Primary Small Cell Carcinoma of the Liver: A Rare and Aggressive Tumor

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Introduction

The lung is the major site for the origin of small cell carcinoma. Pulmonary small cell carcinoma of the lung comprises 20% of all lung cancers.[1-3] However, extra-pulmonary small cell carcinoma has been recognized as a separate entity.[1] Sites include the esophagus, thymus, stomach, pancreas, and the cervix. Extrapulmonary small cell carcinomas comprise only 2.5 to 4.1% of all small cell carcinomas.[1-3] Thus, primary small cell carcinoma of the liver is a rare entity. We compare the clinical course, pathology/immunohistochemical findings and treatment response among reported cases in literature.

Case Report

A 63-year-old woman presented with right upper quadrant pain of gradual onset. She denied any associated symptoms including, but not limited to, nausea, vomiting, diarrhea, fever, chills, and hematemesis. Her prior history included hepatitis C, osteoarthritis, deep vein thrombosis, and pulmonary embolism. She smoked for 20 years. Her physical exam revealed mild tenderness in the right hypochondrium and the liver edge was palpable 1 cm below right costal margin.

A complete blood count and comprehensive metabolic panel were normal. A computed tomography (CT) scan of the abdomen showed a 8.6 x 7.6 cm mass in right lobe of the liver (see Figure 1) with extension in the intrahepatic portion of the portal vein along with celiac adenopathy. Her alfa-fetoprotein was 3.48 ng/ml (0 - 6.1 ng/ml), carcinoembryonic antigen was 3.8 mg/L (0 - 5 mg/L), CA-19-9 was 86 U/ml (< 37 U/ml) and her anti-HCV was positive. Liver biopsy results were consistent with small cell carcinoma.

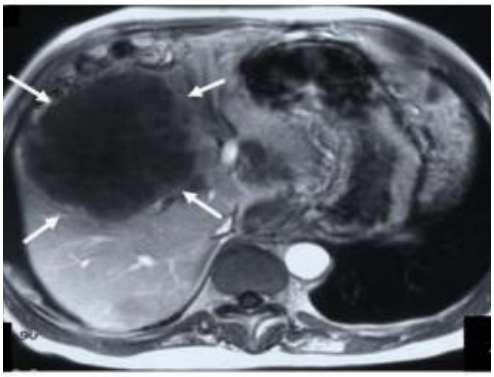

Figure 1. Arrows show a 8.6 x 7.6 cm mass in right lobe of the liver.

In search of the primary site, a chest X-ray, CT of the chest, and positron emission tomography (PET) scan were done. All were negative for any pulmonary lesion. Diagnosis of extrapulmonary small cell carcinoma of the liver was made and the patient was started on chemotherapy including carboplatin and etoposide.

Microscopically, the extrapulmonary small cell carcinoma of the liver tumor exhibited minimal cytoplasm, inconspicuous nucleoli, and diffuse nuclear hyper-chromasia. Immunohistochemical staining showed strong positivity for synaptophysin

and patchy reactivity to CK7 but was negative for AE1:3, chromogranin, CD20, CD3, HepPar1, TTF-1, CK20, and cirrhosis (Figures 2 and 3).

The patient died within 30 days of diagnosis.

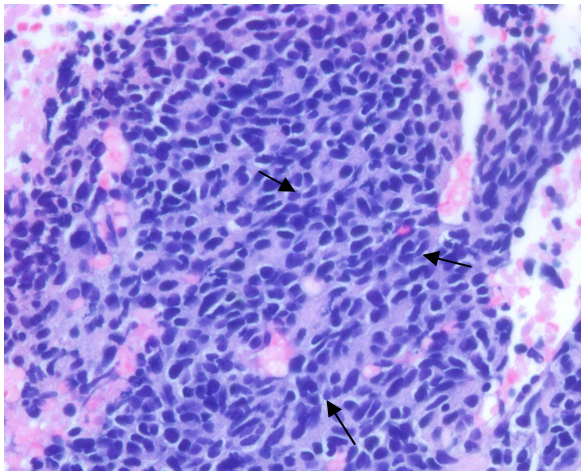

Figure 2. Tumor cells under high resolution (see arrows).

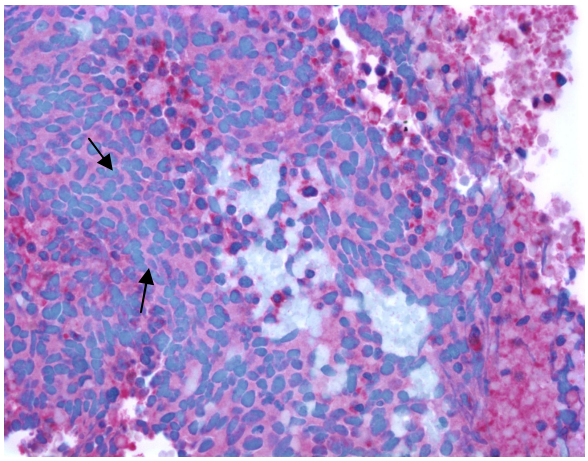

Figure 3. Arrows show positive synaptophysin stain.

Discussion

Extrapulmonary small cell carcinoma comprises 0.1 to 0.4% of all cancers.[4] Small cell carcinoma of the liver is extremely rare and only 14 cases have been reported in the literature (see Table 1). Small cell carcinoma can arise in any tissue of the body beside the lung and liver. Primary reported locations are neck, larynx, head, salivary glands, thyroid, trachea, larynx, esophagus, stomach, cervix, uterus, gall bladder, rectum, breast, and skin.[1-3] More than 50% of extrapulmonary small cell carcinomas are located in the gastrointestinal tract.[11]

Small cell carcinoma of the liver has a slight male predominance with a male to female ratio of 1.8:1; approximately 86% of patients were over 50 years at the time of presentation (Table 1). Most patients presented with upper abdominal pain, lump, loss of appetite, and jaundice. On the basis of histological appearance, it is very difficult to differentiate it from metastatic pulmonary small cell carcinoma; hence, it is mandatory to have a clear chest radiograph, CT scan of the chest, negative sputum cytology, and bronchoscopy or PET scan before making the diagnosis of primary tumor.[6]

In most reported cases, the tumor showed neuroendocrine differentiation, with markers like enolase, synaptophysin and chromogranin. Most cases also reported CD56, thyroid transcription factor-1 (TTF-1), c-kit, cytokeratin, and CEA. However, it is not necessary to find all markers in every case. Presence of vimentin, desmin, CD56, chromogranin, synaptophysin, and S-100 protein is quite specific. Synaptophysin was positive in 100% of the cases and neuron specific enolase was positive in over 85% of the cases.

Due to the small number of reported cases, conclusions about the characteristics of small cell carcinoma of the liver must not be made. Small cell carcinoma of the liver may present with weight loss, jaundice, and high AFP levels as key features.[7] Features like absence of viremia, low AFP, and cirrhosis differentiate small cell carcinoma from the most predominant tumor of liver, hepatocellular carcinoma.

Prognosis of the tumor is variable depending upon its stage and location. More than 90% of cases shown in Table 1 were diagnosed at an advanced age. Overall,

Table 1. Characteristics of patients with primary small cell carcinoma of liver.

Authors	Age / Sex	Presentation	Size (cm)	Stage at Presentation	AFP (ng/ml)	Immuno-histochemical Staining	Treatment	Outcome
Ryu et al.[5]	56 / Male	Weakness, Upper abdominal pain	8	Advanced	3.24	(+) CD56, C-kit, SYN (-) TTF-1	CT (cisplastin, etopside, irinotecan)	Unknown
Kim et al.[6]	53 / Male	Palpable mass	12	Advanced	2.94	(+) CD56, NSE, C-kit, SYN, CK, EMA (-) CK 7, 8, 19, 20, AFP, CEA, TTF-1, Vimentin, Desmin)	Segmentec-tomy and CT (cisplastin, etopside)	Unknown
Zanconati et al.[7]	56 / Male	Abdominal pain	5	Limited	> 200	(+) AE1/ AE3, CK8, 18, 19, NSE, AFP, ERY-1 (-) S-100 protein, CEA	Partial hepatectomy	Unknown
Zanconati et al.[7]	69 / Male	Diabetes, Weight loss	10	Advanced	Unknown	(+) AE1/AE3, CK8, 18, 19 (-) S-100 protein, CEA	Unknown	Died of disease
Zanconati et al.[7]	89 / Male	Jaundice	6	Advanced	150	(+) AE1/AE3, CK8, 18, 19, AFP, NSE (-) CK, CEA	Unknown	Died of disease
Kim et al.[8]	67 / Male	Abdominal pain	12	Advanced	Unknown	(+) SYN, CD56, C-kit (-) CK, CEA, AFP	CT (cisplastin, epirubicin)	Unknown

Sengoz et al.[9]	73 / Female	Unknown	Unknown	Advanced	Unknown	Unknown	Right hepatectomy	Died of disease
Sengoz et al.[9]	63 / Male	Unknown	Unknown	Unknown	Unknown	Unknown	CT (cisplastin)	Died of disease
Kim et al.[1]	Unknown	Unknown	Unknown	Advanced	Unknown	(+) CHR, SYN	Unknown	Unknown
Choi et al.[10]	82 / Female	Abdominal discomfort	6.7	Advanced	3.4	(+) CD56, NSE, SYN, CHR, TTF-1, C-kit (-) Anti-hepatocyte, AFP, Vimentin, Desmin, CK7, 19, 20, CEA, S-100 protein	CT (cisplastin, etoposide)	Unknown
Morikawa et al.[11]	77 / Male	Fatigue, weakness	10	Advanced	27	(+) AE1/AE5, CAM5.2 (-) NSE, Desmin, Vimentin, CEA	CT (cisplastin, etoposide)	Died of disease
Yang-Qing Huang et al.[12]	34 / Male	Incidental finding	Unknown	Unknown	Unknown	Unknown	Right hepatectomy, segment I excision, and TACE for recurrence	Unknown
Kaman et al.[13]	40 / Female	Pain and abdominal lump	13.5	Advanced	2.1	(+) NSE, SYN (-) TTF-1, HepPar 1, CEA	Central bisectionec-tomy and CT (cisplatin, etoposide)	Unknown

Khaw et al.[14]	51 / Male	Incidental finding	3.5	Localized	Unknown	(+) CD56, SYN, CHR	Liver transplant-ation	Died of disease
Our case	63 / Female	RUQ pain	8.6	Advanced	3.5	(+) AE1, SYN, CHR, CD20, CD3 (-) HepPar1, TTF-1, CK20	CT (carboplatin, etopside).	Died of disease

RUQ = right upper quadrant, CT = Chemotherapy, AFP = Alpha-fetoprotein, CEA = Carcinoembryonic antigen, CHR = Chromogranin, CK = Cytokeratin, EMA = Epithelial membrane antigen, NSE = Neuron specific enolase, SYN = Synaptophysin, TTF-1 = Thyroid transcription factor, TACE = transcatheter arterial chemoembolization.

limited disease has a better chance of cure than extensive disease.[11] Treatment options depend upon the tumor staging, and include surgery, chemotherapy, and radiotherapy. Standard chemotherapy includes platinum-based therapy, same as that for pulmonary small cell carcinoma of the lung. In the two cases reported by Sengoz et al.[9], one patient was given chemotherapy and other was operated for right hepatectomy. Both patients survived for more than a year. Ryu et al.[5] treated their patient with platinum-based chemotherapy. The patient responded well to therapy. Out of seven deaths, five died within three months of diagnosis. Our patient was started on platinum-based chemotherapy, but unfortunately due to the aggressive nature of the disease, she died within a month after the diagnosis.

Conclusion

Small cell carcinoma of the liver is rare and details about etiology, risk factors, and treatment options are limited. Reporting more cases will help clinicians to understand the disease aggressiveness, treatment and prognosis.

Acknowledgment

Dr. Ayesha Aziz helped in preparing this manuscript.

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Keywords: small cell carcinoma, liver, case report