Metastatic small cell cancer of the liver

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ABSTRACT

Small cell cancer of extrapulmonary origin (EPSCC) is a rare disease, with an incidence of 0.1% to 0.4%. There is limited data on management of EPSCC due to the rarity of this condition. We report a case of metastatic small cell liver cancer in a 56-year-old woman. The patient presented with obstructive jaundice and was found to have a bilirubin of 292 μmol/L. Computed tomography (CT) scan detected a large liver mass of 7.8 cm encasing a common hepatic artery with intrahepatic biliary dilatation, and a 0.8 cm left hilar lymph node. Despite drainage, her bilirubin remained in the range of 100 μmol/L. After discussing possible side effects and complications, the patient was started on palliative chemotherapy with cisplatin (80% of ideal dose) and etoposide (75% dose reduction). At the end of the sixth cycle, she showed excellent response without significant toxicities. The liver lesion decreased in size to 4.1 cm, with normalized bilirubin; the left hilar lymph node remained stable on the last CT scan. With this case report, we emphasize the consideration of treatment in patients with high bilirubin level, after discussion of possible complications and further investigation.

Keywords: small cell cancer, chemotherapy, extrapulmonary disease

This previously healthy 56-year-old female, an ex-smoker with a 30-pack-year smoking history, presented with abdominal distension and bloating for the last 6 months and recent-onset jaundice. Her vitals were stable; examination of the abdomen was remarkable of liver 8 cm below the rib cage in mid-sternal line. On investigation, she was found to have a large liver mass, measuring 7.8 cm, encasing a common hepatic artery with intrahepatic biliary dilatation (Figure 1), a 0.8 cm left hilar lymph node, and a left lower lobe bilobed pulmonary node of 1.3 cm that looked more like an arteriovenous malformation (AVM) (Figure 2). Bilirubin at the time of presentation was 292 μmol/L, alkaline phosphatase (ALP) was 1628 μ/L, aspartate transaminase (AST) was 218 μ/L, and alanine transaminase (ALT) was 218 μ/L.

The patient underwent endoscopic retrograde cholangiopancreatography (ERCP) with stent insertion; since bilirubin was still in the range of 150 μmol/L, a percutaneous transhepatic biliary drainage was inserted. Bilirubin dropped to around 100 μmol/L and remained stable in this range. The mass was biopsied, and pathology reported small cell carcinoma positively stained for synaptophysin, chromogranin and cytokeratin (Figure 3). Medical oncology was consulted. After long discussion with the patient, carefully reviewing potential side effects and complications, she was started on palliative chemotherapy with etoposide (25% of ideal dose) and cisplatin (80% of ideal dose). After the second cycle, bilirubin dropped to normal range; liver function tests also normalized; ascites resolved; and very little discharge from drain was observed. The patient continued on ideal dose of chemotherapy.

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Informed consent was received from the patient for the production of this case report.
Computed tomography (CT) of the chest, abdomen and pelvis after cycle 3 reported a significant response to treatment, with liver mass of 4.1 cm (Figure 4) and stable pulmonary nodule. Magnetic resonance imaging (MRI) of the head revealed no evidence of metastatic disease; the patient had a discussion about the option of prophylactic whole brain radiation with the radiation oncologist. Another CT was performed during the final week of chemotherapy. It reported stable appearance of liver mass and left lower lobe pulmonary nodule with significant growth of the left hilar lymph node to 2 cm x 3 cm. The patient was informed of possible mixed response to therapy; different management options were discussed, and the patient opted to start on a clinical trial. As part of the protocol requirements, a new CT was requested; it showed resolution of the left hilar lymph node, with a measurement of less than 1 cm (Figure 5). In retrospect, the patient did not report having suffered any cold/infection around the time of the abnormal hilar adenopathy. We suggested deferring any active treatment. Another CT was requested 6 weeks later. The patient feels good and is preparing to return to work.

DISCUSSION
Small cell cancer of extrapulmonary origin is a rare entity with a reported incidence of 0.1% to 0.4%. It is known to arise in different sites, such as skin, larynx, cervix, salivary glands, gastrointestinal (GI) tract (esophagus, stomach, colon, rectum, gallbladder), and genito-urinary tract (bladder, prostate); sometimes a primary site cannot be identified. Due to diverse sites of origin and limited data on management, the staging, treatment and followup protocols used in small cell lung cancer (SCLC) are often applied to extrapulmonary small cell cancer (EPSCC). In contrast to SCLC, where smoking has been identified as the most important risk factor, the incidence of EPSCC, particularly of gastrointestinal (GI) origin, is related to risk factors similar to those known for non-EPSCC at the sites of origin.

INVESTIGATION
Staging of EPSCC includes evaluation of chest, abdomen, and pelvis with CT, while a bone scan with positron emission tomography (PET) could be considered in the primary evaluation and to assess treatment response. In the presence of neurologic symptoms, magnetic resonance imaging (MRI) of the brain is recommended. If the EPSCC is suspected to be of GI origin, endoscopy may be required. Biopsy with immunochemical staining for neuroendocrine markers (chromogranin A, synaptophysin, CD56) confirms diagnosis. Often GI EPSCC stains positive for carcinoembryonic antigen. Of note, about half of GI EPSCCs harbour a non-small cell cancer component.

TREATMENT
The mainstay of EPSCC treatment is chemotherapy. Even in limited-stage disease where surgery may be considered, preoperative chemo/radiation is recommended. There is some evidence of long-term survival following surgical resection with or without chemotherapy; however, the absence of systemic therapy was found to be the most powerful predictor of death. The most common chemotherapy
Regimen is a combination of platinum-based compound with etoposide, which has a near-100% response rate (RR). Other common regimens include cyclophosphamide/doxorubicin/etoposide (ACA) and cyclophosphamide/doxorubicin/vincristine (CAV), with reported RR of 70% to 90%. Interestingly, irinotecan, which has been used in the treatment of many GI malignancies, may induce a partial response in platinum-resistant esophageal EPSCC. Liver dysfunction may induce changes in etoposide metabolism and its pharmacokinetic profile that increase its toxicity. It is recommended that the dose of etoposide be reduced to 50% of ideal if the bilirubin level is between 26 and 51 mmol/L or AST is greater than 180 μ/L. Use of etoposide is contraindicated in patients with severe liver impairment. Radiation may be beneficial as adjuvant therapy in the setting of residual disease, in combined chemoradiation for limited disease, or for palliative purposes. Prescribed doses and fractionations vary depending on the goal of treatment.

The incidence of brain metastases in EPSCC is lower than in SCLC, reported at 6% over a 12-year period in a study of 280 patients. Prophylactic cranial irradiation is therefore often omitted, except in EPSCC of the head and neck. Despite objective response, response duration is usually short, and patients have recurrence with widely spread disease. Upon disease recurrence, a patient may be a candidate for salvage chemotherapy with combination or single-agent chemotherapy. In two phase III trials comparing chemotherapy to best supportive care (BSC) in SCLC, overall survival (OS) and quality of life were significantly improved with chemotherapy; in 141 patients randomized to oral topotecan vs BSC, OS was 26 vs 14 weeks, in favour of chemotherapy. A few experimental agents have been investigated in the setting of recurrent small cell cancer. In a phase II trial of alisertib, an aurora A kinase inhibitor, 10 of 48 patients (21%) with relapsed SCLC achieved partial response. In preclinical trials, the poly(ADP-ribose) polymerase (PARP) inhibitor BMN 673 has shown promising results.

**CONCLUSION**

Overall survival with EPSCC is limited, with fewer than 15% of patients surviving 5 years after diagnosis. Reported median survival varies in different studies for limited, and extensive-stage disease, from 1.4 to 3.5 years and from 8 to 12 months, respectively. The prognosis for patients with EPSCC is often worse than for patients with SCLC, and EPSCC of hepatobiliary and pancreatic origin, the presence of liver metastases, and poor performance status make prognosis even worse. This case report describes the careful investigation required to identify EPSCC and shows the patient achieved good response to chemotherapy. Further studies are necessary to improve outcomes with this disease.

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**FIGURE 4. Abdominal CT in February 2015: a significant response to treatment, with liver mass of 4.1 cm.**

**FIGURE 5. Thoracic chest CT on March 18 (left): left lower lobe pulmonary nodule with a significant growth of left hilar lymph node of 2 cm x 3 cm; and April 24 (right): resolution of left hilar lymph node, with a new measurement of less than 1 cm.**
References


