CASE REPORT

Metastatic small-cell lung cancer presenting as fulminant hepatic failure

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SUMMARY

We report a case of a 75-year-old woman with fulminant hepatic failure due to metastatic small-cell lung cancer (SCLC). The patient was hospitalised for the management of rapidly progressive hepatic failure. Thoracic radiology identified a widened mediastinum, and prior to hospitalisation she had received antibiotics for a urinary tract infection. Consequently, her hepatic failure was deemed to be due to either sarcoidosis with hepatic involvement or an antibiotic-related adverse event and was treated with prednisolone. However, the patient's clinical condition continued to deteriorate and a liver biopsy was obtained. Histopathology and immunohistochemistry tests demonstrated almost complete parenchymal replacement with metastatic SCLC. The patient was considered to be too unwell to receive chemotherapy and hence received best supportive care instead, and died shortly thereafter.

INVESTIGATIONS

Investigations revealed a total bilirubin of 330 µmol/l (<20.0), aspartate aminotransferase (AST) 302 U/l (<31.0), alanine aminotransferase (ALT) 97 U/l (<34.0), alkaline phosphatase (ALP) 687 U/l (53.0–141.0), lactate dehydrogenase (LDH) 612 U/l (150.0–280.0), ammonia (NH₃) 65 µmol/l (<50), paracetamol <10 mg/l and an international normalised ratio of 6.4. Hepatitis B surface antigen, hepatitis C antibody, cytomegalovirus IgM and Epstein-Barr virus were negative. Antinuclear, antismooth muscle antibodies, anti-liver-kidney microsome-1 antibodies and anti-liver cytosol antibody-1 were negative. Serum copper was 31 µmol/l (11–24), ceruloplasmin was 3.26 µmol/l (1.48–2.89) and copper/ceruloplasmin ratio was 9.5 (7.0–10.0). Blood tests performed 2 years prior to admission demonstrated normal liver function tests. Serum ACE level was at the upper limit of normal at 120 U/l (30–130). Chest x-ray demonstrated a widened mediastinum but no pulmonary nodules or masses (figure 1A). A CT scan of the thorax only showed hilar and mediastinal lymphadenopathy but no significant pulmonary pathology (figure 1B). A CT of the brain identified an old left-sided middle cerebral artery infarct but no evidence of an acute intracranial pathology or brain metastases (figure 1C). Due to her deteriorating clinical state, a brain MRI could not be performed.

DIFFERENTIAL DIAGNOSIS

- Working diagnosis: sarcoidosis.
- Differential diagnosis: metastatic lung cancer, adverse drug reaction.

TREATMENT

The patient was treated with prednisolone for the management of presumed sarcoidosis-induced FHF, and the elevated copper and ceruloplasmin levels were deemed to be due to an acute phase reaction. However, despite treatment there was a rapid decline in the patient's clinical condition with the development of confusion, asterixis and worsening hepatic failure. Day 5 postadmission, the total bilirubin increased to 490 µmol/l, AST to 362 U/l, ALT to 120 U/l, ALP to 1674 U/l, LDH to 922 U/l and NH₃ to 98 µmol/l. Sputum analysis was performed and the cell preparation showed multiple groups of atypical-small-sized hyperchromatic cells showing focal moulding, highly suspicious for small-cell carcinoma. Standard white light fibreoptic bronchoscopy did not reveal any intraluminal abnormality. Endobronchial ultrasound was considered but not performed as the patient was deemed a high

BACKGROUND

Fulminant hepatic failure (FHF) is defined as a liver disease that causes encephalopathy within 8 weeks of the onset of symptoms or within 2 weeks of the onset of jaundice in a patient with no prior evidence of liver disease.¹ Drugs, toxins, viruses, vascular and metabolic disorders are the most common causes of FHF. Once FHF develops, unless the underlying cause is identified and appropriate treatment provided quickly, mortality can be expected to occur in 60–80% of patients.

This case illustrates how the diagnosis of FHF due to metastatic small-cell lung cancer (SCLC) can be difficult, and that misdiagnosis may lead to delays in providing treatment.

CASE PRESENTATION

A 75-year-old woman was admitted to our hospital for investigation and management of a 5-week history of right-upper quadrant pain and dark urine. Four weeks prior to admission, she was diagnosed with an uncomplicated urinary tract infection and received two courses of cephalexin (each course was of 5 days duration). Urine culture had isolated mixed enteric and skin flora. Medical history included a 60-pack-year smoking history (she was an exsmoker at the time of presentation), hypertension, dyslipidaemia, atrial fibrillation and cerebrovascular accident. Her medications on presentation were irbesartan and rosuvastatin. Physical examination revealed jaundice, ascites and tender hepatomegaly without encephalopathy.

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Figure 1 Diagnostic chest and brain imaging performed in the patient. (A) Chest radiograph showed mediastinal widening but no nodules or mass within the lung fields. (B) A representative slice of CT scan of the thorax showing an enlarged mediastinal lymphadenopathy. There were no other abnormalities identified within the lung parenchyma. (C) CT scan of the brain which identified an old cerebrovascular infarct but no evidence of metastatic disease.

anaesthetic risk. Triple phase CT of the liver also demonstrated hepatomegaly, ascites, hypoattenuating lesions in several hepatic segments (segments 4a and 4b, segment 3, segment 5 and segment 7; figure 2A, B). A Doppler ultrasound of the abdomen demonstrated an enlarged liver (measuring 18 cm in the mid clavicular line), heterogeneous echotexture with a bullseye-type mass in the liver segment 4a, an anechoic cystic lesion in liver segment 5 and mobile free fluid (figure 2C, D). The gallbladder, spleen and pancreas were normal and there was no dilation of intrahepatic or extrahepatic ducts. Subsequently an ultrasound-guided liver biopsy was organised and samples were obtained from the largest hepatic lesion (located at the junction of segments 4a and 4b in the left hepatic lobe) and surrounding hepatic parenchyma. Microscopic examination of the liver biopsy identified that the liver was infiltrated by malignant tumour characterised by small hyperchromatic nuclei and very scant cytoplasm. The nuclei showed moulding and crush artefact, strongly suggestive of small-cell carcinoma (figure 3A, B). Immunohistochemistry showed that the tumour cells were positive for cytokeratin, CD56, synaptophysin and TTF-1, supporting the interpretation of metastatic small-cell carcinoma of the lung involving the liver. Due to the presence of liver metastases, the patient was deemed to have extensive stage small-cell carcinoma of the lung.

OUTCOME AND FOLLOW-UP

Five days postadmission the patient developed encephalopathy and multisystem organ failure. We consulted with the medical

oncology team in our institution, who upon review of the patient, advised that in the context of the rapid clinical deterioration and pre-existing medical comorbidities, treatment with combination chemotherapy would not be beneficial and recommended palliative measures. After consultation with her family, she received best supportive care and died 10 days after hospital admission. Permission for an autopsy was sought but not granted by the patient's family.

DISCUSSION

Our case report describes a patient with extensive stage SCLC presenting with FHF ultimately resulting in death. Although the liver is a common site for metastatic tumour deposits, FHF is rare. One study found that among 4020 admissions to a hepatic failure unit, only 18 (0.44%) patients with FHF were attributable to malignant hepatic infiltration.² Haematological malignancies are the most common cause of FHF due to malignant hepatic infiltration with less common causes, including primary neoplasms of the lung, gastrointestinal tract, breast, urothelium, nasopharynx and melanomas.³

A limitation of our report is that an autopsy could not be obtained and the diagnosis of metastatic SCLC is based on the histopathology results of the liver biopsy and sputum analysis. Indeed, the histology of the liver parenchyma demonstrated extensive infiltration with SCLC, also confirmed by the immunohistochemistry tests, which were positive for markers of neuroendocrine differentiation (CD56 and synaptophysin) and pulmonary origin (TTF-1 and cytokeratin). Additionally, we did

Figure 2 Abdominal imaging performed in the patient. (A,B) CT coronal sections of the abdomen demonstrating a hypoattenuating lesion at the junction of segments of 4a and 4b (A) and a subtle hyperattenuating lesion in segment 5 (B). (C,D) Doppler ultrasound images of the abdomen demonstrating hepatomegaly, heterogeneous echotexture (18 cm in the mid-clavicular line) (C) and 3.1×2.4 typical Bullseye-type lesion in segment 4a (D).

not identify any other possible explanation for the development of hepatic failure in our patient, specifically, paracetamol, viruses or metabolic causes. Furthermore, there were clinical clues for the diagnosis of FHF secondary to SCLC hepatic infiltration, which were the patient's heavy-smoking history, sputum analysis which was highly suspicious for SCLC and mediastinal lymphadenopathy. Histology confirmation of SCLC as the cause of the mediastinal lymphadenopathy was considered but could not be performed as both endobronchial ultrasound and

mediastinoscopy were contraindicated in our patient due to her rapidly deteriorating clinical condition and worsening encephalopathy.

SCLC comprises about 13% of all lung cancers,⁴ but FHF secondary to metastatic invasion by SCLC has been reported only infrequently.^{5–7} It has been reported that once FHF develops in this group of patients, typically death occurs within days to weeks.⁵ The rapid clinical deterioration noted in these patients precluded the delivery of chemotherapy.^{3–5} Indeed,

Figure 3 A microscopic section of the liver biopsy. (A) H&E section with ×10 magnification demonstrating diffuse infiltration of the liver parenchyma by malignant cells (arrow, left aspect of the field) is seen associated with the loss of hepatocytes (bottom aspect of the liver biopsy). (B) H&E section with ×40 magnification demonstrating cells (block arrow) consistent with a metastatic small-cell carcinoma originating from a lung primary, with large nuclei, inconspicuous nucleoli and minimal cytoplasm showing nuclear moulding and crush-like artefact infiltrate diffusely through liver cell plates. These cells were positive for cytokeratin, TTF-1, CD56 and Synapthophysin.

there is only one report of where chemotherapy was provided following the diagnosis of FHF due to metastatic SCLC, resulting in remission, albeit temporary, of not only the FHF but also the SCLC tumour burden.⁵

The mechanism for the development of FHF in the setting of hepatic metastases is believed to be either due to direct vascular occlusion (by tumour cells or ischaemic necrosis related oedema), postsinusoidal obstruction resulting in hepatocyte death and/or cytokine release by tumour cells causing hepatocyte ischaemia.²⁻⁷ Serum LDH has been proposed to be a prognostic biomarker in SCLC patients with liver metastases, with a high serum LDH levels being associated with an increased risk of developing FHF.³

Learning points

- ▶ Fulminant hepatic failure (FHF) due to metastatic small-cell lung cancer (SCLC) is rare.
- ▶ The diagnosis of metastatic SCLC should be suspected in patients at risk of developing pulmonary malignancy, that is, current or former smokers.
- ▶ In clinical situations of FHF where there is diagnostic uncertainty, a liver biopsy may be helpful in quickly identifying the underlying aetiology.

Competing interests None.

Patient consent Obtained.

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