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Case Report

Extrapulmonary small cell carcinoma of the liver treated with chemotherapy and durvalumab ☆

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ABSTRACT

Two basic criteria must be met for the diagnosis of extrapulmonary small cell carcinoma (EPSCC): the tumor must present histological characteristics of small cell carcinoma and a primary small cell lung carcinoma must be ruled out. We present the case of a 52-year-old woman who presented 8 months prior to consultation with an increase in abdominal circumference, epigastric pain and early satiety. Abdominal MRI showed an enlarged liver secondary to a mass affecting segments IV, V, VI, VII and VIII of 16.9 × 9.4 cm. Biopsy of the liver lesion was performed: small, round, blue cell neoplasm; immunohistochemistry revealed positivity for CKA1/A3, chromogranin, synaptophysin, CD56 and TTF-1. The diagnosis of EPSCC of the liver was made. It was decided to start systemic chemotherapy treatment with carboplatin, etoposide and durvalumab with clinical improvement of the symptoms. The patient died 10 months after starting chemoimmunotherapy treatment. Optimal treatment of EPSCC is generally extrapolated from small lung cell cancer. There is insufficient evidence to routinely recommend the use of immunotherapy in this group of patients.

Introduction

Extrapulmonary small cell carcinoma of the liver (EPSCC) is rare neoplasm that accounts for 2.5% of small cell carcinomas [1]. The most accepted theory about their origin is that EPSCCs arise from a multipotent stem cell capable of divergent differentiation, which explains their mixed morphology [2]. To diagnose EPSCC, 2 basic criteria must be met: the tumor must present histological characteristics of small cell carcinoma and primary small cell lung carcinoma must be ruled out. They have been described in virtually all organs of the body [3]. Here we present a case of EPSCC of the the liver treated with chemotherapy and durvalumab.

Case report

A 52-year-old woman with no medical and surgical history, no family history and nonsmoker presented with an increase in abdominal circumference, epigastric pain, early satiety and

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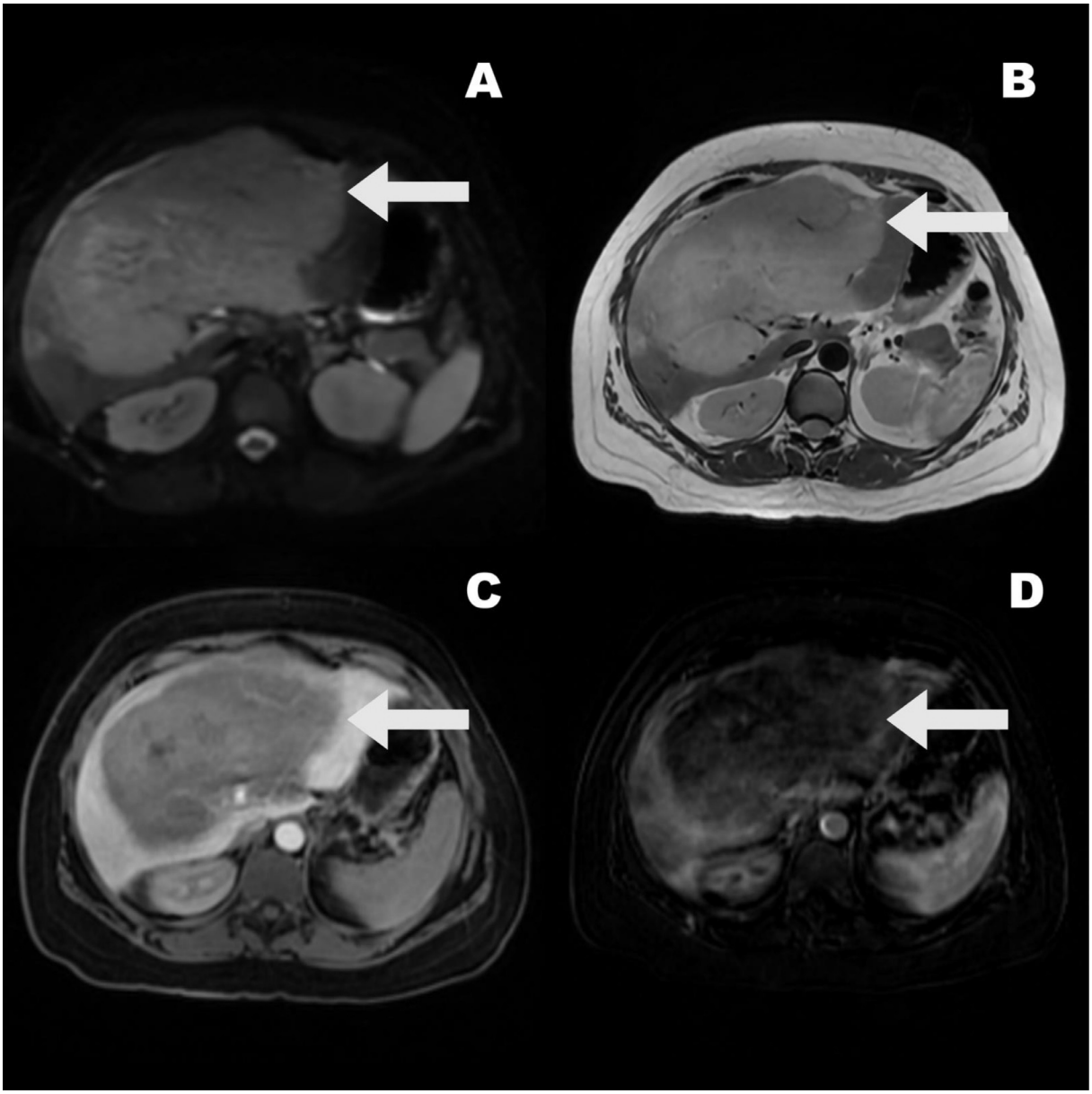

Fig. 1 – Abdominal MRI showed an enlarged liver secondary to a mass (white arrows) affecting segments IV, V, VI, VII and VIII with lobulated contours, with restriction of diffusion of water particles (A), slightly hyperintense on T2 (B), slightly hypointense on T1 with fat saturation (C) and late arterial phase (D).

weight loss eight months prior to consultation. Physical examination revealed slightly painful hepatomegaly; abdominal perimeter was 98 cm. Laboratory tests (alanine aminotransferase, aspartate aminotransferase, total bilirubin, alkaline phosphatase, gamma-glutamyl transferase, albumin, total proteins, lactate dehydrogenase, prothrombin time test, activated partial thromboplastin time, hepatitis B surface antigen, hepatitis C virus) and chest and pelvis CT were normal. Abdominal MRI showed an enlarged liver secondary to a mass affecting segments IV, V, VI, VII and VIII with lobulated contours, slightly hyperintense on T2, slightly hypointense on T1 and minimal enhancement in the arterial and portal phases, measuring 16.9 × 9.4 cm, infiltration of the gallbladder and right portal vein, The bile duct and vascular structures were unremarkable (Fig. 1). A biopsy of the liver lesion was performed for histological analysis: small, round, blue cell neoplasm. Immunohistochemistry revealed negativity for CD45, CD99, CK20, CK7 and P40 and positivity for CKA1/A3, chromogranin, synaptophysin, CD56 and TTF-1 in the nuclei of the tumor cells (Fig. 2). The diagnosis of EPSCC of the liver was made. After discussion in the tumor committee, the possibility of surgery (due infiltration of right portal vein and the inability to perform a partial hepatectomy) and radiotherapy (due risk of bleeding, fibrosis, cirrhosis, radiotherapy-induced liver disease) was ruled out and for easy and quick access to treatment, systemic treatment with carboplatin, etoposide

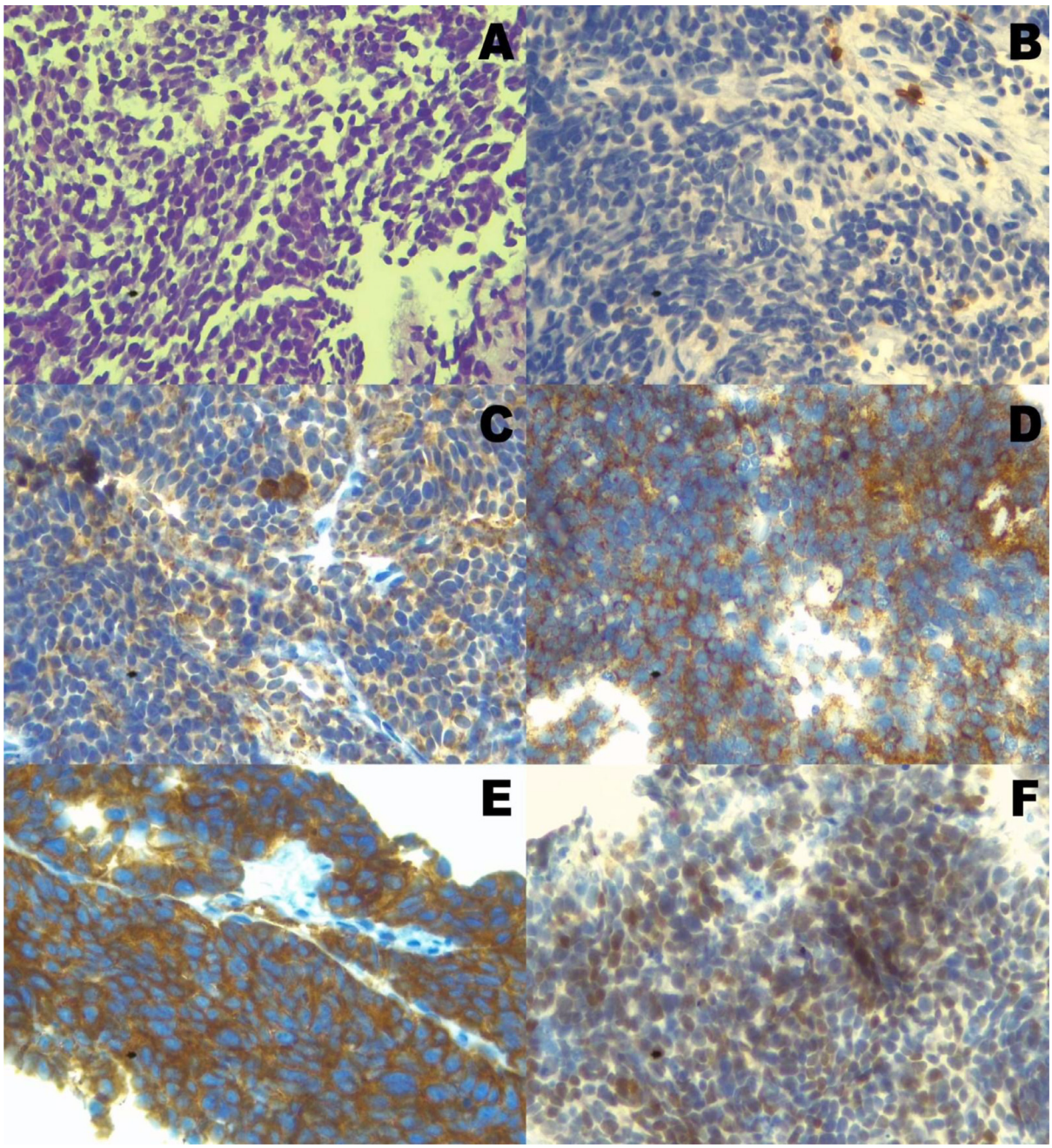

Fig. 2 – (A) Small round blue cells neoplasm (H&E. 40X). (B) Negative IHC for CD45. (C) Positive IHC for CKA1/A3. (D) Positive IHC for synaptophysin. (E) Positive ICH for chromogranin. (F) Positive ICH for TTF-1. H&E: Hematoxylin and eosin; IHC: Immunohistochemistry.

and durvalumab was started every 21 days for 6 cycles and subsequent maintenance with durvalumab with clinical improvement of the symptoms, decrease in abdominal circumference (83 cm) and tolerance to it. After 6 cycles, an abdominal MRI was performed: enlarged liver secondary to a mass with a decrease in size compared to the previous study of 23% with no evidence of other lesions. The patient presented disease progression at 7 months with rapid clinical deterioration. The possibility of radio/chemoembolization was evaluated and was ruled out due to the patient's clinical condition (*Eastern Cooperative Oncology Group Performance Status Scale* 3, *Karnofsky Performance Status Scale* 40%). The patient was referred to palliative care and died 10 months after starting chemo-immunotherapy treatment. The informed consent was obtained.

Discussion

Most small cell carcinomas originate in the lungs. Data on EP-SCC are limited and consist mainly of case reports and small retrospective series.

The immunophenotype of EPSCCs supports both epithelial and primitive neuroendocrine differentiation. Similar to our case, they react with general epithelial markers such as broad-spectrum cytokeratin cocktails and general neuroendocrine markers such as neuron-specific enolase, neurofilament, synaptophysin, leu 7 and chromogranin A. Like small cell lung carcinoma (SCLCs) EPSCC often express TTF-1. Cytokeratin 20 (CK 20) is rarely expressed in EPSCC [2].

Macroscopically, hepatic EPSCCs appear as large, rapidly growing masses with compressive effects on neighboring structures [4,5]. Differential diagnoses of EPSCC of the liver should include hepatoblastoma, hepatocarcinoma, intrahepatic cholangiocarcinoma, lymphomas, and sarcomas [2,4–6].

The general approach and treatment of EPSCC is generally extrapolated from SCLC [7]. In case of unresectable and/or metastatic disease, concurrent or sequential radiotherapy in combination with chemotherapy, or chemotherapy alone is recommended [8,9]. Cytotoxic chemotherapy regimens, such as cisplatin/etoposide or carboplatin/etoposide, FOLFOX, FOLFIRI, and temozolomide with or without capecitabine, are generally used as first-line treatment. The efficacy of second-line or later-line chemotherapy is very limited and survival is short [9]. Choi SJ et al. report a case of EPSCC of the liver treated with surgery. She was alive after 18 months [5]. Mandish SF et al. report the median overall survival of 11.2 months in 1550 patients with gastrointestinal EPSCC treated with surgery, radiotherapy or chemoradiotherapy. None were treated with inmunotherapy [8]. In a phase Ib single-center study of pembrolizumab in combination with chemotherapy in patients with locally advanced or metastatic small cell/neuroendocrine cancers of the prostate and urothelium 14 patients were enrolled. The overall survival rate at 12 months was 79% [10]. A phase II basket trial of pembrolizumab, enrolled 7 women with gynecologic extrapulmonary small cell carcinoma. Pembrolizumab alone showed minimal activity; the median progression-free interval was 2.1 months [11]. In the phase 3 CASPAIN trial, patients were randomized to receive durvalumab plus platinum-etoposide or platinum-etoposide for first-line treatment of SCLC. The median overall survival for the durvalumab plus platinum-etoposide group was 13 months, exceeding the 10.3 months for the platinum-etoposide group [12]. Based on this trial, we decided to start treatment with durvalumab plus etoposide and carboplatin for our patient to obtain greater benefits.

To our knowledge, this is the first case report of unresectable EPSCC of the liver treated with chemotherapy and durvalumab; no survival benefit was achieved in this case. Due to the wide range of anatomical origins, the diagnosis of EPSCC is challenging and depends on the combination of a complete clinical history, laboratory tests, imaging studies, light microscopy and immunohistochemistry. Optimal treatment remains challenging and requires a multidisciplinary approach based on surgery, radiotherapy and chemotherapy. There is insufficient evidence to routinely recommend the use of immunotherapy in this group of patients.

Patient consent

The authors of this manuscript declare that an informed consent for publication of this case was obtained from the patient.

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