Educational Article

Portal venous gas following chemotherapy for colorectal cancer liver metastasis

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Abstract

The standard of care for patients with colorectal liver metastases is a combination of chemotherapy and surgery. New chemotherapy regimens with biologic agents (cetuximab, bevacizumab) have been shown to increase tumor response rates. Although this might be beneficial and this is an expected endpoint, it should be noted that patients with synchronous colorectal and liver metastases are at risk of septic complications. We recently encountered a case of hepatic portal venous gas after two cycles of chemotherapy in a patient with right colon cancer liver metastases. Complete necrosis of the liver metastasis subsequently turned into a liver abscess, which fistulized in the right portal vein. Infection of the necrotized metastasis was thought to be promoted by the colic tumor. Although this is a dramatic situation, it does not contraindicate a curative surgical resection.

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Introduction

In western countries, colorectal cancer is one of the leading causes of death. Approximately, 50% of the patients with colorectal cancer will develop liver metastases (CCLM) during the course of the disease.1 Although no prospective trial has been conducted, it is widely accepted that liver resection, which takes place in a multimodal approach, is the only curative treatment available for patients with CCLM. Neoadjuvant chemotherapy is an important component of the multimodal strategies dedicated to patients with CCLM; Although not curative itself, it plays an important role to downsize the liver tumors for unresectable patients to become resectable.3,4 Sides effects of preoperative oxaliplatin and irinotecan based chemotherapy are being intensively studied5–7 and may lead to impaired outcomes.8 In addition to oxaliplatin or irinotecan based chemotherapy, cetuximab,9 a recombinant antibody that blocks the receptor for human epidermal growth factor (EGFR) and bevacizumab,10,11 which inhibits angiogenesis by targeting the activity of human vascular endothelial growth factor (VEGF), are now being increasingly used. Controlled trials assessing the efficacy of these new biological agents in addition to irinotecan or oxaliplatin have demonstrated a gain in overall survival, disease free survival and response rate.9,11,12 Although the use of these new biologic agents does not appear to increase morbidity following hepatic resection13,14 these new regimens are aggressive12 and need to be further evaluated. We herein report a case that highlights chemotherapy related side effects and especially a potential major drawback of a complete and rapid tumor response to chemotherapy. Liver

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abscess and presence of air in the portal system were detected after two cycles of chemotherapy in a patient with stage IV colorectal cancer. Secondary infection of the necrosis was believed to be promoted by the primary colic location. Hepatic Portal Venous Gas (HPVG)\textsuperscript{16} is a dramatic complication of liver or porto-mesenteric sepsis which can lead to death in up to 75–90\%\textsuperscript{17} without adequate care. In patients with synchronous CCLM, good responders to preoperative chemotherapy are at high risk of septic complication, which, at the worst, may cause HPVG. Physicians should be aware of such a complication because early detection is the key to a better prognosis.

Case report

A 51-year-old patient was referred to our center for a right colon cancer with synchronous liver metastasis. She had no medical or surgical past history. Her performance status was good; body mass index was 28 kg/m\textsuperscript{2}, blood test did not show any abnormality, despite a moderate anemia (9 g/dl). Lower tract endoscopic examination and biopsies confirmed the diagnosis. Radiological assessment revealed 5 lesions located into the right liver. The diameter of the largest liver metastasis was 15 cm (Fig. 1). Lungs were free of disease and there was no contraindication for a synchronous resection of both primary tumor and liver metastasis. After a multidisciplinary oncological evaluation the patient underwent a first line chemotherapy with oxaliplatin and cetuximab, preoperatively. Both first and second cures were well tolerated. During the third course, clinical examination revealed that patient’s temperature was 38.4°C, heart rate was 104 bpm, arterial blood pressure was 121/76 cm H\textsubscript{2}O and she was jaundiced. Biological values beyond the normal range were: Hemoglobinemia (9 g/dl), White blood cells (15,900/ml) and C reactive protein (305 mg/L). Enhanced CT-scan showed a complete tumor necrosis and air density was observed mainly into the largest lesion. Portal vein gas (HPVG) was exclusively located into the right liver. The mesenteric vein and portal trunk were free of gas. Given these findings, a fistula between the infected metastasis and the right portal vein was suspected (Fig. 2). The patient underwent a synchronous resection of both primary and secondary location after two days of medical rehabilitation in intensive care unit. Resection of the primary consisted in a right ileocolic resection with lymphadenectomy whereas a right liver resection (segment V, VI, VII and VIII) was performed to remove the liver metastasis. Presence of air in the portal system had no consequence on the liver resection procedure which was performed considering informations obtained on preoperative CT-scan and intraoperative ultrasound. Briefly, right portal pedicle elements were electively ligated in the porta hepatitis, parenchymal transection was performed using an ultrasonic dissector, hemostasis and biliostasis were performed using the bipolar forceps or elective ligation. At

![Figure 1. Enhanced CT-scan before chemotherapy administration revealing a 15 cm colorectal cancer liver metastasis in the right liver lobe.](image1)

![Figure 2. Enhanced CT-scan showing tumor necrosis following 2 courses of chemotherapy with oxaliplatin and cetuximab (a) air in the right portal system (b).](image2)
the end of the parenchymal transection the right biliary duct was sectioned in the hilar plate and cross sutured. The right hepatic vein was stapled and divided. Postoperative course was uneventful. Gross and microscopic examination of both colon and liver specimen confirmed a R0 resection with negative margins.

Discussion

This is the first report of portal venous gas associated with a complete CCLM necrosis and subsequent infection in a patient receiving an association of oxaliplatin and cetuximab. Portal venous gas has been previously reported in a patient receiving cisplatin and irinotecan for a locally advanced esophageal cancer. In their report, Kung et al. described HPVG to be secondary to pneumatosis intestinalis, which was a consequence of irinotecan and cisplatin intestinal toxicity.

HPVG has been reported for the first time in 1955 by Wolfe and Evans who described air in the portal system in infants with enterocolitis. Since its first description HPVG has been reported by several authors and many etiologies have been described. It is mainly thought to arise from gas embolism via the mesenteric system and has been associated with any disease or pathological events that may lead to bowel mucosa lesion, bowel lumen pressure elevation or sepsis. Although there is a pathologic correlation, it was initially described as a radiologic sign and diagnosis was usually delayed due to the lack of sensitivity and specificity of imaging devices. As a consequence, prognosis was poor with reported mortality rate up to 75–90%. That dramatic prognosis was probably related to a delayed diagnosis in patients who mostly suffered from extensive abdominal wall necrosis. Nowadays, the increasingly routine use of CT-scan in patients presented with abdominal pain is probably responsible for an improved prognosis since it gives the opportunity of an early diagnosis and may also avoid unnecessary surgery.

In the case herein reported, we do not believe that presence of air in the portal system was directly related to the primary colic location. First, neither preoperative CT-scan nor gross and microscopic pathological examination revealed any sign of intestinal mucosa lesion or disruption and there was no evidence of endothelial barrier disruption or colic ischemia. Second, although the primary colon cancer was large, it was not occlusive and it could not be related to an augmentation of the pressure within the colic lumen. Third, pathological examination did not reveal any sign of tumor infection, abscess or perforation in the colon. Finally, air distribution in the portal system was limited to the right portal vein, close to the liver metastasis, which was completely necrotized and infected. The main portal trunk and the superior mesenteric system were free of gas. For these reasons, we believe that the mechanism is likely to be explained by a complete necrosis of the liver metastasis with a subsequent infection and pyogenic abscess of the right liver that fistulized in the right portal system.

In patients with CCLM the use of biologic agents (cetuximab, bevacizumab) in addition to oxaliplatin or irinotecan based chemotherapy is dramatically increasing as controlled trials have shown a benefit in survival and tumor progression. These new regimens are very aggressive and may even lead to a complete pathologic response with tumor clearance in patients with advanced cancer. To date, published reports do not show any evidence of increased postoperative morbidity in patients receiving biologic agents in addition to oxaliplatin or irinotecan based chemotherapy as compared to these latter regimen alone. In addition, it is known that patients with a colorectal cancer are at increased risk of developing a pyogenic liver abscess and we have to be aware that a fast and complete tumor necrosis in patients with synchronous colorectal locations may increase this risk even more. The colorectal tumor presence may promote the infection of the liver necrotic mass and facilitate the development of a subsequent liver abscess.

Finally, this is important to note that such a situation is not a contraindication for a curative surgery. Patients should undergo an intensive medical rehabilitation and benefit of multidisciplinary cares. At the best, they may benefit from intensive care unit. Surgery should be performed according to the rules and standards of oncologic surgery for colorectal cancer and liver metastases, even if performed as an emergency procedure. Presence of air in the portal system itself is not an indication for surgery, and surgeons should avoid any major or extended liver resection without considering the liver remnant, especially in patients who received chemotherapy.

Conclusion

The case herein reported supports the high tumor response rate after cetuximab and oxaliplatin based chemotherapy. In patients presented with synchronous liver metastasis from colorectal cancer, good responders to preoperative chemotherapy are at high risk of septic complications, as the colorectal tumor may promote infection of necrotized liver metastases. At the worst it may lead to the presence of air in the portal system, prognosis of which is dramatic. Physicians should be aware of such septic outcome and liver ultrasound or enhanced CT-scan should be systematic in case of sepsis following chemotherapy. Careful medical rehabilitation should be undertaken prior to surgery but HPVG itself do not preclude a curative synchronous resection.

Conflict of interest

The authors have no conflict of interest.
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