased risk for developing PES, a finding likely attributable to differences in arterial microcirculation secondary to fibrosis, resulting in increased distribution of cytotoxic compounds to the liver parenchyma.¹

Another potential contributor to the development of PES relates to a well-known complication of transcatheter intraarterial chemoembolization: extrahepatic, nontarget embolization.^{5–7} Chemotherapeutic agents can be inadvertently directed into gastrointestinal mucosa via gastric or duodenal branches, into the gallbladder via the cystic artery, to the diaphragms via the phrenic arteries or to the skin via the falciform artery, all of which may lead to PES (Figs. 3, 4, 5).⁵ Awareness of this complication through preprocedural planning, close inspection of cross-sectional imaging to identify variant anatomy, and mapping mesenteric angiography can significantly prevent unintentional delivery of chemotherapeutic agents to nontarget locations.⁶ However, despite superselective catheterization, minimal amounts of nontarget embolization are sometimes unavoidable, which can also contribute to the symptoms seen in PES. In addition, important considerations are necessary for normal anatomical variants of the regional hepatic inflow, including a replaced right hepatic artery and a gastrohepatic trunk, as seen in our case. According to Lewandowski et al, several small esophageal, phrenic, and gastric perforators are commonly present, particularly arising from the horizontal portion of a variant left hepatic artery/gastrohepatic trunk (Fig. 3). If possible, microcatheter placement should be distal to these vessels. If this is not possible or if reflux of chemotherapeutic agents is of concern, these vessels should be embolized before administration of chemotherapy, functionally converting the gastrohepatic trunk into a left

Figure 3 Celiac axis arteriogram obtained via a 5 French catheter: white arrow indicates right gastric artery, black arrowheads indicate accessory right gastric artery, long black arrow indicates gastrohepatic trunk, curved white arrow indicates left hepatic artery, and short black arrow indicates left gastric artery.

hepatic artery. In addition, the use of intraoperative C-arm CT can help detect and further avoid nontarget embolization by demonstrating perfusion to nontarget tissues, prior to the administration of the chemotherapeutic embolic agents.⁶

Figure 4 Common hepatic arteriogram via a 3 French catheter: black arrow indicates the coil embolized right gastric artery. Black arrowheads indicate an accessory right gastric artery.

Figure 5 Common hepatic arteriogram via a 3 French catheter: black arrowheads now indicate the coil embolized accessory right gastric artery.

A few studies have attempted to determine risk factors for developing PES, and although no definite preprocedural risk factors have been identified, Leung et al described a higher incidence of PES with intraoperative cystic artery embolization and/or increased embolic dose, as well as a lower incidence of PES in previously embolized patients. Additionally, in one study, hepatic tumors greater than 9 cm were associated with a greater prevalence of PES.⁸ Surprisingly, as previously described, Paye et al did not find a statistical difference in the extent of tumor necrosis, which is likely attributable to the multifactorial etiology of PES. Prophylactic antibiotics in patients who underwent transcatheter intraarterial chemoembolization did not prevent development of postembolization fever or decrease duration of hospital stays.⁹ Several preprocedural and periprocedural methods have also been described to decrease postprocedural pain and narcotic administration, such as periprocedural intraarterial lidocaine and celiac plexus blocks, but none have shown to prevent the remaining symptoms of fever, nausea, and vomiting, ultimately leading to no change in hospital stay duration.^{10,11}

The majority of the previous studies describing PES use patient populations with hepatocellular carcinoma or colorectal metastases. However, in our case, the patient had extensive neuroendocrine hepatic metastatic disease that was treated with chemoembolization. Because neuroendocrine tumors are relatively uncommon, the rarity of these tumors contributes to the small amount of publications examining outcomes and complications associated with the procedure. Although systemic chemotherapy has had limited success in the treatment of patients with metastatic neuroendocrine tumors, long-acting octreotide therapy is commonly used before arterial therapy is initiated, as demonstrated in our case. Use of octreotide has been shown to result in

significant inhibition of tumor growth in the majority patients with neuroendocrine tumors.¹² Unfortunately, correlation with complications in the setting of transarterial chemoembolization, including PES, has not currently been studied.

Since the syndrome is self-limiting, standard of care treatment includes as-needed intravenous and oral antiemetics, pain relievers, and/or hydration, all of which are utilized to treat the patient's symptoms until resolution is satisfactory. Changes in dietary regimens are frequently needed, as patients cannot tolerate oral intake due to nausea and appetite loss. Despite the mild leukocytosis seen in our case, conservative work-up was still obtained, although ultimately negative and likely unnecessary. These timely and expensive workups should be limited to those patients who experience prolonged pain lasting greater than 5 days or a persistently elevated white blood cell count. In those patients, severe complications should be excluded, such as abscess formation, spontaneous bacterial peritonitis, sepsis, hepatic infarction, or tumor rupture. In general, patients with PES do not require an imaging or clinical workup, and clinicians participating in the care of chemoembolization patients should be educated to avoid unnecessary medical costs.⁸

CONCLUSION

Transcatheter arterial chemoembolization is a widely performed alternative to surgery for the treatment of primary and metastatic lesions of the liver. There are many well-known complications of this procedure, one of the most common being the above-described, post-embolization syndrome, as demonstrated by multiple gastrointestinal and systemic symptoms several hours to days after the embolization procedure. Awareness of this complication is essential to avoid unnecessary, costly medical workups and protracted inpatient hospital stays. Careful attention to potentially avoidable causes, including nontarget embolization, can likely decrease the incidence and severity of this complication.

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