

Multimicrobial Sepsis Including *Clostridium perfringens* after Chemoembolization of a Single Liver Metastasis from Common Bile Duct Cancer

Florian Eckel^a Christian Lersch^a Wolfgang Huber^a Wolfgang Weiss^b
Hermann Berger^b Ewert Schulte-Frohlinde^a

Departments of ^aMedicine II and ^bInterventional Radiology, Technical University of Munich, Klinikum rechts der Isar, Munich, Germany

Key Words

Clostridium perfringens, sepsis · Bile duct cancer · Chemoembolization · Hyperbaric oxygen · Hemolysis

Abstract

A 65-year-old woman underwent resection of a distal common bile duct carcinoma (Whipple's procedure). Twelve months later a single hepatic metastasis was detected and a chemoembolization was performed. Immediately after chemoembolization the patient developed a multimicrobial sepsis including *Clostridium perfringens*. CT scans depicted pathognomonic signs of gas-containing abscess in the necrotic liver metastasis. She was subsequently treated with broad-spectrum antibiotics, abscess drainage and hyperbaric oxygen therapy. We conclude that antibiotic prophylaxis is recommendable for chemoembolization of liver metastasis in patients with risk factors like intestinal biliary reflux (bilioenteric anastomosis or papillotomy and biliary stenting) and bile duct cancer, otherwise severe sepsis including clostridium bacteremia may occur.

Copyright © 2000 S. Karger AG, Basel

Introduction

Clostridial bacteremias are unusual but not extraordinary events. Mainly patients with malignancies such as acute leukemia, genitourinary or gastrointestinal tumors are affected. Clostridia grow fast under anaerobic conditions especially in tissue with low redox potential [1]. Chemoembolization of liver tumors induces necrosis which creates ideal growth conditions for anaerobic bacteria. Mediated by necrotizing and hemolyzing toxins, fulminant courses of clostridial infections occur with fever, hemolysis and septic shock, leading to death within 24 h if therapeutic measures are not taken immediately. We report a case of multimicrobial sepsis including *Clostridium perfringens* after chemoembolization of a hepatic metastasis from bile duct cancer.

Case Report

A 65-year-old woman with a carcinoma of the common bile duct was treated by duodenopancreatectomy, cholecystectomy and hepaticojunostomy (Whipple's procedure). A regular follow-up CT examination 12 months after surgery revealed a single intrahepatic metastasis (4 × 3 × 3 cm, segment 7). MR imaging confirmed this metastasis without signs of abscess or necrosis. Transcatheter arterial chemoembolization (TACE) of the single liver metastasis was per-

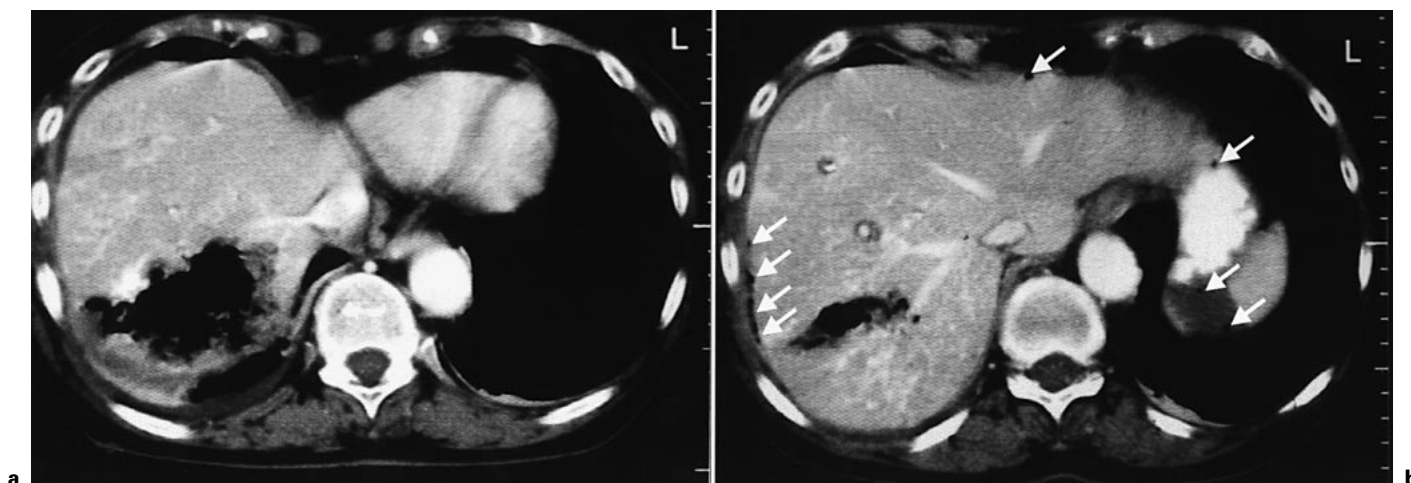


Fig. 1. Examination by CT after chemoembolization revealed a necrotic region (7 × 5 cm) in the liver filled with gas and foamy liquid in the right lobe of the liver (a). Additional gas collections (arrows) were found in the peritoneum particularly between the liver and the diaphragm close to the abscess. A wedge-shaped zone of hypodensity with some gas in the spleen corresponds to an acute infarction of the spleen (b).

formed with 25 mg epirubicin emulsified in 2.5 ml iodized oil (Lipiodol) and with 25 mg cisplatin dissolved in 10 ml physiologic saline solution with the addition of 300 mg starch microspheres (Spherex). They were mixed just before injection using the usual push-and-pull method with two syringes connected by a three-way stopcock. The lesion could not be detected in the angiogram because it was not hypervascular. Therefore the catheter tip was placed in a branch of the right hepatic artery according to the findings of the CT scan. Antiemetics (8 mg ondansetron i.v.) and analgesics (7.5 mg piritramide i.v.) were administered on a regular basis.

After 1 day, subfebrile temperature (38.4°C) occurred. Two days after TACE, body temperature increased to 39.4°C associated with mild pain in the right upper abdomen and mild leukocytosis. Blood cultures were taken and fever was successfully treated with antipyretics. On the following day the general condition of the patient had worsened. Circulation was still sufficient with a blood pressure of 130/70 mm Hg and a heart rate of 92 beats/min. The temperature was again 39.4°C. A distinct increase of the abdominal pain and tenderness in the right upper abdomen was noted. Proper bowel sounds could be distinguished on auscultation. The liver showed a normal size and consistency by palpation.

WBC increased to 13,000/μl (normal value 4,000–9,000), platelets and hemoglobin slightly decreased to 129,000/μl (150,000–450,000) and 11.2 g/dl (12.0–16.0), respectively. The following laboratory values increased: bilirubin from 0.3 to 4.6 mg/dl (<1.2), transaminases (GOT 42 U/l (<15), GPT 59 U/l (<17)), LDH (350 U/l (80–240)), and C-reactive protein (28.0 mg/ml (<0.5)). There was no sign of disseminated intravascular coagulation.

Examination by ultrasound and CT was performed. Lipiodol was distributed in segments 5, 7 and 8 of the liver. Subphrenically there was a necrotic region (7 × 5 cm) filled with gas and foamy liquid. Small collections of gas were found in the peritoneum, particularly between the liver and the diaphragm close to the abscess. A wedge-shaped zone of hypodensity with some gas was depicted in the spleen

corresponding to an acute infarction which was not caused by Lipiodol (fig. 1). No gas was observed in the portal venous system. A blood culture taken 2 days after TACE grew gram-positive and gram-negative rod-shaped bacilli. These findings indicated a polymicrobial sepsis with beginning hemolysis shortly after embolization of the liver metastasis.

We started to treat the patient with penicillin, 4 × 6 million units/day and 3 × 2 g mezlocillin in combination with 3 × 1 g sulbactam. Under CT guidance, a 8.4-Fr drainage catheter was inserted into the liver abscess. Hyperbaric oxygen therapy (100% oxygen, pressure 2.5–2.8 bar, 2 h duration) was started the same day and was repeated every 12 h to a total of 5 courses. While fever and WBC were decreasing, an anemia with a hemoglobin of 8.7 g/dl occurred, which was treated with blood transfusions.

The first blood culture grew *C. perfringens* and *Escherichia coli*, the second *Enterococcus faecalis* and *Streptococcus bovis*. We additionally administered 240 mg of gentamycin and added fluconazole because of *Candida albicans*, found in the drainage secretion.

The patient recovered quickly and was discharged 20 days after TACE in good general condition. The drainage catheter remained inserted with a daily secretion of 50 ml. Eight days after discharge a sonographic control showed a decreasing extension of the abscess (4 × 1.6 cm). Secretion volume decreased to 10–20 ml/day at last. Thirty-nine days after TACE the patient died at home unexpectedly, despite prompt resuscitation by an emergency physician. An autopsy was denied.

Discussion

A case of multimicrobial sepsis including *C. perfringens* occurred after chemoembolization of a single hepatic metastasis from bile duct cancer. Single hepatic metasta-

sis of colorectal cancer or uninodular hepatocellular carcinoma can be curatively resected if possible. However, resection of hepatic metastasis of bile duct cancer is not curative generally and therefore resection of the single hepatic metastasis in the patient presented was declined by our surgeons. Therefore, based on an individual decision and with palliative intention, chemoembolization was performed which was complicated by a multimicrobial sepsis including *C. perfringens*.

Clostridial species represent a widely divergent group of organisms ranging from sporulating to nonsporulating species, from strict anaerobes to aerotolerant species, and from pathogens producing virulent toxins to harmless saprophytes. They are ubiquitous in nature and reside in the gastrointestinal and female genital tract usually in humans; occasionally they can be isolated from the skin or the mouth. Clostridial species are an infrequent cause of bacteremia among general hospital populations. Isolation of clostridial species is reported in 2–3% of all positive blood cultures [2]. Clinically relevant infections caused by clostridial species are the pseudomembranous colitis (*C. difficile*), tetanus (*C. tetani*), and gas gangrene (mostly *C. perfringens* or *C. septicum*).

Clostridial species, especially *C. perfringens*, produce a variety of virulence factors, such as the α -toxin (phospholipase C), and the κ -toxin (collagenase). Other virulence factors act primarily on the vascular endothelium, causing capillary leakage (β -, ϵ - and ι -toxin) or are essentially hemolysins (δ - and θ -toxins) [3]. The fulminant nature of shock in patients with gas gangrene caused by *C. perfringens* is the result of direct effects of toxins and their ability to induce production of potent endogenous mediators [4].

In our patient, hemolysins most likely caused anemia, which had to be treated with blood transfusions. A severe complication of hemolysis is renal failure [5, 6]. However, in our patient, creatinine levels remained normal.

Superselective TACE is an established modality for the treatment of uninodular hepatocellular carcinoma that reduces tumor growth [7] and prolongs survival with a good quality of life [8, 9]. The complication rate is low [10], even in patients with main portal vein obstruction [11]. Fatal complications may occur if other distribution pathways were embolized by mistake.

Chemoembolization was performed selectively in our patient with the catheter tip placed in a branch of the right hepatic artery. On the other hand, the lesion was not hypervascular so that not only the artery that fed the lesion could be embolized exclusively. Therefore, Lipiodol was depicted by CT scan in segment 7 as well as in

segments 5 and 8, but not in the spleen or other extrahepatic regions.

In bile duct cancer, no standard chemotherapy exists. The intra-arterial administration of antitumor agents and embolization reduces the maximum plasma concentration and the area under the plasma concentration time curve (AUC) [12]. In patients with hepatic metastasis of distal bile duct cancer and with intrahepatic cholangiocarcinoma who underwent resection after chemoembolization according to our protocol, we observed histologically proven complete tumor necrosis. Therefore, this regimen was used in the patient presented.

Clostridial infections are often associated with malignancies such as acute leukemia, genitourinary or gastrointestinal carcinoma and the occurrence of necrotic tissue due to radiation, chemotherapy or embolization. Deaths after clostridial bacteremia following chemoembolization had been reported before [13, 14]. The proposed mechanism of entry in the blood circulation is a defective colonic mucosa, allowing clostridial organisms to invade tissues which are able to support their growth [2]. In cancer patients this mucosal defect is caused by cytotoxic drugs.

However, in our patient, intestinal biliary reflux due to hepaticojejunostomy and embolization are suspected mechanisms of infection. Intestinal biliary reflux may also be favored by papillotomy and stenting of the common bile duct which enables bacteria to ascend into the biliary tract. Usually, this creates no problems, but the goal of embolization is to induce a complete necrosis which creates an ideal growth medium for bacteria. The infection or superinfection of necrotic tissue after embolization may be prevented by prophylactic antibiotics. However, infection rates are 2–4% (4/172 [15] and 7/176 procedures [16]) with a rate of liver abscess in 1.1% (5/452) [17] after chemoembolization without prophylactic antibiotics. Therefore, prophylactic antibiotics have not been administered on a regular basis in our institution. During 370 chemoembolizations without prophylactic antibiotics, we observed infections after chemoembolization in only 2 patients (0.5%) with bile duct cancer. In a randomized controlled trial no bacterial infection was observed after chemoembolization with or without prophylactic antibiotics, but the number of patients was very low (61 patients, 75 procedures) [18]. The rate of hepatic abscess after chemoembolization with prophylactic antibiotics is 0.6–1.3% (3/489 [14] and 6/480 procedures [19]). However, whether the rate or severity of infection after chemoembolization can be decreased by prophylactic antibiotics remains unclear. Risk factors of developing liver abscesses after

chemoembolization are intestinal biliary reflux caused by bilioenteric anastomosis or biliary stenting and neuroendocrine cancer [14, 20]. Our patient had a bilioenteric anastomosis and a common bile duct cancer.

Another possible source of infection after embolization is the skin where clostridium can be found in humans. Bacteria may ascend through the arterial sheath and the catheter leading to a primarily asymptomatic bacteremia during the embolization procedure. However, in a recently published study, only 2 of 287 (0.7%) catheter-tip cultures yielded *Staphylococcus epidermidis* and none of the inguinal skin swab and catheter-tip cultures yielded the same microorganism responsible for infectious complications [16].

In contrast to self-limiting clostridial bacteremia in women with septic abortion, mortality of patients with clostridial sepsis associated with malignancies is high, particularly in infections with *C. perfringens* or *C. septicum*. Unfavorable prognostic factors are a significant hemolysis, polymicrobial infections, particularly with gram-negative bacteria and septic shock [2]. Fulminant courses of clostridial infections require prompt therapy. In case of suspected infection with anaerobes, treatment must be initiated immediately after a CT scan and assessment of blood cultures. The importance of an immediate antibiotic therapy could be demonstrated for metronidazole and clindamycin in a murine model of gas gangrene [21]. These agents inhibit the synthesis of clostridial toxins and are therefore superior to cell-wall active agents in the treatment of experimental gas gangrene [22]. In humans the treatment of choice of clostridial infections is still penicillin G, 20–40 million units/day in adults. Clostridia are frequently, but not universally, susceptible in vitro to clindamycin and metronidazole. A combination of clindamycin or metronidazole and penicillin is indicated in infections with other anaerobic bacteria than clostridia. Because of a blood culture taken 1 day before the worsening of the patient, we knew the infectious microorganism. Therefore, we treated the clostridial infection specifically with penicillin. Because of the mixed infection with gram-negative bacteria, we added the broad-spectrum antibiotic mezlocillin in combination with sulbactam. In addition, mezlocillin is weakly active in anaerobic bacteria. Sensitivity testing showed susceptibility to this regimen. Later on we administered additionally gentamycin, because aminoglycosides can be used for the aerobic gram-negative bacteria in mixed infections.

The value of hyperbaric oxygen as an efficient treatment for clostridial sepsis is uncertain. An oxygen tension of 1,500–2,100 mm Hg is necessary to kill *C. perfringens*.

But oxygen at a pressure of 3 atm, which can be reached in man, inhibits the production of α -toxin and affects the activity of oxygen-labile cytolysins such as θ -toxin. Other mechanisms discussed are the augmented ability of polymorphonuclear leukocytes to destroy ingested pathogens by hyperbaric oxygen. Furthermore, a synergistic effect of metronidazole and penicillin with hyperbaric oxygen was proposed and under conditions with less favorable factors such as a large inoculum or delays in the institution of treatment the most benefit from hyperbaric oxygen therapy was gained [21]. Our patient presented such conditions: after chemoembolization of a rather large area in the liver, she suffered from a polymicrobial sepsis of *C. perfringens*, *E. coli*, *E. faecalis* and *S. bovis* with consecutive hemolysis. Start of antibiotic treatment was delayed for 24 h because her initial symptoms were nonspecific. The so-called postembolization syndrome with fever and mild abdominal pain occurs in 60–100% after embolization and may mask infections. Nevertheless, the multimodal treatment including different antibiotics, interventional drainage and hyperbaric oxygen was successful. It is not possible to assess which treatment modality was the decisive one. Possibly the multimodality of treatment is of importance for a successful outcome. However, the rapid course of a clostridial sepsis and the high lethality especially of a multimicrobial one, leading to death frequently in less than 24 h, requires prompt and maximal treatment.

After treatment our patient completely recovered and was discharged in good general condition and ambulant controls showed no signs of an ongoing infection. Her sudden death was absolutely unexpected. The reasons of her death remain unclear but a connection to the multimicrobial sepsis after chemoembolization appears unlikely.

In conclusion, two points should be emphasized. First, patients who receive chemoembolization have several of the well-known risk factors of clostridial infection, such as gastrointestinal malignancy, chemotherapy and necrosis due to embolization. Second, intestinal biliary reflux on the basis of bilioenteric anastomosis or biliary stenting may represent an additional risk factor as well as bile duct and neuroendocrine cancer. Prophylactic antibiotics should therefore be administered on a regular basis in these high-risk patients.

References

- 1 Weinstein L, Barza MA: Gas gangrene. *N Engl J Med* 1973;289:1129–1131.
- 2 Bodey GP, Rodriguez S, Fainstein V, Elting LS: Clostridial bacteremia in cancer patients. A 12-year experience. *Cancer* 1991;67:1928–1942.
- 3 Smith LD: Virulence factors of *Clostridium perfringens*. *Rev Infect Dis* 1979;1:254–262.
- 4 Stevens DL, Bryant AE: Pathogenesis of *Clostridium perfringens* infection: Mechanisms and mediators of shock. *Clin Infect Dis* 1997; 25(suppl 2):S160–S164.
- 5 Tsai IK, Yen MY, Ho IC, Yu KW, Liu CY, Cheng DL: *Clostridium perfringens* septicemia with massive hemolysis. *Scand J Infect Dis* 1989;21:467–471.
- 6 Rogstad B, Ritland S, Lunde S, Hagen AG: *Clostridium perfringens* septicemia with massive hemolysis. *Infection* 1993;21:54–56.
- 7 Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire: A comparison of Lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. *N Engl J Med* 1995;332:1256–1261.
- 8 Bronowicki JP, Vetter D, Dumas F, Boudjema K, Bader R, Weiss AM, Wenger JJ, Boissel P, Bigard MA, Doffoel M: Transcatheter oily chemoembolization for hepatocellular carcinoma. A 4-year study of 127 French patients. *Cancer* 1994;74:16–24.
- 9 Taniguchi K, Nakata K, Kato Y, Sato Y, Hamasaki K, Tsuruta S, Nagataki S: Treatment of hepatocellular carcinoma with transcatheter arterial embolization. Analysis of prognostic factors. *Cancer* 1994;73:1341–1345.
- 10 Stefanini GF, Amorati P, Biselli M, Mucci F, Celi A, Arienti V, Roversi R, Rossi C, Re G, Gasbarrini G: Efficacy of transarterial targeted treatments on survival of patients with hepatocellular carcinoma. An Italian experience. *Cancer* 1995;75:2427–2434.
- 11 Lee HS, Kim JS, Choi IJ, Chung JW, Park JH, Kim CY: The safety and efficacy of transcatheter arterial chemoembolization in the treatment of patients with hepatocellular carcinoma and main portal vein obstruction. A prospective controlled study. *Cancer* 1997;79:2087–2094.
- 12 Mouridsen HT, Alfthan C, Bastholt L, Bergh J, Dalmark M, Eksborg S, Hellsten S, Kjaer M, Peterson C, Skovsgard T, et al: Current status of epirubicin (Farmorubicin) in the treatment of solid tumours. *Acta Oncol* 1990;29:257–285.
- 13 Gerson LB, Pont A, Cummins RT: Clostridial bacteremia and death following chemoembolization for hepatocellular carcinoma. *J Vasc Interv Radiol* 1994;5:167–170.
- 14 de Baere T, Roche A, Amenabar JM, Lagrange C, Ducreux M, Rougier P, Elias D, Lasser P, Patriarche C: Liver abscess formation after local treatment of liver tumors. *Hepatology* 1996;23:1436–1440.
- 15 Wong E, Khardori N, Carrasco CH, Wallace S, Patt Y, Bodey GP: Infectious complications of hepatic artery catheterization procedures in patients with cancer. *Rev Infect Dis* 1991;13: 583–586.
- 16 Chen C, Tsang YM, Hsueh PR, Huang GT, Yang PM, Sheu JC, Lai MY, Chen PJ, Chen DS: Bacterial infections associated with hepatic arteriography and transarterial embolization for hepatocellular carcinoma: A prospective study. *Clin Infect Dis* 1999;29:161–166.
- 17 Chen C, Chen PJ, Yang PM, Huang GT, Lai MY, Tsang YM, Chen DS: Clinical and microbiological features of liver abscess after transarterial embolization for hepatocellular carcinoma. *Am J Gastroenterol* 1997;92:2257–2259.
- 18 Chang JM, Tzeng WS, Pan HB, Yang CF, Lai KH: Transcatheter arterial embolization with or without cisplatin treatment of hepatocellular carcinoma. A randomized controlled study [erratum in *Cancer* 1995;75:1218]. *Cancer* 1994; 74:2449–2453.
- 19 Reed RA, Teitelbaum GP, Daniels JR, Pentecost MJ, Katz MD: Prevalence of infection following hepatic chemoembolization with cross-linked collagen with administration of prophylactic antibiotics. *J Vasc Interv Radiol* 1994;5: 367–371.
- 20 Okajima K, Kohno S, Tamaki M, Hosono M, Kawamoto M, Nishiyama Y, Sugano M, Miyaoka T: Bilio-enteric anastomosis as a risk factor for postembolic hepatic abscesses. *Cardiovasc Intervent Radiol* 1989;12:128–130.
- 21 Stevens DL, Bryant AE, Adams K, Mader JT: Evaluation of therapy with hyperbaric oxygen for experimental infection with *Clostridium perfringens*. *Clin Infect Dis* 1993;17:231–237.
- 22 Stevens DL, Maier KA, Laine BM, Mitten JE: Comparison of clindamycin, rifampin, tetracycline, metronidazole, and penicillin for efficacy in prevention of experimental gas gangrene due to *Clostridium perfringens*. *J Infect Dis* 1987; 155:220–228.