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Pyogenic abscess after hepatic artery embolization: A rare but potentially lethal complication

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Abstract

Background—Hepatic artery embolization (HAE) is used commonly to treat liver tumors or hemorrhage. Infectious complications are rare, but carry high morbidity and mortality. Identification of clinical factors associated with post-embolization abscess may improve management and outcome.

Methods—Clinical and pathologic variables of patients treated with HAE were collected and analyzed to determine the etiology, incidence, and outcome of pyogenic hepatic abscess.

Results—From January 1998 to January 2010, 971 patients underwent 2,045 HAE procedures. Fourteen patients developed a pyogenic hepatic abscess following embolization for an overall rate of 1.4%. Thirty-four patients (4%) had a history of bilioenteric anastomosis (BEA) and 21 patients (2%) lacked a competent sphincter of Oddi due to the presence of a biliary stent (N=19) or a prior sphincterotomy (N=2). Eleven (33%) of the 34 patients with a BEA and 2 (10%) of 21 patients with an incompetent sphincter developed abscesses, in contrast to only 1 abscess (0.05%) among the 916 patients with apparently normal sphincters (0.1%, OR 437.6 (95% CI 54.2 – 3,533, $p < 0.0001$). Gram negative and gram positive aerobes were the most common bacteria isolated following drainage. Percutaneous drainage was the initial management strategy in all patients; 2 patients (14%) required subsequent surgical drainage and hepatectomy and 3 (21%) died.

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Conclusion—Pyogenic hepatic abscess is rare after HAE. A history of BEA or an incompetent sphincter of Oddi due to a biliary stent or prior sphincterotomy substantially increases in the likelihood of this highly morbid and potentially fatal complication.

Keywords

hepatic artery embolization; pyogenic liver abscess; infection; malignancy; drainage

Introduction

Hepatic arterial embolization (HAE) is a commonly utilized palliative procedure for patients with hepatocellular carcinoma (HCC) and neuroendocrine tumors (NET).(1–2) It is also performed, although less commonly, for patients with sarcoma and other gastrointestinal malignancies.(3) At our institution, small particle embolization is the procedure of choice for treatment of hypervascular liver tumors, having an outcome and complication profile similar to chemoembolization (TACE).(4–5) HAE using coils, rather than particle embolics, is used to arrest bleeding from the hepatic arterial circulation.

Major complications following HAE are rare but can be devastating in patients with advanced malignancy.(5–7) Known complications include postembolization syndrome (pain, nausea/vomiting, and fever), liver failure, tumor rupture, cholecystitis, pulmonary embolism, and biloma formation. Minor complications such as transient renal insufficiency, cardiac arrhythmias, and groin hematoma are also well documented.(5) Pyogenic hepatic abscess is a rare and potentially fatal complication associated with TACE and HAE, with a reported incidence of less than 0.5%.(8–11) The objective of this study was to determine clinical variables associated with abscess formation after HAE, with the ultimate goal of identifying high risk patients and possible areas for intervention.

Patients and Methods

Following review board approval, our institutional Interventional Radiology Database was queried for all embolization procedures performed between January 1, 1998 and January 1, 2010. Patients who had hepatic artery branches embolized for bleeding using coils were included. The medical record was evaluated for tumor type, history of bilioenteric anastomosis, history of recent biliary intervention with either percutaneous or endoscopic stent placement or sphincterotomy, and history of abscess formation. Tumor size was recorded; when more than one tumor was embolized, the size of the largest embolized tumor was recorded.

Criteria for pyogenic hepatic abscess were the presence of the following: clinical symptoms of infection (fever, leukocytosis, bacteremia), imaging consistent with the diagnosis of abscess, and a positive drainage culture. Fluid collections that were aspirated and found not to be pyogenic abscesses were excluded. Imaging criteria for liver abscess have been previously described and consist of both simple rim-enhancing fluid collections with or without air-fluid levels as well as complex septated masses.(12) Examples of these are shown in Figure 1.

The authors' technique for HAE has been previously reported.(13) Briefly, we exclusively utilize small particle embolization for tumor intervention and employ coil embolization for patients being treated for acute hemorrhage. Our routine antibiotic prophylaxis for HAE includes first generation cephalosporin, which is administered at the time of the embolization and for two doses post-procedure. When patients have a bilioenteric anastomosis or stent, our protocol is to utilize a broad spectrum antibiotic with biliary penetration. During the course of the study period, we evolved to using piperacillin/tazobactam or cefotetan at the time of the procedure and for five days post-procedure. If patients are discharged early they receive oral antibiotic therapy to complete five days of therapy.

Results

During the study period, there were 2,167 procedures performed in 1,255 patients; patients who had embolization procedures outside of the hepatic arterial system (N=284) were excluded from analysis. There were 971 patients who underwent 2,045 embolization procedures remaining for analysis. Clinicopathologic variables are outlined in Table 1. The majority of patients were treated for HCC (57%) or NET (26%). The remaining tumor types included sarcoma (4%), melanoma (2%), and other tumors of gastrointestinal primary origin. Four patients underwent coil embolization to treat hemorrhage. One embolization procedure was performed in 517 patients (55%); the median number of embolization procedures for the entire cohort was 1 (range 1 – 14).

Fifty-five patients had had biliary tract procedures prior to HAE. Thirty-four patients (4%) had a history of a prior BEA, including 22 patients (2%) who had undergone a pancreaticoduodenectomy (PD). Twenty-one patients (2%) had a history of a sphincterotomy (N=2), a metallic stent (N=6) or an internal/external drain (N=13) in place at the time of the embolization procedure.

Fourteen patients (1.4%) developed a pyogenic hepatic abscess after embolization (Table 2). Of these, only one patient (7%) had not previously undergone a biliary procedure. Of note, none of the 14 patients had evidence of portal vein thrombosis. Eleven of these patients (79%) had a prior BEA and 2 (14%) had an incompetent sphincter of Oddi. As shown in Table 2, the risk of abscess formation in patients with a BEA was 33% and 10% in patients with a disrupted sphincter (stent placement or sphincterotomy). The risk of abscess formation was significantly increased in patients with a BEA (11/34, 33%) compared to patients with an intact sphincter of Oddi (1/916, 0.1%), OR 437.6 (95% CI 54.2 – 3,533), $p<0.0001$.

Characteristics of the 14 patients who developed a liver abscess after embolization are listed in Table 3. Twelve patients had particle embolization for tumors and 2 had coil embolization for bleeding. Eight patients (62%) developed an abscess after one HAE, while the remaining 6 (28%) had had one or more prior embolizations without complication. Two patients (14%) had coil embolization for hemorrhage. The median time from embolization to abscess diagnosis was 12 days (range 6 – 28). In patients with malignant disease, the median size of the largest tumor in the abscess group was 3.2cm (range 2.4 to 9.2) and was similar to

median tumor size from the no abscess group (5.0cm, range 1.0 to 15.2), $p=0.23$. Two patients did not receive antibiotic prophylaxis at the time of embolization.

Bacteriology from the abscess drainage cultures is shown in Table 4. The most common bacteria were aerobes, both gram negative and gram positive. There were two patients (17%) whose cultures grew resistant isolates; one patient had methicillin-resistant *Staphylococcus aureus* MRSA) and another had vancomycin-resistant *Enterococcus* VRE). Both patients had a history of infections with these bacteria and had undergone prior biliary intervention procedures. Culture sensitivities revealed that 9/14 (64%) patients had been given antibiotics that adequately covered the bacterial cultures from the abscess cavity.

All patients were initially treated with percutaneous drainage. Two patients (14%) required operative drainage due to persistent septic shock despite percutaneous drainage. Both patients had an initial exploratory laparotomy and drainage but ultimately required formal hepatic resection. One of these patients died of sepsis postoperatively. Two additional patients died of cancer progression and hepatic failure, respectively. The overall mortality rate in patients who developed a hepatic abscess was 21%.

Discussion

Pyogenic hepatic abscess after HAE is rare, but is associated with significant morbidity and mortality,(6–10) especially in patients with advanced malignancy.(14–15) Moreover, abscess formation impairs recovery in patients who already suffer from terminal malignancy and may preclude future embolization procedures or other cancer-directed therapy. This series, in line with other reports, demonstrates that abscess formation after embolization is exceedingly rare without predisposing factors (<1%) (Table 5). However, the presence of a BEA or a sphincter of Oddi compromised by a biliary stent or sphincterotomy increases the likelihood of abscess formation by more than 30-times the baseline risk.

Common complications after embolization include fever, leukocytosis, nausea and vomiting, elevation in liver function tests, and pain--a compilation of signs & symptoms comprising post-embolization syndrome.(6) The ability to discern this common syndrome from development of an abscess is pertinent to the management of these patients. In particular, early radiographic intervention may be indicated and may change the threshold for percutaneous drainage. Unfortunately there is considerable overlap in the radiographic findings of tumor necrosis, which is expected following embolization, and those suggestive of abscess. Embolized tumors undergo liquefactive necrosis and become low-density on CT. In addition, tumors frequently contain gas within the first few weeks following embolization, so that imaging may not clearly distinguish expected post-embolization findings from an abscess.

Standard cephalosporin prophylaxis may not be sufficient to prevent liver abscess in patients with BEA undergoing hepatic embolization. Some investigators have attempted to prevent this complication by changing antibiotics, modifying the timing and duration of prophylaxis, and adding an oral bowel preparation.(16–17) Geschwind et al. reported a series of 8 patients, 7 of whom had prior bilioenteric anastomosis and 1 who had a cholecystectomy

and papillotomy.(16) The patients were divided into two groups: group 1 received one preprocedure dose of cephalexin (standard prophylaxis), and group 2 received piperacillin/tazobactam for a median of 3 days, beginning 24–36 hours before embolization. Group 2 also received an oral bowel preparation with neomycin, erythromycin, and Fleets Phospho-Soda one day prior to the procedure. All 4 patients in group 1 developed a hepatic abscess compared to none in group 2. Although these results are interesting, the small number of patients preclude and definitive conclusions or recommendations for prophylaxis.

Another group switched the standard prophylactic regimen of cefazolin and metronidazole to levofloxacin and metronidazole. This new regimen was initiated 2 days prior to and was continued for 2 weeks following HAE; they also utilized an oral bowel preparation 24 hours prior to embolization.(17) There were seven patients treated; 2 had prior pancreaticoduodenectomy and 5 had a biliary stent in place at the time of embolization. Pyogenic hepatic abscess developed in 2 of 7 patients after 2 of 16 procedures. However, there was a trend toward a lower rate of abscess formation in these high-risk patients when compared to historical controls (6 of 7 patients ($p=.103$) and 6 of 14 procedures ($p=.101$).

The authors' current protocol is to administer one pre-procedure dose of piperacillin/tazobactam or cefotetan, both of which have excellent biliary penetration, and then to continue for 5 days after embolization. When patients are discharged before five days, an oral equivalent antibiotic is utilized. Culture analysis (Table 4) indicates that the standard regimen is sufficiently broad in terms of coverage. In addition, the majority of recovered organisms from liver abscess and blood cultures show continued sensitivity to the previously administered prophylactic agent(s). It is possible that antibiotic delivery to embolized parts of the liver may be hampered by poor vascularization. The reports by Geschwind(16) and Patel(17) suggest that alternative measures to reduce the microbial load (i.e., adding a bowel preparation and starting prophylaxis at least one day prior to procedure) may be helpful. However, the numbers in both studies are too small to draw definitive conclusions, so the role of bowel preparation in addition to the optimal timing and duration of prophylaxis have yet to be determined.

Based on this experience, it is clear that patients with altered biliary anatomy or a compromised sphincter of Oddi are at significantly increased risk for hepatic abscess after HAE for tumors or bleeding. The best method for prevention in high risk patients is unclear, but given the significant morbidity and mortality of this complication, the authors recommend an intravenous antibiotic regimen of appropriate spectrum and biliary penetrance before and after the procedure. Equally important are a heightened awareness and high clinical suspicion for early recognition and intervention, which could potentially improve outcome.

Abbreviations

BEA	bilioenteric anastomosis
HAE	hepatic artery embolization
HCC	hepatocellular carcinoma

NET	neuroendocrine tumor
TACE	transarterial chemoembolization
PD	pancreaticoduodenectomy
GI	gastrointestinal

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Figure 1. Pyogenic hepatic abscess after hepatic artery embolization

Panel A – B. A 35 year old female who had a pancreaticoduodenectomy 5 years prior presented with new hepatic metastasis in the left hemiliver (arrows). The patients received 2 grams of cefotetan at the time of her procedure, which continued for 5 days after the procedure.

Panel C – D. The patient was discharged home and returned on post-procedure day 10 with fevers and rigors. CT scan revealed a rim enhancing collection with air (asterisk). Percutaneous drainage revealed gram negative anaerobic infection consistent with pyogenic hepatic abscess.

Table 1

Clinicopathologic features of 971 patients treated with HAE

Variable	N (%)
<u>Tumor Type</u>	
HCC	557 (57)
Carcinoid/Neuroendocrine	249 (26)
Sarcoma	34 (4)
Melanoma	19 (2)
GIST	19 (2)
Cholangiocarcinoma	16 (2)
Adenoma	13 (1)
Colorectal liver metastasis	11 (1)
Thyroid	11 (1)
Breast	10 (1)
Other	32 (3)
<u>Type of embolization</u>	
Particle	967 (99)
Coil	4 (1)
<u>Number of embolization procedures per patient</u>	
1	517 (53)
2	200 (21)
3	112 (12)
4	49 (5)
5	93 (10)
<u>Bilioenteric Anastomosis</u>	
Pancreaticoduodenectomy	22 (65)
Hepaticojejunostomy	10 (30)
Choledochojejunostomy	2 (6)
<u>Prior Biliary Procedure</u>	
Sphincterotomy	2 (10)
Metal Stent	6 (29)
Internal/External Drain	13 (62)

Table 2

Incidence of pyogenic hepatic abscess following hepatic artery embolization

	Patients N (%)	Number of Procedures Performed	Patients with Abscess N (%)[*]
All patients	971	2,045	14 (1.4)
Normal anatomy	916	1,948	1 (0.1)
Bilioenteric Anastomosis	34 (4)	67	11 (33)
Biliary Intervention [#]	21 (2)	33	2 (10)
Bilioenteric Anastomosis or Biliary Intervention	55 (6)	100	13 (24)

^{*} No patient had more than one abscess

[#] Bilioenteric drain, stent, or prior sphincterotomy

Table 3

Characteristics of 14 patients who developed pyogenic hepatic abscess after embolization

Variable	N (%)
First embolization	8 (62)
<u>Type of embolization</u>	
Particle	12 (86)
Coil	2 (14)
Median time from embolization to development of abscess (days, range)	12 (6 – 28)
<u>Periprocedural antibiotics</u>	
None	2 (14)
Fluoroquinolone	1 (7)
Clindamycin/aminoglycoside	2 (14)
First generation cephalosporin	3 (21)
Second generation cephalosporin	2 (14)
Piperacillin/tazobactam	4 (29)
Initial treatment was percutaneous drainage	14 (100)
Required operative drainage	2 (14)
Median hospital stay (days, range)	2 (6 – 115)
ICU admission	3 (21)
Deaths	3 (21)

Table 4

Microbiology from abscess drainage

Variable	N (%)
Positive Gram Stain	12 (86)
Positive Abscess Culture	14 (100)
Polymicrobial	8 (57)
Gram Negative	11 (79)
Gram Positive	13 (93)
Anaerobic	12 (86)
Yeast	0 (0)
Positive Blood Culture	9 (64)
Abscess cultures *	
<i>Enterococcus</i> species *	7 (50)
<i>Escherichia coli</i>	5 (36)
<i>Enterobacter</i> species	5 (36)
<i>Klebsiella</i> species	3 (21)
<i>Citrobacter</i> species	3 (21)
<i>Streptococcus</i> species	3 (21)
<i>Staphylococcus</i> species **	2 (14)
<i>Clostridium perfringens</i>	1 (7)
<i>Prevotella</i> species	1 (7)

* one patient had vancomycin-resistant enterococcus

** one patient had methicillin-resistant *Staphylococcus aureus*

Table 5

Prior studies of pyogenic hepatic abscess formation after embolization

Reference	Patients (N)	Type of HAE	Tumor Type	Abscess N (%)	Patients with Abscess Formation		
					BE Anastomosis/Stent	N (%)	Mortality N (%)
de Baere, 1996	181	TACE	Carcinoid/NET	3 (2)		3 (100)	1 (33)
Sakamoto, 1998	850	TACE	NR	5 (0.6)		NR	NR
Song, 2001	2,439	TACE	HCC; GI tumors	14 (0.6)		4 (29)	4 (29)
Kim, 2001	157	TACE	NET; GI tumors	7 (4)		6 (86)	NR
Geschwind, 2002	258	TACE	HCC; GI tumors; NET	4 (2)		4 (100)	0 (0)
Huang, 2003	1,374	TACE	HCC	7 (0.3)		0 (0)	0 (0)
Ong, 2004	3,878*	TACE	HCC	9 (0.2)		0 (0)	4 (44)
Current Series	971	Small particle	HCC; GI Tumors Carcinoid/NET	14 (1.4)		13 (93)	3 (21)

HAE = hepatic artery embolization; TACE = transarterial chemoembolization; NET = neuroendocrine tumor; NR = not reported; GI = gastrointestinal

* number of procedures performed