Nontarget Embolization Complicating Transarterial Chemoembolization in a Patient with Hepatocellular Carcinoma

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ABSTRACT

Nontarget embolization during transarterial chemoembolization, although infrequent, can be a serious complication. The authors describe a case of nontarget gastric embolization to the stomach after transarterial chemoembolization and describe the published incidence of nontarget embolization to various organs, its diagnosis, treatment, and possible outcomes.

KEYWORDS: Chemoembolization, hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy in the world. Although surgery or transplantation remain the only definitive treatments, transarterial chemoembolization is recommended for patients with surgically unresectable HCC.¹ The frequency of major complications for patients undergoing transarterial chemoembolization is ~4–6% and include nontarget embolization, liver failure, and hepatic abscess.^{1,2} Chemoembolization material can frequently be found outside of the liver during a transarterial chemoembolization procedure. Although the exact incidence of nontarget embolization is unknown, the risk of a major complication due to nontarget embolization is thought to be low.³

CASE REPORT

A 57-year-old man with hepatitis B-related cirrhosis presented to the interventional radiology (IR) depart-

ment for consultation regarding treatment options for recurrent HCC. The patient had a prior history of laparoscopic radiofrequency (RF) ablation for a segment 4a HCC. On routine follow-up imaging, the patient was found to have developed multiple new lesions in the left hepatic lobe, consistent with multifocal HCC (Fig. 1). The patient was not deemed a surgical candidate given his underlying cirrhosis. He was therefore referred to IR for transarterial chemoembolization as palliative treatment as well as a possible bridge to liver transplantation.

During transarterial chemoembolization, a catheter was utilized to select the celiac artery and an angiogram was performed, demonstrating conventional celiac arterial anatomy (Fig. 2). A microcatheter was advanced into the left hepatic artery and an additional angiogram was performed (Fig. 3). A mixture of 50 mg doxorubicin and 10 cc of Ethiodol[®] (Savage Laboratories, Melville, NY) was slowly infused into the left hepatic artery under fluoroscopic guidance. During the

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Figure 1 Axial contrast medium-enhanced T1-weighted fat-saturated magnetic resonance image demonstrates multiple small, ill-defined, arterially enhancing lesions in the left hepatic lobe. The lesions demonstrated washout on delayed images, consistent with hepatocellular carcinoma.

Figure 3 Digital subtraction angiogram with a microcatheter in the proximal left hepatic artery demonstrates multiple branches off the left hepatic artery. Chemoembolization was performed at this position.

latter portion of the infusion, Ethiodol[®] was visualized depositing in the region of the gastric cardia (Fig. 4); this deposition was not noted initially. The finding was consistent with nontarget embolization of the stomach secondary to an anomalous collateral vessel coursing from the distal left hepatic artery to arterial branches supplying the gastric cardia, in this case an accessory left gastric artery. After about two-thirds of the doxorubicin/Ethiodol[®] mixture had been given, the infusion was stopped due to the nontarget chemoembolization. Particle embolization, usually in the form of microspheres delivered after infusion of the doxorubicin/Ethiodol[®] mixture, was not performed.

The patient's routine postprocedure noncontrast computed tomography (CT) scan of the abdomen demonstrated Ethiodol[®] uptake in the left hepatic lobe and

diffusely in the gastric rugae, consistent with nontarget embolization to the stomach (Fig. 5).

The patient was admitted for inpatient observation overnight as well as counseled that he would likely be at increased risk for gastric ulceration and/or necrosis given the complication. He was started on intravenous pantoprazole and oral ranitidine during admission. The patient had 1 episode of nonbloody emesis overnight and experienced mild nausea relieved by metoclopramide and ondansetron. After tolerating a diet without any further abdominal discomfort or nausea on postprocedure day 1, the patient was discharged home. The patient was discharged with a

Figure 2 Digital subtraction angiogram with a reverse-curve catheter positioned in the celiac trunk demonstrates conventional celiac artery anatomy.

Figure 4 Angiogram with a microcatheter in the proper hepatic artery after chemoembolization had been performed demonstrates contrast within all hepatic branches. Additionally, there is increased density within the stomach, consistent with Ethiodol[®] uptake.

Figure 5 Noncontrast axial (A) computed tomography scans with coronal reconstruction (B) show distribution of Ethiodol[®], which is present in the left hepatic lobe, caudate lobe, and the gastric rugae.

30-day, outpatient regimen of both pantoprazole and ranitidine gastric ulcer prophylaxis.

The patient returned to the IR clinic 1 month after the procedure for follow-up. The patient reported no symptoms of abdominal pain, nausea, vomiting, nor did he report any symptoms to suggest an upper-gastrointestinal bleed in the interim. Routine laboratories drawn prior to the patient's clinic visit were unremarkable.

Follow-up magnetic resonance imaging (MRI) 2 months after his last transarterial chemoembolization demonstrated no findings to suggest recurrent HCC. Enhancement was no longer present in the previously enhancing left hepatic lobe lesions.

DISCUSSION

Published Incidence

Patients undergoing transarterial chemoembolization frequently experience symptoms related to the post-embolization syndrome, consisting of transient abdominal pain, nausea, fever, and ileus. However, serious complications can occur in up to 4–6% of patients, including liver abscess, liver failure, and nontarget embolization.¹

According to Gates et al,³ uptake of chemoembolization material outside of the liver during transarterial chemoembolization is a common occurrence. Sites of material deposition during transarterial chemoembolization include the lung, stomach, pancreas, gallbladder, duodenum, diaphragm, and spleen. However, the risk of a significant complication due to nontarget embolization is low.

Small arteriovenous shunts within HCC's are common and allow for chemoembolization material to reach the lungs via the hepatic veins. Although these shunts may not be visible during angiography, postprocedure CT scans can demonstrate lung or pleural uptake

(via injection into phrenic arteries) in up to 25% of patients undergoing the procedure.³

Nontarget embolization to the pancreas can also occur during transarterial chemoembolization. Most commonly this occurs by reflux of chemoembolic material into the dorsal pancreatic or gastroduodenal artery and is uncommonly of clinical significance. However, cases of acute pancreatitis have been reported.⁴

Chemoembolization material within the gallbladder after transarterial chemoembolization has been reported in up to 14% of cases. This occurs via infusion through the cystic artery, which usually arises off the proximal right hepatic artery. Despite this incidence, there is rarely an adverse or clinically significant outcome. In one series, less than 0.4% of patients required intervention such as cholecystectomy.³

Gastric uptake of chemoembolization material visualized on CT has been reported in only 1% of cases and is usually asymptomatic.³ This can occur by reflux of chemoembolization material from the point of infusion to the right or left gastric arteries or via flow through an anatomic variant such as in our presented case. To our knowledge, the actual reported incidence of nontarget embolization specifically involving the stomach is unknown.

In one prospective study, 26 patients who underwent transarterial chemoembolization also underwent endoscopy both pre- and posttransarterial chemoembolization.⁵ Postchemoembolization endoscopy demonstrated new gastrointestinal lesions in 62% of patients. Six patients had endoscopic findings of gastritis, 5 had evidence of hemorrhagic gastritis, and 9 patients had evidence of gastroduodenal erosions. All of these patients were reported to be asymptomatic. A similar study by Hirakawa, demonstrated the development or exacerbation of gastroduodenal lesions in 45% of patients who underwent transarterial chemoembolization.⁶ Massive gastric ulceration and massive upper gastrointestinal

bleed after transarterial chemoembolization have been reported, but nontarget embolization was not thought to be a causative factor in these cases.^{7,8}

Diagnosis

Hepatic arterial variants are frequently encountered during transarterial chemoembolization, and it is essential for the interventionalist to be both familiar with and recognize them. Not only is it important for directing therapy, but also to prevent nontarget embolization. It is the standard of care in the workup of a patient referred for liver-directed therapy to undergo either multiphase liver CT or MRI prior to a planned intervention. Common arterial anatomic variants can frequently be identified on CT and the interventional radiologist can appropriately plan an arterial approach based on imaging findings. At the time of transarterial chemoembolization, the following angiograms are routinely performed to identify vascular anatomy and evaluate for possible anatomic variants: superior mesenteric angiogram, celiac angiogram, and selective left or right hepatic arteriogram (depending on tumor location).⁹ During transarterial chemoembolization, chemoembolization material is infused slowly, so as to avoid significant reflux and possible embolization of other adjacent organs, including the stomach.

Nonhepatic branches arising from the hepatic arteries are a common finding in the general population, and are a potential source for nontarget embolization. In a recent study by Song et al,¹⁰ 205 of 250 patients (85%) studied had nonhepatic branches arising from the hepatic arteries on angiography. The most commonly encountered nonhepatic vessel arising from the hepatic arteries is the right gastric artery in 78% of studied patients (most frequently arising from the proper hepatic artery), followed by the hepatic falciform artery seen in 52% of studied patients (most frequently arising from the left hepatic artery), followed by an accessory left gastric artery, as presented in our patient, seen in 17% of patients studied. In patients with an accessory left gastric artery, 88% arise from the left hepatic artery and the remaining 12% arise from the proper hepatic artery. Other nonhepatic vessels include the cystic, supraduodenal, and retroduodenal arteries.

Treatment and Prognosis

When encountered unexpectedly, a vascular anatomic variant causing nontarget embolization should prompt the interventionalist to abort the infusion of chemoembolization material immediately so as not to cause adverse effects or potential organ injury. Our patient had received most of his chemotherapy dose before the accessory left gastric artery was visualized. Although he potentially may have required additional treatments via

selective left hepatic artery transarterial chemoembolization, he was fortunate to have no signs of recurrent disease upon routine follow-up imaging. Had our patient required additional therapy via selective left hepatic artery chemoembolization, or had the accessory left gastric artery been visualized prior to infusion of the chemoembolic agent, prophylactic embolization of the accessory vessel would have been required to prevent nontarget embolization.

In the setting of known nontarget embolization to the stomach, no standard of care for treatment or prevention of a gastroduodenal injury currently exists. Had the patient experienced signs or symptoms of an acute upper gastrointestinal bleed, gastroenterology consultation with possible endoscopy may have been indicated. As described previously, cases of massive hemorrhage or ulceration have been described following transarterial chemoembolization.^{7,8} However, given that the patient was stable postprocedure with minimal symptoms (nausea and 1 episode of nonbloody emesis), prophylaxis to prevent a gastrointestinal bleed was initiated.

Secondary to a high degree of concern for chemotherapeutic-induced tissue necrosis because embolization material was visualized in the stomach on the patient's postprocedure CT scan of the abdomen, gastroduodenal prophylactic therapy was initiated. The use of acid-suppressing drugs such as a proton-pump inhibitor (PPI) is based on the stability of a blood clot in a low acid/high pH environment.¹¹ Therefore, a gastric ulcer that has bled (or when suspected tissue injury has occurred, as in this case) has the best chance of healing in a low-acid environment. If one were to extrapolate the debatable topic of gastrointestinal prophylaxis and therapy for acute peptic ulcer bleeding from the medical literature, a recent Cochrane Database review showed that PPIs significantly reduced rebleeding rates in cases of known gastroduodenal ulcers when compared with controls (10.6% vs 17.3%, respectively).¹² Surgery rates were also reduced (6.1% on PPI vs 9.3% on control). No difference was demonstrated in all-cause mortality rates between PPI and control, but in patients with active bleeding or those who had a nonbleeding visible vessel on endoscopy, PPI treatment reduced mortality (OR 0.53), rebleeding, and surgery. Although there is no convincing evidence to support the use of H2 receptor antagonists because these drugs do not reliably increase the gastric pH, they are often used because the medications' toxicity profile is low.¹¹

CONCLUSION

Although infrequent, nontarget embolization is a recognized complication associated with transarterial chemoembolization. Knowledge of variant hepatic anatomy and nonhepatic arteries originating from the hepatic

arteries will assist the interventional radiologist at avoiding this complication. In the case presented of nontarget gastric chemoembolization, the patient fortunately experienced no significant adverse outcome. In addition, slow and cautious infusion of chemoembolization material will minimize reflux into adjacent vessels therefore minimizing the effect to surrounding organs.

Although there is no clear evidence nor are there clear recommendations currently in the literature regarding treatment of gastric nontarget embolization, it may be beneficial to commence PPI therapy postprocedure to prevent occurrence of erosive or ischemic gastritis. In the case of acute upper gastrointestinal bleeding, gastroenterology consultation and possible endoscopy would be indicated for further evaluation.

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