Hepatic Abscess Complicating Transarterial Chemoembolization in a Patient with Liver Metastases

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ABSTRACT

Hepatic abscess following transarterial chemoembolization is an uncommon complication. The authors describe a case of liver abscess after transarterial chemoembolization for neuroendocrine liver metastases, including risk factors, prophylaxis, treatment, and outcomes.

KEYWORDS: Abscess, chemoembolization

Over the last several decades, transarterial chemoembolization has emerged as a treatment choice for many patients with primary and secondary liver malignancies. The hypervascular nature of many hepatic tumors allows for local delivery of chemotherapeutic agents followed by embolization of the arterial source while the surrounding parenchyma can be spared by nature of the dual blood supply to the liver. This rationale is based on the fact that treatable tumors stimulate neovascularity and may derive much or all of their blood supply from the hepatic artery. For example, some hepatic metastases may have a mixed blood supply, whereas hepatocellular carcinomas receive nearly all of their blood supply from the hepatic artery.¹ Transarterial chemoembolization is often performed on medically complex patients, and is not without complications. Serious adverse events complicate ~5% of chemoembolization procedures, with the most common serious events including liver infarction and abscess.²

CASE REPORT

A 60-year-old woman with a small bowel primary neuroendocrine tumor was treated for metastatic disease of the liver. The patient, with a past medical history significant only for hyperlipidemia, had received systemic chemotherapy for her tumors consisting of capecitabine and temozolomide. She had no prior abdominal surgery or biliary procedure. Two months after the completion of chemotherapy, the patient underwent transarterial chemoembolization. The first procedure targeted the left hepatic lobe. The second procedure, performed 8 weeks later, targeted the right hepatic lobe (Fig. 1). For each procedure, the patient was given a prophylactic antibiotic regimen consisting of intravenous (IV) ciprofloxacin and metronidazole. Chemoembolization consisted of a mixture of doxorubicin 50 mg, cisplatin 100 mg, and mitomycin 10 mg in 10 mL of dilute contrast material with 10 mL of lipiodol. This was slowly infused into the lobar hepatic artery. This was followed by 300–500 micron acrylic particles (Embospheres[®], Biosphere Medical,

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Figure 1 Angiogram during transarterial chemoembolization demonstrates a microcatheter in the right hepatic artery with contrast opacification of the right hepatic artery and its branches. A chemoembolic mixture was subsequently infused into the right hepatic artery.

Rockland, MA) suspended in contrast agent that was slowly infused into the vessel until near-stasis was achieved. Both procedures were initially well tolerated and the patient was discharged the following day.

Thirty-nine days following transarterial chemoembolization, the patient presented to the emergency department complaining of 2–3 weeks of intermittent fevers with increasing fatigue, abdominal pain, nausea, and vomiting. Her laboratory tests were notable for a leukocytosis of 19 k/ μ L and elevated liver enzymes including: AST 200 U/L, ALT 229 U/L, alkaline phosphatase 452 U/L, total bilirubin 2 mg/dL, and direct bilirubin 1.2 mg/dL.

Admission computed tomography (CT) demonstrated an irregular hypodense lesion within the right

Figure 3 Computed tomography image obtained after ultrasound-guided drain placement demonstrates a pigtail catheter within the fluid collection.

lobe of the liver consistent with an abscess (Fig. 2). Subsequently, a 10 French (Fr) percutaneous pigtail drain was placed into the collection under ultrasound guidance (Fig. 3), and purulent material was drained. Initial empiric antibiotics included IV vancomycin, metronidazole, and aztreonam (due to penicillin allergy). Cultures of both aspirated fluid and blood grew *Streptococcus milleri*, and antibiotics were narrowed to ceftriaxone. Following drainage and initiation of antibiotics, the patient defervesced, and her leukocytosis and elevated hepatic enzymes corrected. The patient was discharged 8 days after admission in satisfactory condition. At the time of this writing, the patient is doing well. The hepatic drain has remained in place due to persistent output, possibly due to a persistent biliary fistula.

DISCUSSION

Abscess is an unusual complication of hepatic transarterial chemoembolization. Reported rates vary, ranging up to 4.5% of patients and 2% of procedures,³ and likely reflect heterogeneous populations, variation in chemoembolization treatment, and numbers of patients

Figure 2 Axial (A) and coronal (B) contrast-enhanced computed tomography scans demonstrate a large thick-walled fluid collection in the right hepatic lobe, consistent with an abscess.

studied. Several risk factors have been suggested, including portal vein thrombosis, metastatic tumor, and gastrointestinal mucosal malignancy. However, only biliary obstruction or a prior biliary procedure has been shown to represent an increased risk for postchemoembolization abscess.

In a retrospective study, investigators reviewed the risk of liver abscess in 6,255 transarterial chemoembolization procedures in 2,439 patients with hepatocellular carcinoma (HCC) or metastatic tumors.⁴ Fifteen abscesses occurred in 14 patients, representing 0.2% of all procedures. Uni- and multivariate analysis revealed a significantly increased risk of abscess in patients who had any biliary abnormality that predisposed to ascending infection. These abnormalities were defined as biliary intervention including endoscopic papillotomy, bilioenteric anastomosis or fistula, external biliary drainage, or pneumobilia of unknown source.

Similarly, in a retrospective review of 1374 patients who underwent a total of 2581 transarterial chemoembolization procedures, 7 cases (0.51% of patients; 0.27% of procedures) of hepatic abscess were diagnosed.⁵ After abscess was diagnosed, cases were retrospectively reviewed for possible associated factors including biliary tract disease; prior abdominal surgery; diabetes mellitus; endocrine, autoimmune or hematologic disease; malignancy; antibiotic or steroid use. Four of 7 occurred in patients with prior biliary tract disease (including cholelithiasis, choledocholithiasis, and tumor invasion of the common bile duct). Adrenal insufficiency was identified in a fifth patient while the 2 remaining patients had no identifiable risk factor. Underlying biliary disease or other comorbidities in patients not affected by abscess were not discussed.

In a different study comprised of primarily of patients with metastatic tumor, 8 liver abscesses occurred in 7 of 157 patients following 397 transarterial chemoembolization procedures (2% of procedures).³ In this case-control study, the authors reviewed risk factors for the development of hepatic abscess following transarterial chemoembolization. Six of the seven patients with liver abscess had a history of bilioenteric anastomosis (Whipple procedure), while only 1 of 150 patients (0.7%) who had not had a bilioenteric anastomosis developed hepatic abscess. The odds ratio for development of liver abscess in the presence of bilioenteric anastomosis was 894 (95% CI, 50–16,000). This risk was seen despite the routine use of prophylactic antibiotics. Other studies have noted an increased incidence of hepatic abscess following transarterial chemoembolization in patients with a biliary abnormality.^{5–7}

The mechanism for abscess formation after transarterial chemoembolization is incompletely understood. However, the mechanism for infection in patients with bilioenteric anastomosis is thought to involve retrograde

colonization of the biliary tree with intestinal flora.³ Bacterial colonization of the bile has been described in over 90% of patients with bilioenteric anastomosis.⁸ In most patients this colonization is asymptomatic, but following transarterial chemoembolization, biliary necrosis associated with arterial embolization allows for breakdown of the barrier separating the colonized biliary tree with subsequent inoculation of ischemic tumor.⁹ Further, bilioenteric anastomosis such as the Whipple procedure involves sacrificing the common bile duct artery, which is a major supplier of biliary collateral arterial flow. Absence of this collateral supply may accentuate the bile duct ischemia produced by transarterial chemoembolization.⁶

Supporting enterobiliary contamination as a source of infection is the variety of organisms reported in the literature as isolated from patients with abscess following transarterial chemoembolization. The list includes primarily pathogens such as gram-negatives including *Klebsiella*, *E. coli*, and other enteric organisms.⁵ This is not without exception however, as nonenteric gram positives and fungi such as the *Candida* species have been reported.^{4,7}

Prophylaxis

To date, no randomized controlled trials have been performed to establish the role of prophylactic antibiotics in transarterial chemoembolization. In the absence of prophylactic antibiotic use, fatal sepsis within 24 hours following chemoembolization has been described.¹⁰ Therefore, although not universal, prophylactic antibiotics are routinely prescribed for most patients undergoing transarterial chemoembolization.¹¹ Because of the lack of data, suggestions for routine prophylaxis have been proposed. These include 1.5–3 g ampicillin-sulbactam IV, 1 g cefazolin IV $\pm$ 500 mg metronidazole IV, or 1 g ceftriaxone IV.¹⁰

Given the trend in the literature demonstrating higher risk of abscess in patients with bilioenteric anastomosis or biliary instrumentation, more-aggressive prophylactic antibiotic regimens have been investigated. In a study limited by small sample size in high risk patients, investigators compared standard prophylaxis to an aggressive regimen including preprocedure bowel cleansing with oral neomycin and erythromycin followed by metronidazole and levofloxacin starting 48 hours prior to transarterial chemoembolization and continuing for 2 weeks after the discharge.¹² Standard prophylaxis included 1 dose of cefazolin and metronidazole preprocedure and continuing until discharge followed by amoxicillin/clavulanate for 5 days. Seven high-risk patients received the aggressive regimen for a total of 16 procedures. Liver abscess occurred in 2 of 7 (28.6%) high-risk patients after 2 or 16 (12.5%) procedures compared with 6 of 7 (85.7%)

historical controls (standard regimen) after 6 of 14 procedures. Although the difference in abscess rate did not reach statistical significance, authors concluded that a trend was demonstrated ($p = 0.103$ and $p = 0.101$ for patients and procedures, respectively).

Diagnosis

The diagnosis of hepatic abscess, a relatively rare complication, is confounded by the constellation of signs and symptoms seen in postembolization syndrome, a frequent adverse reaction to transarterial chemoembolization. Postembolization syndrome is characterized by fever, nausea, vomiting, abdominal pain, and leukocytosis, and occurs with such frequency as to be considered expected outcome rather than complication.¹¹ Although patients with hepatic abscess demonstrate similar symptoms as those with postembolization syndrome, the time course can generally be used to differentiate the two. Symptoms of postembolization syndrome typically abate by 1 week, whereas presentation of hepatic abscess is usually delayed. Liver abscess should be considered in any patient with suggestive symptoms beyond 7 days. Time until diagnosis of abscess is variable; following transarterial chemoembolization, abscess has been diagnosed at 2 days⁵ and up to 4 months, but generally occurs within 7 weeks. Song et al published a median of 20 days until diagnosis in 15 patients,⁴ and Kim et al reported a mean of 19 days.³

Imaging plays a crucial role in establishing the diagnosis. Imaging characteristics of hepatic abscess include an irregular hypodense liver mass that may contain gas. Abscesses may appear as hypoechoic masses at ultrasound. Gas present within the abscess may manifest as echogenic foci with sonographic reverberation shadows. The finding of gas within postchemoembolization abscesses has been variably reported, from a minority up to 100% of cases in small series.⁵ However, the presence of gas is not specific to hepatic abscess and has been described in uninfected patients following transarterial chemoembolization. Diagnostic aspiration of a suspicious mass may be necessary.

Blood cultures may also be helpful. For example, Song et al reported positive blood cultures in 10 of 15 patients.⁴ Finally, elevation of hepatic enzymes has been described.¹³

Treatment

The treatment of choice for hepatic abscess is percutaneous drainage¹⁴; however, simple aspiration is considered by some when the collection is relatively small (< 3 cm). Percutaneous drainage is typically done under ultrasound guidance. Management of percutaneous

drains will not be discussed here. Rarely, surgical management of hepatic abscess may be necessary if capsular rupture occurs with extension of infection into the peritoneum. Drainage or aspiration is always combined with IV antibiotics. Prior to culture results, empiric antibiotic coverage should be broad and cover enteric organisms as well as anaerobes. Depending on clinical response and culture results, some choose to narrow the antibiotic regimen spectrum once a specific pathogen is identified.

Outcome

Death is the feared consequence of hepatic abscess and has been reported in up to 50% of patients in one series,⁶ although small sample size likely leads to an overestimation of the actual rate. Song et al reported a mortality rate related to liver abscess was 13.3% (2 of 15 patients)⁴; Chen et al reported mortality of 20% (1 of 5 patients), which was partially attributed to hepatic abscess.¹³ Others report a favorable outcome in all patients who experienced postchemoembolization abscess.^{3,5,7} Although hepatic abscess may be cured, irreversible deterioration of hepatic function has been described as a consequence.⁴ Development of biliary fistula may necessitate prolonged or indefinite placement of a percutaneous drain.

Conclusion

With a significant morbidity and mortality, hepatic abscess is an uncommon, but dreaded complication following transarterial chemoembolization. Although several risk factors have been proposed, biliary abnormality (most commonly bilioenteric anastomosis) has emerged as the only major risk factor. The signs and symptoms of postembolization syndrome and hepatic abscess are similar; however, the former generally subsides by 7 days. Liver abscess should be considered in any patient with fever, leukocytosis, abdominal pain, nausea, and vomiting greater than 1 week following transarterial chemoembolization.

Although there are no data to support use of prophylactic antibiotics, routine prophylaxis is prescribed by many. Additionally, there is no evidence that special prophylactic antibiotic regimens in patients with biliary abnormality are effective; however, bowel cleansing regimens may be of benefit.

Diagnosis is based on clinical suspicion, clinical examination, laboratory tests, and imaging. Although mortality is a serious concern, most patients are cured of infection following treatment, which typically consists of percutaneous drainage and IV antibiotics. Initial antibiotics should be broad in spectrum, and include coverage for enteric organisms while cultures are pending.

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