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Small Cell Neuroendocrine Carcinoma of Liver – a rare entity

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Abstract:

Background: Small cell neuroendocrine carcinoma (SCNEC) of the liver is an exceptionally rare and aggressive malignancy. It is classified as a high-grade poorly differentiated neuroendocrine tumor, characterized by rapid disease progression, late-stage diagnosis, and poor prognosis. Due to its rarity, SCNEC presents significant diagnostic and therapeutic challenges, distinguishing it from more common hepatic tumors, such as hepatocellular carcinoma (HCC), and metastatic neuroendocrine tumors.

Case Presentation: We present the case of a 47-year-old postmenopausal woman who presented with right-sided abdominal pain, progressive swelling, significant weight loss, and anorexia. Imaging studies revealed a large hepatic mass with evidence of metastatic disease. Histopathological examination and immunohistochemistry confirmed the diagnosis of primary SCNEC of the liver, stage cT3 cN1 cM1. The patient was treated with first-line platinum-based chemotherapy (cisplatin and etoposide), along with supportive care.

Discussion: SCNEC of the liver exhibits distinct pathophysiological features, including high mitotic activity and genetic abnormalities such as TP53 and RB1 mutations. Accurate diagnosis relies on histopathology and immunohistochemical markers like synaptophysin and chromogranin A. Management involves a multidisciplinary approach, with systemic chemotherapy as the cornerstone of treatment. Surgical resection and liver-directed therapies may be feasible in select cases. Emerging therapies, such as immune checkpoint inhibitors and targeted treatments, offer potential but require further clinical validation.

Conclusion: SCNEC of the liver is a rare and aggressive malignancy with limited therapeutic options and poor prognosis. Early detection, molecular profiling, and personalized treatment strategies are critical for improving outcomes. This case contributes to the limited literature, emphasizing the importance of a collaborative approach and the need for further research to optimize management and survival.

Keywords: Small cell neuroendocrine carcinoma, liver cancer, neuroendocrine carcinoma of liver.

Introduction:

Neuroendocrine tumors (NETs) are neoplasms that arise from neuroendocrine cells, which are primarily located in the gastrointestinal tract and other organs. These tumors exhibits a wide range of malignancy,

varying from indolent growth to aggressive disease progression [1]. NETs are broadly classified into two main categories: well-differentiated tumors, which are usually of lower grade and associated with better prognoses, and poorly differentiated tumors, which tend to be highly aggressive and carry a poorer prognosis [2, 3]. Well-differentiated NETs are often referred to as carcinoid tumors, whereas poorly differentiated neuroendocrine carcinomas (NECs) represent a high-grade form, marked by their aggressive clinical behavior [1, 2].

The classification of NETs plays a crucial role in determining treatment strategies and predicting patient outcomes, as the clinical course, therapeutic approach, and prognosis vary significantly between well-differentiated and poorly differentiated forms [4].

Small cell neuroendocrine carcinoma (SCNEC) of the liver is a rare and aggressive subtype of poorly differentiated NETs, characterized by small cells with neuroendocrine features. Classified as a high-grade malignancy, SCNEC is distinct from more common liver tumors, such as hepatocellular carcinoma (HCC), and exhibits unique histopathological features [1, 5]. Histologically, SCNEC is marked by small to medium-sized cells arranged in solid nests or trabecular patterns, with prominent mitotic activity and necrosis. Diagnostic confirmation relies on immunohistochemical staining for neuroendocrine markers such as chromogranin A and synaptophysin [6, 5].

SCNEC differs significantly from other primary hepatic tumors. Unlike HCC, which frequently develops in the context of cirrhosis, SCNEC typically arises independently of chronic liver disease and presents a more aggressive clinical course with a worse prognosis compared to well-differentiated NETs and HCC [7, 8]. Furthermore, SCNEC must also be distinguished from metastatic neuroendocrine tumors involving the liver, as its primary hepatic origin influences treatment and prognosis [1, 3].

This study is significant as it addresses a rare and poorly characterized malignancy. Integrating clinical findings with a comprehensive literature review not only provides insights into the clinical behavior and therapeutic challenges of rare tumors but also contributes to identifying knowledge gaps. This paper aims to highlight a case of SCNEC of the liver, integrating detailed clinical observations with a review of the literature to provide a broader perspective on the diagnosis and management of this rare tumor.

Case History:

A 47-year-old postmenopausal woman presented with complaints of persistent right-sided abdominal pain and low-grade fever for the past 5 months. Over this period, she noticed a progressive swelling on the right side of her abdomen, which had gradually increased in size and was associated with significant weight loss (~6–8 kg) and reduced appetite. The abdominal pain was dull, persistent, and non-radiating, without any relieving or aggravating factors. There was no history of jaundice, hematemesis, or melena. The patient also reported generalized fatigue but denied symptoms such as dyspnea, cough, or chest pain. She had no significant past medical or surgical history. She was a chronic bidi smoker, consuming approximately 10 bidis per day for 20 years. She denied any history of alcohol consumption or intravenous drug use. Her menstrual history revealed she had been postmenopausal for 20 years. Obstetric history included seven full-term deliveries (P7, A0, L7), with no history of abortions.

On general examination, the patient appeared pale and malnourished, with a poor nutritional status and thin build. Her ECOG performance status was 1. There was no peripheral lymphadenopathy, icterus, cyanosis, clubbing, or pedal edema.

Abdominal examination revealed a large, firm, irregular, non-tender mass approximately 18 × 16 cm in size occupying the right hypochondriac and epigastric regions. The mass extended inferiorly to the

umbilical region. There were no signs of ascites, and liver dullness on percussion extended to the right iliac fossa. Other systemic examinations, including cardiovascular, respiratory, and neurological systems, were unremarkable.

Laboratory investigations revealed mild anemia (hemoglobin: 8.4 g/dL) with normal white blood cell and platelet counts. Liver function tests showed mild elevations in ALT (78 IU/L), AST (92 IU/L), and alkaline phosphatase (180 IU/L). Tumor marker chromogranin A was markedly elevated (~750 ng/mL), while AFP levels were within normal limits.

Histopathological examination of the liver mass confirmed small cell neuroendocrine carcinoma. Immunohistochemistry (IHC) was positive for AE1/AE3, synaptophysin, and chromogranin A, with a high MIB-1 labeling index (80–90%) (Figure 1, 2).

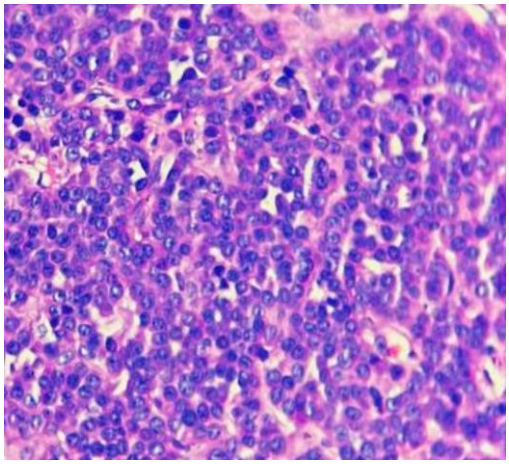

Figure 1: Section shows cores of fibrocollagenous tissue infiltrated by cells exhibiting poorly differentiated morphology with areas of necrosis and crushing

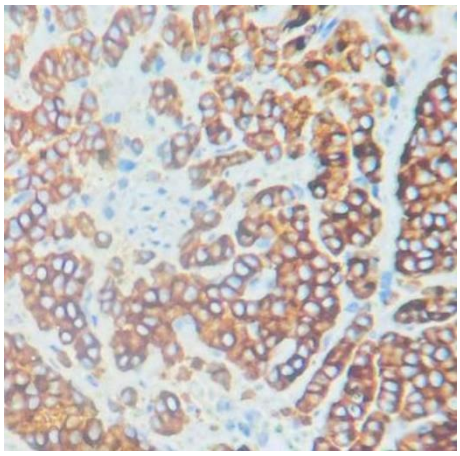

Figure 2: Section shows tumor cell positivity for synaptophysin

CECT of the thorax, abdomen, and pelvis revealed a large mass (18 × 20 × 17 cm) involving the entire right lobe of the liver and a smaller lesion (2.8 × 3.0 cm) in the left lobe. Additional findings included bilateral adrenal masses (largest ~2.6 × 5.0 cm), a right kidney mass (2.1 × 2.8 cm), and multiple enlarged lymph nodes at the porta hepatis and retroperitoneum (largest ~3.3 × 2.9 cm). The portal vein was splayed and thinned out. A PET-CT scan performed one month later showed metabolic activity in the liver mass

with central necrosis (SUVmax 12.2), enlarged gastrohepatic and periportal lymph nodes (SUVmax 10.1), and additional sites of metastatic disease.

Based on these findings, the patient was diagnosed with small cell neuroendocrine carcinoma of the liver, stage cT3 cN1 cM1 (AJCC 8th Edition). A multidisciplinary team initiated treatment with first-line platinum-based chemotherapy using cisplatin and etoposide. Supportive care, including nutritional supplementation and anemia management, was also implemented. The patient was advised to follow up with serial tumor marker evaluations and repeat imaging after two chemotherapy cycles to assess treatment response

Discussion:

Small cell neuroendocrine carcinoma (SCNEC) of the liver is an extremely rare and aggressive malignancy, with only a limited number of cases reported in the literature. The overall incidence of neuroendocrine tumors (NETs) in the liver is low, and SCNEC constitutes a small fraction of these cases, making it challenging to establish precise prevalence rates. Most patients diagnosed with SCNEC are older adults, often with a history of smoking or other risk factors, consistent with the demographic patterns observed in other neuroendocrine carcinomas [3, 5].

SCNEC originates from neuroendocrine cells, which are more commonly found in the gastrointestinal tract but can also arise in the liver. These tumors are frequently associated with genetic abnormalities, such as mutations in TP53 and RB1 genes. These mutations lead to the loss of tumor suppressor functions, facilitating unchecked cellular proliferation and the aggressive nature of SCNEC [1, 8]. Compared to well-differentiated neuroendocrine tumors, SCNEC exhibits markedly higher mitotic activity and a tendency for rapid disease progression, contributing to its poorer prognosis [1].

SCNEC of the liver typically presents with non-specific symptoms such as abdominal pain, jaundice, weight loss, and anorexia, reflecting the advanced disease stage at diagnosis. Imaging studies often reveal large hepatic masses, which may be localized or diffuse. Distinguishing SCNEC from metastatic small cell lung cancer is a critical diagnostic challenge due to overlapping histopathological features. Accurate diagnosis relies on a combination of imaging, biopsy, and immunohistochemistry. Neuroendocrine markers such as synaptophysin and chromogranin A are essential for confirming the neuroendocrine origin, while molecular profiling may provide additional insights into tumor characteristics [5, 11].

The management of SCNEC involves a multidisciplinary approach, as treatment options are limited and outcomes remain poor. Systemic chemotherapy with etoposide and platinum-based agents remains the cornerstone of treatment, showing modest efficacy in controlling disease progression. Surgical resection, when feasible, offers the best chance for long-term remission, particularly in patients with localized disease. Liver-directed therapies, such as transcatheter arterial chemoembolization (TACE) and radiofrequency ablation, have been explored as adjunctive treatments to reduce tumor burden and improve prognosis in select cases [3, 4]. Radiation therapy can be used as a palliative measure or as adjuvant therapy in cases where surgical resection is not viable [3].

Emerging therapies, including targeted treatments and immunotherapy, hold promise for improving outcomes in SCNEC. Although clinical evidence is limited, early data suggest that immune checkpoint inhibitors may have a role in managing aggressive neuroendocrine tumors. Further research is needed to establish the efficacy of these therapies in SCNEC of the liver [8].

SCNEC of the liver has a poorer prognosis compared to other primary liver cancers, such as hepatocellular carcinoma, primarily due to its aggressive nature and late-stage presentation. Key prognostic factors

include the tumor stage at diagnosis, Ki-67 index, and the presence of metastases. A higher Ki-67 index correlates with increased tumor aggressiveness and worse outcomes. Additionally, mutations in TP53 and RB1 have been associated with poor survival, highlighting the need for molecular characterization to guide risk stratification and treatment planning [3, 5].

Effective management of SCNEC requires a collaborative, multidisciplinary approach involving oncologists, surgeons, radiologists, and pathologists to optimize outcomes. Emphasis on early detection through advanced imaging and biomarker analysis may improve survival. Personalized treatment strategies, informed by molecular profiling and tumor characteristics, are crucial for improving patient outcomes [3, 12].

Dedicated clinical trials focusing on SCNEC of the liver are essential to establish evidence-based treatment protocols. The development of targeted therapies and immunotherapy represents a promising avenue for improving survival in these patients. Advances in molecular and genetic profiling can aid in the identification of actionable mutations, enabling personalized treatment approaches. Collaborative efforts between multidisciplinary teams are critical to translating research findings into clinical practice, ultimately enhancing care for patients with this rare and challenging malignancy.

Conclusion:

Small cell neuroendocrine carcinoma (SCNEC) of the liver is a rare and aggressive malignancy, representing a diagnostic and therapeutic challenge due to its rarity, late presentation, and poor prognosis. The case presented in this paper highlights the clinical complexity and rapid progression of SCNEC, emphasizing the importance of a multidisciplinary approach in its diagnosis and management.

Histopathological confirmation and immunohistochemical analysis remain cornerstones for accurate diagnosis, distinguishing SCNEC from other primary liver tumors and metastatic neuroendocrine carcinomas. Treatment strategies predominantly rely on systemic chemotherapy, with platinum-based regimens offering modest survival benefits. Surgical resection and liver-directed therapies may be considered in select cases, while emerging therapies, such as immunotherapy and targeted treatments, hold promise for future management.

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