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Title:

Evolving Management of Gallbladder Neuroendocrine Carcinoma: A Longitudinal Case Study and Literature Overview

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Abstract

Rationale:

Neuroendocrine neoplasms (NENs) arise in various tissues including the thyroid, respiratory tract, and gastrointestinal system. Among these, gallbladder neuroendocrine carcinoma (GB-NEC) is an exceptionally rare malignancy, accounting for roughly 0.5% of all NENs and approximately 2.1% of gallbladder cancers. Due to its scarcity, there is limited knowledge regarding its clinical course and optimal treatment approaches.

Patient Concerns:

A 52-year-old male patient presented with acute right upper quadrant abdominal discomfort persisting for two days, with no other associated symptoms.

Diagnoses:

Initial imaging studies, including ultrasound and contrast-enhanced computed tomography (CT), suggested gallbladder malignancy. Histopathological evaluation following radical surgery confirmed GB-NEC with a minor adenocarcinomatous component. Immunohistochemical (IHC) profiling supported the diagnosis.

Interventions:

The patient underwent radical cholecystectomy followed by adjuvant chemotherapy with etoposide and cisplatin. Upon disease progression at 16 months post-surgery, therapy was adjusted to include cisplatin plus irinotecan, in combination with the anti-angiogenic agent anlotinib and the immune checkpoint inhibitor paimiplimab.

Outcomes:
The patient initially achieved a partial response to therapy. Despite subsequent tumor progression, continuous treatment adjustments enabled prolonged survival and maintained an acceptable quality of life.

Lessons:
GB-NEC typically exhibits aggressive behavior and poor outcomes. Early detection, thorough pathological evaluation, and an integrated, multimodal therapy regimen—including surgery, chemotherapy, targeted therapy, and immunotherapy—may improve survival. Further multicenter prospective studies are needed to establish standardized treatment protocols for this uncommon entity.

1. Introduction

Neuroendocrine neoplasms (NENs), originating from cells with both endocrine and neural features, can be found in multiple organ systems including the thyroid, bronchopulmonary tract, and gastrointestinal organs.[1] Although their incidence has increased in recent decades, gallbladder neuroendocrine carcinoma (GB-NEC) remains exceedingly uncommon, representing only a small fraction of all NENs and gallbladder cancers.[2] Limited clinical reports and a scarcity of large-scale

studies have hindered the development of evidence-based management strategies.

Recent advances in imaging, endoscopy, and immunohistochemistry have facilitated the earlier detection and more accurate characterization of NENs. Nonetheless, GB-NEC remains poorly understood, with no consensus on optimal therapeutic approaches. In 2019, the World Health Organization (WHO) refined its classifications for neuroendocrine tumors in the biliary tract, highlighting the importance of precise pathological definitions to guide management decisions.[5]

Here, we present a rare case of GB-NEC with subsequent hepatic metastases appearing 16 months after curative surgery. We outline the evolving therapeutic approach, including surgical intervention, systemic chemotherapy, targeted therapy, and immunotherapy, and review the current literature on diagnosis, treatment, and prognosis. This case emphasizes that comprehensive, dynamic treatment strategies may enhance survival outcomes in this challenging malignancy.

2. Case Presentation

A 52-year-old man sought medical attention due to a two-day history of acute right upper quadrant abdominal pain, without fever, jaundice, or other systemic symptoms. Physical examination revealed localized tenderness in the right upper quadrant but no rebound tenderness. Basic laboratory evaluations, including carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), were within normal limits.

Imaging Studies:

Ultrasound imaging showed an irregularly thickened gallbladder wall and an intraluminal, hypoechoic mass. Contrast-enhanced CT and magnetic resonance imaging (MRI) raised suspicion of a gallbladder tumor (Fig. 1A, B). Following multidisciplinary discussion, a radical cholecystectomy was performed, given the high suspicion of gallbladder malignancy.

Pathological Findings:

Microscopic examination revealed a predominantly neuroendocrine carcinoma with approximately 5% adenocarcinoma component. The lesion infiltrated the serosal fibrofatty tissue, with perineural invasion noted. Immunohistochemistry (IHC) demonstrated Ki-67 ~70% positivity, along with positive staining for CK7, EMA, CKpan, CgA, and CD56, and weak Synaptophysin positivity (Fig. 1C, D). These findings confirmed a high-grade NEC of the gallbladder.

Postoperative Course and Follow-up:

The patient received postoperative chemotherapy with etoposide and cisplatin. Serial follow-up imaging did not identify metastatic disease until 16 months later, when CT scans revealed multiple liver nodules and a tumor thrombus in the left branch of the portal vein (Fig. 2A). At this time, CA19-9 had risen to 90.4 U/mL. Subsequent positron emission tomography-computed tomography (PET-CT) demonstrated increased FDG uptake in hepatic lesions, suggesting metastatic involvement (Fig. 2B).

Second-line and Subsequent Therapies:

The treatment regimen was adjusted to cisplatin and irinotecan chemotherapy combined with anlotinib and paimiplimab. The patient initially showed partial response. However, MRI scans at later follow-up indicated tumor progression in the liver and persistence of the portal vein tumor thrombus (Fig. 2C). A biopsy of a

hepatic lesion again confirmed small cell NEC. IHC was consistent with previous profiles, including CgA (+) and CD56 (+) (Fig. 2D).

Despite evidence of progression, the patient maintained a favorable performance status, and therapy was further optimized. At the time of writing, he continued to show stable overall condition and was under regular follow-up.

3. Discussion

GB-NEC is an exceedingly rare malignancy, representing a minor subset of both gallbladder cancers and neuroendocrine neoplasms.[2–4] Its pathogenesis remains elusive, as neuroendocrine cells are not typically present in the normal gallbladder mucosa. Proposed mechanisms include the transformation of stem cells or the neuroendocrine differentiation of existing adenocarcinomatous lesions.[6–10]

Epidemiology and Clinical Features:

Data from the literature suggest a slight female predominance and a mean age at diagnosis in the late 60s, though reporting biases may influence these statistics.[19] Patients often present with nonspecific symptoms—abdominal pain, jaundice, and nonspecific malaise—leading to late detection and advanced disease at diagnosis. Functional syndromes related to hormone secretion are rare but can occur in some NECs, resulting in symptoms such as flushing, diarrhea, or Cushing-like features.[15,20–22]

Diagnosis:

Diagnosis relies heavily on imaging and histopathological examination. Imaging modalities may identify gallbladder wall thickening or masses but do not

distinguish NEC from other gallbladder malignancies. Definitive diagnosis requires histology and IHC, with markers such as CgA, Synaptophysin, and CD56.[7]

Treatment Strategies:

Surgical resection remains the cornerstone for localized disease. However, because most patients present with advanced disease, systemic therapy is often necessary. Although no consensus guidelines exist due to the rarity of GB-NEC, platinum-based chemotherapy regimens are frequently employed in metastatic settings, similar to protocols for small cell carcinoma of the lung.[23–25] Recent guidelines from the European Neuroendocrine Tumor Society (ENETS) recommend platinum-etoposide combinations as first-line therapy in advanced cases, and suggest irinotecan-based combinations as second-line options.[24,25]

Targeted therapies and immunotherapies, such as anlotinib and immune checkpoint inhibitors, may offer additional survival benefits, although data are limited.[27,28] The present case highlights how iterative, individualized treatment adjustments, including a shift from etoposide-cisplatin to cisplatin-irinotecan, plus anlotinib and paimiplimab, can prolong survival and maintain quality of life.

Prognosis:

The prognosis for GB-NEC is generally poor, often worse than that of gallbladder adenocarcinoma.[19,26] Median overall survival ranges from a few months to just over a year, although multimodal therapy may extend survival.[27,28] Earlier diagnosis and the integration of modern systemic therapies may gradually improve outcomes.

4. Conclusion

GB-NEC is a rare and aggressive malignancy with limited treatment guidelines and poor outcomes. Early recognition, definitive histopathological diagnosis, and aggressive, multimodal therapy—encompassing surgical intervention, chemotherapy, and emerging targeted and immunotherapy agents—can potentially improve patient survival. Larger, prospective studies and collaborative efforts are needed to establish standardized treatment algorithms for this challenging disease.

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Conflicts of Interest:
The authors declare no conflicts of interest related to this publication.

Abbreviations:
ACTH = adrenocorticotropic hormone
AFP = alpha-fetoprotein
CA19-9 = carbohydrate antigen 19-9
CEA = carcinoembryonic antigen
CgA = chromogranin A
CK = cytokeratin
CT = computed tomography
EMA = epithelial membrane antigen
ENETS = European Neuroendocrine Tumor Society
FDG = fluorodeoxyglucose
GB-NEC = gallbladder neuroendocrine carcinoma
IHC = immunohistochemical

LCA = leukocyte common antigen

MiNENs = mixed neuroendocrine-non-neuroendocrine neoplasms

mOS = median overall survival

MRI = magnetic resonance imaging

NENs = neuroendocrine neoplasms

NSE = neuron-specific enolase

OS = overall survival

PET-CT = positron emission tomography-computed tomography

PR = partial response

SEER = Surveillance, Epidemiology, and End Results

Syn = synaptophysin

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