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SHORT COMMUNICATION

Hepatic portal venous gas in a patient with metastatic non-small cell lung cancer on bevacizumab therapy: a case report and review of the literature

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Abstract
Background The presence of hepatic portal venous gas (HPVG) is a rare finding. It is most commonly caused by bowel necrosis and typically carries a grave prognosis. Bevacizumab has emerged as an effective standard therapy in the frontline management of advanced non-small cell lung cancer (NSCLC). Although bevacizumab is associated with gastrointestinal perforation, it has not been shown to cause HPVG.
Case A 75-year-old man, diagnosed with metastatic NSCLC, was treated with palliative chemotherapy consisting of paclitaxel, carboplatin, and bevacizumab for six cycles. He continued on maintenance bevacizumab after that for a total of six doses, given every 3 weeks, with continued stable disease. During a surveillance CT scan 4 weeks after the last dose of bevacizumab, HPVG was shown.
Conclusion This is the first case of HPVG associated with bevacizumab therapy in a patient with metastatic NSCLC. The HPVG may have been an early warning sign of impending bowel perforation, and bevacizumab was immediately discontinued, with HPVG completely resolving on follow-up CT scan 2 weeks later. We recommend that bevacizumab therapy be immediately and permanently discontinued whenever HPVG is observed, as this may help avoid a potentially catastrophic outcome.

Keywords Portal veins · Bevacizumab · Carcinoma, non-small cell lung cancer · Intestinal perforation

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Introduction

Patients with advanced non-small cell lung cancer (NSCLC) derive significant improvements in progression-free and overall survival from the addition of bevacizumab to standard chemotherapy with paclitaxel and carboplatin [1]. Gastrointestinal perforation is a well-described complication of bevacizumab therapy in colorectal cancer patients, as well as in patients with ovarian cancer. However, an association between hepatic portal venous gas (HPVG) and bevacizumab therapy has never been described. HPVG is a rare, and typically ominous, finding that is most commonly due to an underlying bowel necrosis. Herein, we describe a patient with metastatic NSCLC who was placed on bevacizumab monotherapy after having completed six cycles of paclitaxel, carboplatin, and bevacizumab and who subsequently developed HPVG, as observed on a staging computed tomography (CT) scan.

Case report

A 75-year-old man presented with metastatic NSCLC to the spine, left acetabulum, and pelvis. Six months before presentation, he had been involved in a motor vehicle accident, which resulted in a sternal fracture. Despite recovering from the accident, the patient had continued left hip pain. Magnetic resonance imaging of the left hip revealed a 4.9 × 2.2-cm lesion in the left acetabulum and additional lesions in the right and left ilia. A CT-guided biopsy of the acetabulum lesion was performed, with pathology showing an adenocarcinoma, grade 3, consistent with primary lung cancer.

Staging studies were performed. CT of the thorax showed a 3.5-cm mass in the left lower lobe, extending to

the inferior aspect of the left hilum. Positron emission tomography (PET)/CT scan showed intense uptake in the left lower lobe mass, as well as uptake in the left hilum and pericarinal lymph nodes. There was also intense uptake in the T2 vertebral body, T11 vertebral body, both sacroiliac joints, left ilium, left ischium, coccyx, left 11th rib, and in a small focus in the upper left femoral diaphysis. At presentation, the patient complained of continued and worsening left hip pain. He had no back pain or neurological symptoms and no pulmonary or constitutional symptoms. His ECOG performance status was 1. He quit smoking cigarettes 50 years ago and had previously smoked for only 4 years.

The patient went on to receive palliative radiation therapy to the left hip and the involved vertebral bodies. Treatment with zoledronic acid was initiated. He also had curettage of the left acetabulum lesion with cement packing for stabilization of the femur. He was then treated with palliative chemotherapy (paclitaxel, carboplatin, bevacizumab) for six cycles, which resulted in stable disease. He continued on maintenance bevacizumab after that for a total of six doses, given every 3 weeks, with continued stable disease.

On follow-up visit 4 weeks after the last dose of bevacizumab, the patient had a CT scan of the thorax and abdomen done for surveillance. Again, stable disease was observed; however, there was an incidental finding of new portal venous air within the liver (Fig. 1). Of note, the patient denied any abdominal pain, abdominal distension, nausea, vomiting, diarrhea, or gastrointestinal bleeding. In addition, the patient had no history of inflammatory bowel disease. As the patient was completely asymptomatic, our surgical consultants recommended observation only. Bevacizumab therapy was discontinued at this time because of its likely association with HPVG. A repeat CT scan 2 weeks later (6 weeks after the last dose of bevacizumab was administered) showed complete resolution of the portal venous air in the liver (Fig. 2). Two months later, he was started on second-line therapy with pemetrexed. The patient, presently at 26 months since the initial diagnosis of metastatic NSCLC, has continued on pemetrexed therapy with stable disease and an excellent performance status. In addition, the patient gets restaging CT scans approximately every 2 months, which have shown no recurrence of the HPVG.

Discussion and literature review

HPVG is a rare finding that is typically associated with a grave prognosis. Before this report, there have been no documented cases of HPVG associated with bevacizumab therapy. The most common reported cause of HPVG is bowel necrosis.

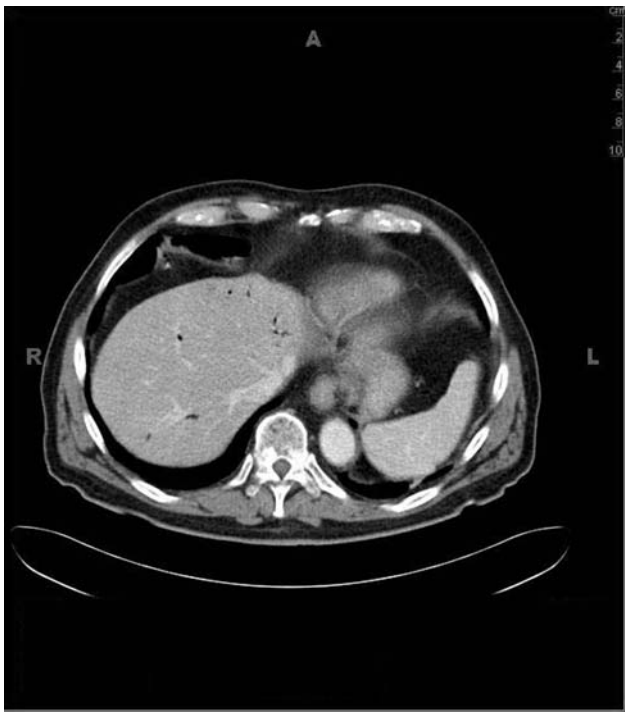

Fig. 1 CT scan of the abdomen showing the new incidental finding of portal venous air in the liver

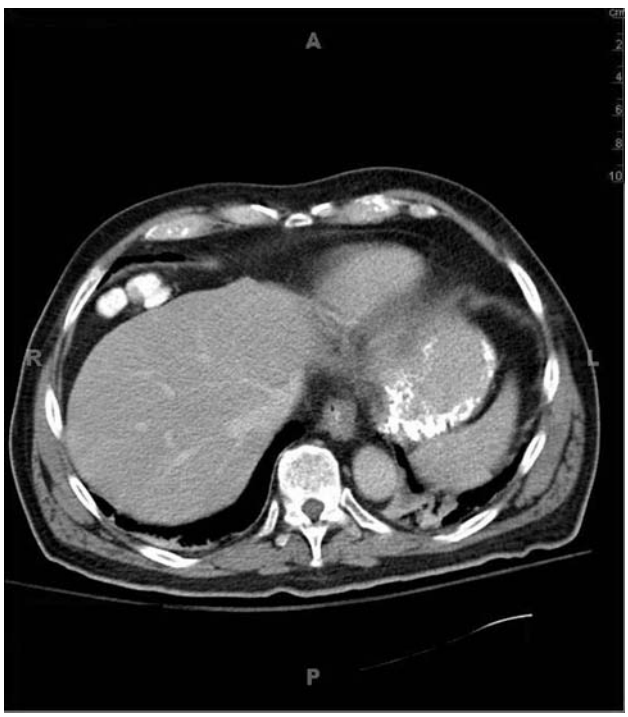

Fig. 2 Follow-up CT scan of the abdomen showing complete resolution of the hepatic portal venous gas

Chemotherapy has been the suspected cause of HPVG in at least two other patients [2, 3]. Kung et al [2] reported on a 69-year-old man with type I diabetes mellitus and locally

advanced esophageal cancer who received a chemotherapy regimen that included cisplatin and irinotecan. Five weeks post-therapy, the patient had generalized abdominal tenderness, with no peritoneal signs. A CT scan revealed pneumotosis and some thickening of the right colon, in addition to the presence of portal venous air. The patient received an exploratory laparotomy where findings included a normal colon and small bowel without evidence of inflammation. The patient was treated with supportive care and was discharged 12 days after surgery in good condition.

In the other reported case, a 51-year-old woman with colon cancer and hepatic metastases received concomitant administration of oxaliplatin and cetuximab [3]. The patient received two courses of oxaliplatin and cetuximab without incident. During the third course, the patient became febrile, tachycardic, and noticeably jaundiced. A CT scan revealed complete tumor necrosis and air density mainly in the largest lesion. Portal venous gas was observed. The mesenteric vein and portal trunk were gas free. The patient underwent a resection of the primary and secondary lesions. Presence of air in the portal system had no consequence on liver resection.

In a 2001 review of the literature, Kinoshita et al [4] identified 182 cases of HPVG and found the underlying clinical events associated with HPVG to be bowel necrosis (43%), digestive tract dilatation (12%), intraperitoneal abscess (11%), ulcerative colitis (4%), gastric ulcer (4%), Crohn disease (4%), complications of endoscopic procedures (4%), intraperitoneal tumor (3%), and other (15%). The overall mortality was 39%, but this varied depending on the underlying disease. In a more recent retrospective review of Swiss records, 11 patients with HPVG were identified by CT scan [5]. Of these patients, nine (81.8%) showed an associated pneumatosis intestinalis. In 6 of the 11 patients (54.6%), acute mesenteric ischemia was the underlying disease. For patients with HPVG alone, the mortality rate was 27.3%; for patients with HPVG related to mesenteric bowel disease, the mortality rate was 50%.

In patients with colorectal cancer, gastrointestinal perforation is a well-described complication of bevacizumab therapy. In a pivotal phase III trial, 6 gastrointestinal perforation events (1.5%) occurred in 393 patients given bevacizumab plus irinotecan, bolus fluorouracil, and leucovorin, compared with no events in the control group of 397 patients [6]. Since then, similar rates of gastrointestinal perforation have been observed in other large trials.

Gastrointestinal perforation has also been described as a complication of bevacizumab therapy in patients with ovarian cancer. However, only phase II trials have been completed and published, with varying rates of gastrointestinal perforation. In one phase II trial with bevacizumab monotherapy (GOG170D study), 62 patients with relapsed epithelial ovarian cancer who received only one or two previous chemotherapy regimens were enrolled, 26 of whom were platinum resistant [7]. Bevacizumab therapy was shown to be well tolerated, with no reported events of gastrointestinal perforation. In a second phase II bevacizumab monotherapy trial, 44 heavily pretreated patients with relapsed epithelial ovarian cancer (Genentech AVF 2949 trial) were enrolled, all of whom were platinum resistant [8]. The rate of spontaneous bowel perforation was 11%. The authors noted that exposure to three previous chemotherapy regimens was strongly associated with development of gastrointestinal perforation (in 5 of 21 (23.8%) such patients) but did not occur in the 23 patients who had received two previous regimens.

In an MD Anderson record review, 1442 patients who had received bevacizumab over a 2-year period were identified [9], with medical records reviewed for reports of confirmed bowel perforation or fistula. Overall, perforation occurred in 24 patients (1.7%). The incidence was reported by disease site: ovarian (3/50, 6%), gastroesophageal (2/38, 5.3%), pancreatic (7/141, 5%), unknown primary (1/60, 1.7%), lung (1/67, 1.5%), renal cell (4/269, 1.5%), and colorectal (6/478, 1.3%).

In a randomized trial conducted by the Eastern Cooperative Oncology Group (ECOG 4599 trial), the addition of bevacizumab to paclitaxel plus carboplatin in the treatment of selected patients with recurrent or advanced NSCLC significantly improved overall survival by 21% and progression-free survival by 34% [1]. Exclusion criteria included squamous cell pathology, hemoptysis, and central nervous system metastases. Patients who were given bevacizumab had significantly more neutropenia, febrile neutropenia, thrombocytopenia, hyponatremia, hypertension, proteinuria, headache, rash, and bleeding events than patients who did not receive bevacizumab. In the trial, there were two deaths attributed to gastrointestinal hemorrhage but no reported cases of bowel perforation or HPVG. Gray et al. [10] recently documented the only case of gastrointestinal perforation in the literature in a patient with metastatic NSCLC receiving bevacizumab therapy. The perforation was associated with metastatic nodules to the small bowel mesentery.

The etiology of gastrointestinal perforation associated with bevacizumab therapy is unclear. Bevacizumab inhibits tumor neovascularization, which can result in tumor regression. Treatment with bevacizumab also leads to reduced tumor vessel permeability and causes vascular regression, which may improve delivery of chemotherapy and oxygen (a known radiation sensitizer) [11]. Furthermore, a single infusion of bevacizumab has been shown to decrease tumor perfusion, vascular volume, microvascular density, and interstitial fluid pressure [12].

In this report of the first case of HPVG associated with bevacizumab therapy in a patient with metastatic NSCLC,

HPVG was an incidental finding on surveillance CT scan. It is likely that the HPVG was an early warning sign of impending bowel perforation. As such, bevacizumab was immediately discontinued. As the patient was asymptomatic, he did not undergo surgical exploration. With observation alone, the HPVG completely resolved on follow-up CT scan 2 weeks later, and the patient, who continues to have restaging CT scans every 2–3 months, has had no evidence of recurrence of HPVG. We recommend immediate and permanent discontinuation of bevacizumab therapy whenever HPVG is observed, as this may help avoid a potentially catastrophic outcome.

Conflict of interest statement The authors have no conflicts of interest or disclosures to report.

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