

Incidental Metastatic High-Grade Neuroendocrine Carcinoma Diagnosed by Liver Biopsy During Cholecystectomy: A Case Report

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Abstract

Neuroendocrine neoplasms range from relatively indolent well-differentiated tumors to aggressive poorly differentiated neuroendocrine carcinomas (NECs). Diagnosis can be challenging when nonspecific symptoms coexist with another disease that provides a plausible explanation for the presentation. A 70-year-old woman developed nausea, vomiting, and epigastric abdominal pain several weeks after pelvic reconstructive surgery. Evaluation demonstrated abnormal liver tests, cholelithiasis, and a heterogeneous nodular liver initially concerning for cirrhosis. Magnetic resonance cholangiopancreatography showed no choledocholithiasis or significant biliary dilation. She underwent laparoscopic cholecystectomy with liver wedge biopsy. Gallbladder pathology confirmed chronic cholecystitis, cholelithiasis, and porcelain gallbladder; unexpectedly, the liver biopsy demonstrated high-grade NEC, small-cell type. Persistent abdominal pain and cholestatic liver abnormalities after cholecystectomy prompted further evaluation. Staging demonstrated extensive hepatic involvement, a right middle-lobe pulmonary lesion, bulky mediastinal and hilar lymphadenopathy, and multifocal osseous metastatic disease. The overall pattern favored metastatic small-cell NEC of pulmonary origin, although the thoracic disease was not biopsied in the available records. She received carboplatin and etoposide, later with atezolizumab, but developed neutropenia, pneumonia, recurrent hospitalizations, progressive cancer-related pain, weight loss, and worsening metastatic disease. With progressive hepatic and osseous disease, declining functional status, and worsening hepatic dysfunction, she ultimately elected comfort-focused treatment and home hospice. This case demonstrates how an aggressive metastatic malignancy can remain obscured by legitimate concurrent diagnoses. Persistence of findings unexplained by the initial diagnosis and failure to improve as expected after appropriate treatment should prompt diagnostic reassessment.

Categories: Palliative Care, Oncology, Gastroenterology

Keywords: cholecystectomy, diagnostic delay, hospice and palliative care, incidental diagnosis, liver metastasis, neuroendocrine carcinoma, small-cell carcinoma

Introduction

Neuroendocrine neoplasms comprise a heterogeneous group of malignancies ranging from well-differentiated, relatively indolent neuroendocrine tumors (NETs) to poorly differentiated neuroendocrine carcinomas (NECs) with aggressive clinical behavior. Contemporary classification separates well-differentiated NETs from poorly differentiated NECs because these entities differ substantially in their biology, natural history, prognosis, and treatment. Poorly differentiated NECs include small-cell and large-cell morphologic variants and are considered high-grade by definition [1,2]. High-grade neuroendocrine neoplasms are uncommon, and their evaluation can be challenging because accurate pathologic classification, determination of the primary site, staging, and treatment frequently require integration of pathology, imaging, and multidisciplinary clinical assessment [3].

This patient's available medical record extends back more than 20 years. In 2003, she was hospitalized for exertional chest pain and underwent a negative cardiac evaluation. In retrospect, knowledge of her later suspected pulmonary malignancy makes it tempting to interpret this remote presentation as an early manifestation of the cancer. The available evidence does not support such a connection. Well-differentiated NETs can follow an indolent course over many years or even decades, whereas poorly differentiated small-cell NECs generally demonstrate substantially more aggressive biological behavior [4]. A continuously occult 22-year course would therefore be difficult to reconcile with the high-grade small-cell NEC diagnosed in 2025. The 2003 encounter is better regarded as an unrelated historical event rather than evidence of prolonged diagnostic latency.

The clinically relevant diagnostic interval occurred in 2025. The patient's gastrointestinal symptoms developed shortly after major pelvic reconstructive surgery. She was subsequently found to have objective gallbladder disease and a markedly heterogeneous, nodular liver that initially appeared cirrhotic on imaging. Each finding provided a reasonable explanation for at least part of her presentation. Importantly, the gallbladder disease was not simply a misleading radiographic finding: hepatobiliary iminodiacetic acid (HIDA) imaging supported cholecystitis, and subsequent pathology confirmed chronic cholecystitis,

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cholelithiasis, and porcelain gallbladder. The unexpected finding of high-grade small-cell NEC on a liver wedge biopsy obtained during cholecystectomy therefore did not replace an incorrect diagnosis; it established a second, more consequential disease process.

This case illustrates the distinction between a correct diagnosis and a complete diagnosis. The initial hepatobiliary diagnosis was supported by objective evidence, yet it did not adequately explain the patient's persistent abdominal pain, cholestatic liver abnormalities, or subsequent clinical course. The purpose of this report is to describe how metastatic high-grade NEC was incidentally identified during treatment of concurrent gallbladder disease and to highlight the diagnostic value of reconsidering the differential when the patient's trajectory remains discordant with the expected response to treatment. This principle is particularly relevant in neuroendocrine neoplasms, in which nonspecific presentations and uncertainty regarding the primary site can complicate diagnosis and subsequent management [5,6].

Case Presentation

The patient was a 70-year-old woman with no previously diagnosed malignancy who underwent pelvic reconstructive surgery for symptomatic stage 3 pelvic organ prolapse, stress urinary incontinence, and vaginal atrophy. Smoking history, occupational exposures, and family history of malignancy were not available in the records reviewed.

The major diagnostic, treatment, and disease-progression events are summarized chronologically. For clarity, the pelvic reconstructive operation was designated Day 0, and subsequent events are reported relative to that index event. The overall clinical course is summarized in Table 1.

Day	Clinical Event	Key Findings	Treatment/Intervention	Outcome/Clinical Significance
Day 0	Pelvic reconstructive surgery	Symptomatic stage 3 pelvic organ prolapse, stress urinary incontinence, and vaginal atrophy	Supracervical hysterectomy, sacrocolpopexy, bilateral salpingo-oophorectomy, mid-urethral sling placement, and posterior repair	Initial postoperative recovery was uncomplicated
Day 21	Postoperative follow-up	No complaints; appropriate healing	Routine postoperative care	No evidence that subsequent abdominal symptoms originated from the pelvic surgical site
Day 27	New gastrointestinal symptoms	Three days of nausea, vomiting after eating, diarrhea, and epigastric tenderness; reassuring pelvic examination and urinalysis	Symptomatic treatment with ondansetron and emergency precautions	Beginning of the symptomatic illness that ultimately led to the cancer diagnosis
Day 31	Hepatobiliary evaluation	Hepatomegaly, hepatic steatosis, cholelithiasis, and markedly heterogeneous and nodular hepatic morphology; no significant biliary dilation or choledocholithiasis on MRCP	Hepatobiliary evaluation	Confirmed gallbladder disease while identifying unexplained abnormal hepatic morphology
Day 32	Surgery and tissue diagnosis	HIDA scan consistent with cystic duct obstruction/acute cholecystitis; liver wedge biopsy demonstrated high-grade NEC, small-cell type	Laparoscopic cholecystectomy, lysis of adhesions, and liver wedge biopsy	Gallbladder pathology confirmed chronic cholecystitis, cholelithiasis, and porcelain gallbladder; liver biopsy unexpectedly established malignancy
Days 43-44	Readmission and evaluation of cholestasis	Persistent abdominal symptoms and cholestatic liver abnormalities; repeat imaging showed no mechanical biliary obstruction	Empiric piperacillin-tazobactam; General Surgery and Gastroenterology evaluation	Attention increasingly shifted toward malignant hepatic involvement
Day 44	Cancer staging	3.6 × 1.0 cm right middle-lobe pulmonary opacity, extensive mediastinal/right hilar lymphadenopathy including a 3.0 × 4.0 cm precarinal node, and extensive hepatic disease	Oncology staging evaluation	Thoracic findings combined with small-cell liver pathology favored a pulmonary primary

Subsequent staging	Central nervous system and osseous staging	No intracranial metastases; multiple marrow-replacing calvarial and cervical spine lesions	Staging evaluation	Established disseminated osseous metastatic disease
Day 48	Systemic therapy initiated	Extensive metastatic disease with marked hepatic dysfunction	Dose-reduced carboplatin and etoposide	Cancer-directed systemic treatment initiated
Late first treatment cycle	Treatment complications	Pneumonia, pancytopenia, severe neutropenia, and concern for Mediport infection	Broad-spectrum antibiotics, Mediport removal, Zarxio, and supportive care	Significant infectious and hematologic complications
Early subsequent course	Rehospitalization	Marked leukocytosis after recent Zarxio and concurrent COVID-19	Hematology evaluation and supportive care	Leukocytosis considered reactive and multifactorial
Day 78	Oncology reassessment	Approximately 20-lb weight loss in one month, assistance with some activities of daily living, and Eastern Cooperative Oncology Group performance status 2	Treatment goals and risks reassessed	Patient wished to continue cancer-directed therapy
Day 83	Second systemic treatment cycle	Persistent advanced metastatic disease	Dose-reduced carboplatin and etoposide with growth-factor support; atezolizumab added	Cancer-directed treatment continued
Day 89 onward	Progressive metastatic disease	Increasing thoracic adenopathy, recurrent falls, right L2 transverse-process fracture, and extensive skeletal metastases including a 14-mm left lesser trochanter lesion	Oncology, Radiation Oncology, and symptom-directed management	Progressive thoracic and osseous metastatic burden
Day 116	Radiographic progression	Interval enlargement of right hilar malignant mass with persistent liver metastases and porta hepatis adenopathy	Continued oncologic and supportive management	Evidence of progression despite systemic treatment
Day 125	Planned chemotherapy held and final hospitalization	Worsening abdominal pain, poor oral intake, constipation, declining function, hepatomegaly, extensive hepatic metastases, third spacing, small-volume ascites, and no biliary obstruction	Chemotherapy held; Oncology and Palliative Care reassessment	Progressive disease and hepatic dysfunction limited additional systemic treatment
Day 128	Hospice discharge	Progressive metastatic high-grade NEC with declining functional status	Home hospice; do-not-resuscitate/do-not-intubate and comfort-measures-only status	Transition to exclusively comfort-focused care

TABLE 1: Day-Wise Clinical Course From Pelvic Surgery Through Diagnosis, Treatment, Disease Progression, and Hospice.

CT: computed tomography; DNR/DNI: do not resuscitate/do not intubate; ECOG: Eastern Cooperative Oncology Group; HIDA: hepatobiliary iminodiacetic acid; MRCP: magnetic resonance cholangiopancreatography; NEC: neuroendocrine carcinoma; RML: right middle lobe; US: ultrasonography

Pelvic organ prolapse and surgery

The patient was receiving care for symptomatic stage 3 pelvic organ prolapse, stress urinary incontinence, and vaginal atrophy. She initially responded to pessary treatment but subsequently chose surgical management. On Day 0, she underwent supracervical hysterectomy, sacrocolpopexy, bilateral salpingo-oophorectomy, mid-urethral sling placement, and posterior repair. At follow-up on Day 21, she reported no complaints and was healing appropriately.

On Day 27, she returned with three days of nausea, vomiting after eating, diarrhea, and epigastric tenderness. She denied pelvic pain, dysuria, fever, chills, chest pain, and shortness of breath. Pelvic examination remained reassuring, and urinalysis was negative for leukocytes and nitrites. She was treated symptomatically with ondansetron and given emergency precautions.

Gallbladder disease and the unexpected liver biopsy

On Day 31, persistent abdominal symptoms and abnormal liver tests prompted hospital evaluation. Computed tomography demonstrated hepatomegaly, hepatic steatosis, and cholelithiasis. Ultrasonography confirmed gallstones. Magnetic resonance cholangiopancreatography (MRCP) demonstrated a partially contracted gallbladder containing a gallstone without a common bile duct stone or significant biliary dilation. The liver was markedly heterogeneous and nodular, with an appearance concerning for cirrhosis. Representative hepatobiliary imaging is shown in Figure 1.

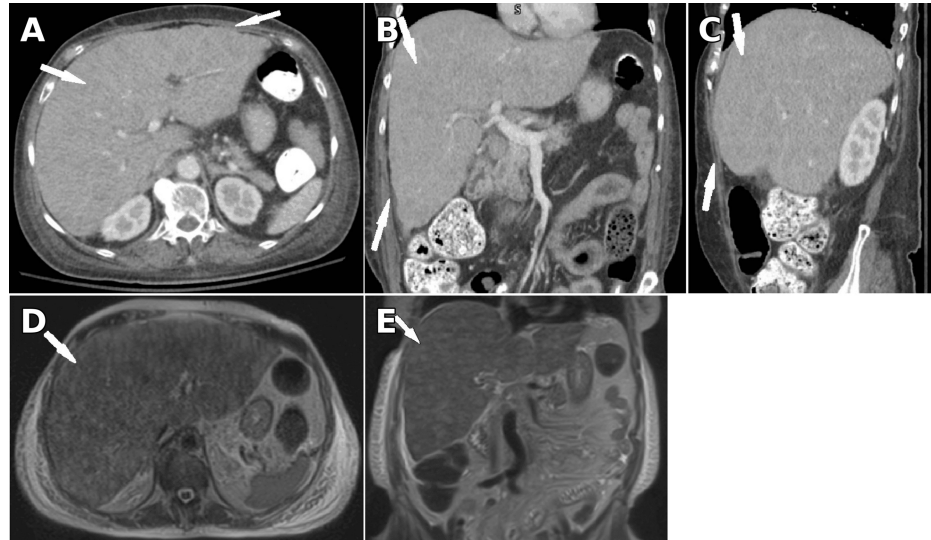


FIGURE 1: Hepatic Involvement by Metastatic Neuroendocrine Carcinoma.

(A-C) Computed tomography (CT) images of the abdomen demonstrate marked hepatic heterogeneity, nodularity, and extensive metastatic-appearing hepatic involvement (arrows).

(D-E) Magnetic resonance cholangiopancreatography (MRCP) images demonstrate heterogeneous nodular hepatic morphology without significant biliary ductal dilation or choledocholithiasis (arrows). The hepatic morphology initially raised concern for cirrhosis; however, subsequent liver biopsy demonstrated high-grade neuroendocrine carcinoma, small-cell type, with extensive malignant hepatic involvement. A pseudocirrhotic appearance related to metastatic disease was considered, although coexisting chronic liver disease could not be definitively excluded.

On Day 32, a HIDA scan was consistent with cystic duct obstruction and acute cholecystitis. Hepatocellular function was impaired, although the common bile duct remained patent. She underwent laparoscopic cholecystectomy, lysis of adhesions, and liver wedge biopsy. Gallbladder pathology confirmed chronic cholecystitis with cholelithiasis and dense mural fibrosis and calcification consistent with porcelain gallbladder. No gallbladder malignancy was identified.

Unexpectedly, the liver wedge biopsy demonstrated high-grade NEC, small-cell type, subsequently confirmed on outside pathology review. Representative histopathology is shown in Figure 2.

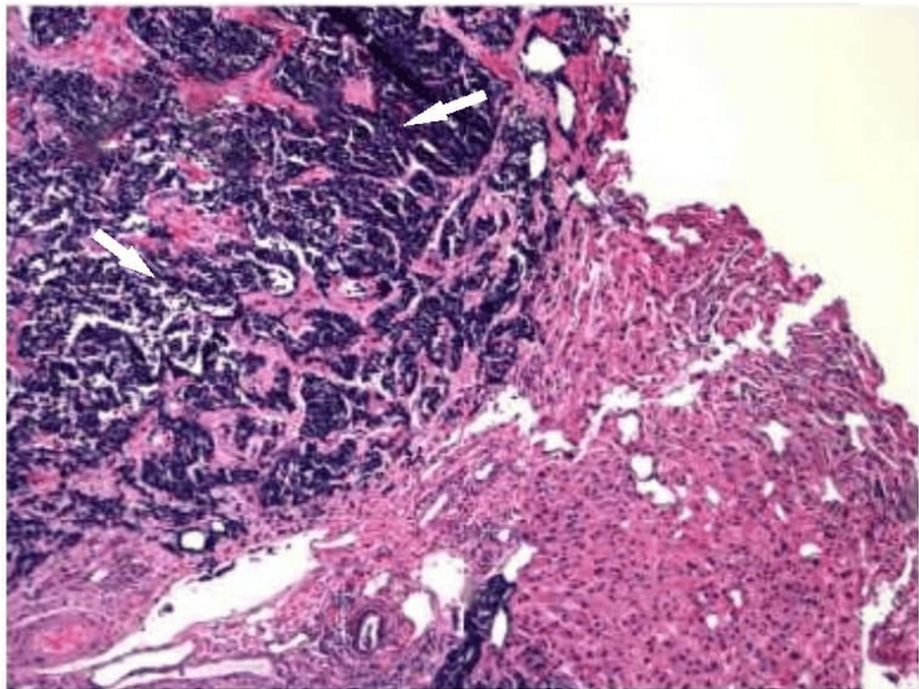


FIGURE 2: Histopathologic Diagnosis of Small-Cell-Type High-Grade Neuroendocrine Carcinoma in the Liver.

Representative sections from the liver wedge biopsy were obtained. Hematoxylin and eosin (H&E) image showing carcinoma involving the hepatic parenchyma, with morphological features consistent with small-cell-type high-grade neuroendocrine carcinoma (original magnification $\times 40$).

Persistent abdominal pain and cholestatic liver injury

Despite cholecystectomy, the patient's abdominal pain and liver test abnormalities persisted. Repeat MRCP showed no significant biliary dilation or choledocholithiasis. Postoperative ileus was considered, and she was discharged after tolerating oral intake and having bowel movements.

On Day 43, she returned with worsening generalized abdominal pain, nausea, vomiting, weakness, and a ground-level fall. The pertinent laboratory findings from this presentation, later treatment complications, and the final hospitalization are consolidated in Table 2. She had leukocytosis and a predominantly cholestatic pattern of liver injury with hyperbilirubinemia. Computed tomography demonstrated a small amount of fluid in the gallbladder fossa but no abscess or biloma. Repeat MRCP demonstrated no choledocholithiasis or biliary dilation.

Clinical Time Point	Laboratory Test	Result	Unit	Standard Adult Reference Range
Initial readmission	White blood cell count	15.8	$\times 10^3/\mu\text{L}$	4.5-11.0
Initial readmission	Aspartate aminotransferase	89	U/L	9-32
Initial readmission	Alanine aminotransferase	92	U/L	7-33
Initial readmission	Alkaline phosphatase	438	U/L	30-100
Initial readmission	Total bilirubin	6.5	mg/dL	0.0-1.0
Initial readmission	Direct bilirubin	4.4	mg/dL	0.0-0.3*
Initial readmission	Albumin	3.0	g/dL	3.3-5.0
Initial readmission	International normalized ratio	1.1	-	0.8-1.2*
After first chemotherapy cycle	Absolute neutrophil count	Approximately 400	cells/ μL	1,800-7,700
Subsequent hospitalization	White blood cell count	67	$\times 10^3/\mu\text{L}$	4.5-11.0
Hepatocellular carcinoma evaluation	Alpha-fetoprotein	3.0	ng/mL [†]	<10 [†]
Final hospitalization	Total bilirubin	3.4	mg/dL	0.0-1.0
Final hospitalization	Aspartate aminotransferase	87	U/L	9-32
Final hospitalization	Alanine aminotransferase	63	U/L	7-33
Final hospitalization	Alkaline phosphatase	455	U/L	30-100

TABLE 2: Pertinent Laboratory Findings During the Clinical Course.

Reference intervals shown are representative standard adult ranges and may vary according to laboratory methodology.

* The direct bilirubin reference interval and international normalized ratio reference interval are representative standard ranges; the reporting laboratory's specific intervals were not available in the source record.

[†] The alpha-fetoprotein unit (ng/mL) and reference interval (<10 ng/mL) are conventional values; the original laboratory report should be verified before final publication.

She was initially treated with piperacillin-tazobactam while infection and a postoperative biliary complication were evaluated. General Surgery and Gastroenterology were involved. Neither service identified a lesion requiring surgical or biliary intervention. With repeated imaging showing no mechanical obstruction, attention increasingly shifted toward biopsy-proven malignancy and extensive hepatic involvement as the explanation for the persistent liver abnormalities.

Staging and probable pulmonary origin

On Day 44, computed tomography of the chest and abdomen demonstrated a 3.6 × 1.0 cm linear patchy nodular opacity in the right middle lobe and extensive mediastinal and right hilar lymphadenopathy, including a 3.0 × 4.0 cm precarinal lymph node. The thoracic findings supporting a probable pulmonary primary are shown in Figure 3.

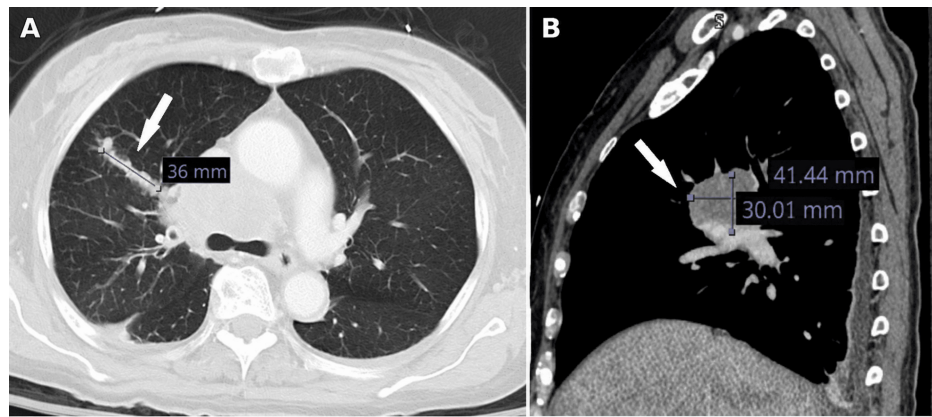


FIGURE 3: Thoracic Computed Tomography (CT) Findings Supporting a Probable Pulmonary Primary.

(A) Axial lung-window image demonstrates a 3.6 × 1.0 cm linear patchy nodular opacity in the right middle lobe (arrow).

(B) Axial mediastinal-window image demonstrates extensive mediastinal and right hilar lymphadenopathy, including a 3.0 × 4.0 cm precarinal lymph node (arrow). In the setting of small-cell neuroendocrine carcinoma identified on liver biopsy, these findings favored a pulmonary primary; however, the pulmonary lesion and mediastinal lymph nodes were not separately biopsied in the available records.

The liver was extensively involved by metastatic-appearing disease, and bilateral pleural effusions were present. Brain magnetic resonance imaging demonstrated no intracranial metastases but showed multiple marrow-replacing lesions involving the calvarium and visualized cervical spine, consistent with osseous metastatic disease. Subsequent imaging demonstrated additional skeletal metastases and marked hepatomegaly from extensive hepatic tumor burden (Figure 4).

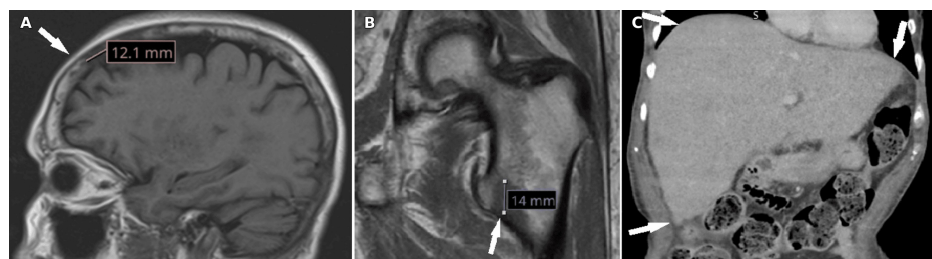


FIGURE 4: Disseminated Metastatic Disease Involving the Skeleton and Liver.

(A) Brain magnetic resonance imaging demonstrates multiple marrow-replacing lesions involving the calvarium, consistent with osseous metastatic disease (arrow); no intracranial metastases were identified.

(B) Magnetic resonance imaging of the left hip demonstrates extensive skeletal metastatic disease, including a 14-mm metastatic lesion involving the left lesser trochanter (arrow), which was considered to confer increased risk for an avulsion-type fracture.

(C) Computed tomography of the abdomen demonstrates marked hepatomegaly with extensive metastatic involvement of the liver, illustrating the substantial hepatic tumor burden (arrows).

Taken together, the biopsy-proven high-grade NEC, small-cell type, and the thoracic imaging findings favored a pulmonary primary. However, because the pulmonary lesion and mediastinal lymph nodes were not separately biopsied and complete immunohistochemical details were not available in the records reviewed, the primary site is best described as probable rather than pathologically confirmed.

Treatment and complications

Given the extent of hepatic, thoracic, and osseous metastatic disease at presentation, the patient was not considered a candidate for curative local therapy. The available records did not document biopsy of the pulmonary lesion or mediastinal lymph nodes, nor did they document consideration of a local procedure

directed at the thoracic lesion.

On Day 48, she began carboplatin and etoposide. Because of marked hyperbilirubinemia, treatment was dose-reduced. Palliative care became involved early for cancer-related abdominal pain, and her opioid regimen was progressively adjusted. Constipation also became an important contributor to her symptoms and required a bowel regimen.

Following the first chemotherapy cycle, she returned with generalized weakness and concern for drainage around her Mediport. Computed tomography demonstrated a new right upper-lobe infiltrate with persistent metastatic disease, and she was treated for pneumonia with broad-spectrum antibiotics. She subsequently developed pancytopenia and severe neutropenia; the nadir absolute neutrophil count is included in Table 2. Her Mediport was removed because of concern for infection, although no purulent material was observed in the pocket. She was subsequently discharged with Zarxio.

During a subsequent hospitalization, marked leukocytosis occurred after recent Zarxio administration in the setting of concurrent COVID-19. The white blood cell count is presented in Table 2. Hematology considered the leukocytosis reactive and multifactorial rather than representative of a new hematologic malignancy.

By Day 78, she had lost approximately 20 lb in one month, required assistance with some activities of daily living, and had an Eastern Cooperative Oncology Group performance status of 2. She nevertheless wished to continue cancer-directed therapy. On Day 83, she received another dose-reduced cycle of carboplatin and etoposide with growth-factor support, and atezolizumab was added.

Disease progression

Beginning around Day 89, the course was characterized by recurrent emergency department visits, pain, weakness, and falls. A ground-level fall resulted in a minimally displaced right L2 transverse-process fracture. Subsequent magnetic resonance imaging of the left hip demonstrated extensive skeletal metastatic disease, including the 14-mm metastatic lesion of the left lesser trochanter shown in Figure 4B.

Thoracic disease also progressed. Computed tomography angiography demonstrated bulky precarinal and retrocaval lymphadenopathy measuring up to approximately 6.3 cm and near-compressive occlusion of a right upper-lobe pulmonary arterial branch by surrounding adenopathy. By Day 116, imaging demonstrated interval enlargement of the right hilar malignant mass with persistent hepatic metastases and porta hepatis adenopathy. Radiation Oncology evaluated the patient for painful calvarial metastases, and palliative radiation was considered.

Final hospitalization and transition to hospice

By Day 125, abdominal pain had become increasingly difficult to control despite long-acting morphine and breakthrough oxycodone. She also experienced poor oral intake, recurrent constipation, and declining function. Planned chemotherapy was held because of her clinical deterioration and abnormal liver tests, which are presented in Table 2.

Computed tomography demonstrated marked hepatomegaly with numerous metastatic lesions throughout the liver, third spacing, and small-volume ascites without biliary ductal obstruction. She had progressive metastatic disease, recurrent severe pain, worsening hepatic dysfunction, poor oral intake, and declining functional reserve despite treatment. Oncology concluded that additional chemotherapy was unlikely to provide sufficient benefit relative to its anticipated toxicity.

Following goals-of-care discussions with Oncology and Palliative Care, the patient elected comfort-focused care and declined further hospitalization or life-prolonging treatment. On Day 128, she was discharged home with hospice with do-not-resuscitate/do-not-intubate and comfort-measures-only status.

Discussion

This case demonstrates a recurring challenge in diagnostic medicine: establishing one correct diagnosis does not guarantee that the diagnosis completely explains the patient's illness. The patient had objective evidence of gallbladder disease, including cholelithiasis, an abnormal HIDA scan, and subsequent pathology demonstrating chronic cholecystitis, cholelithiasis, and porcelain gallbladder. The cholecystectomy therefore addressed independently documented hepatobiliary disease. At the same operation, however, an incidental liver biopsy identified a second and ultimately more consequential process.

The critical diagnostic information emerged from the patient's subsequent trajectory. If gallbladder disease had been the principal explanation for the abdominal symptoms and cholestatic liver abnormalities, substantial improvement after definitive treatment would have been expected. Instead, abdominal pain and cholestasis persisted. Multiple subsequent MRCP examinations demonstrated neither choledocholithiasis nor significant biliary dilation. This discordance between the established diagnosis, its treatment, and the patient's clinical course appropriately shifted attention toward malignant hepatic involvement.

Cirrhotic-appearing liver and malignant infiltration

The abnormal hepatic morphology created another potential diagnostic anchor. Imaging repeatedly described a markedly heterogeneous and nodular liver with a cirrhotic appearance. Morphologic findings alone, however, did not establish the cause of the liver abnormality. Liver biopsy demonstrated metastatic high-grade NEC, and subsequent imaging showed extensive malignant hepatic involvement.

A pseudocirrhotic appearance related to extensive malignant replacement was considered clinically. However, the available pathology summary does not sufficiently characterize background hepatic fibrosis or architecture to exclude coexisting chronic liver disease. Accordingly, this report does not establish pseudocirrhosis as a definitive diagnosis. The more supportable conclusion is that extensive malignant hepatic involvement contributed substantially to the abnormal hepatic morphology and progressive liver dysfunction, while concomitant chronic liver disease could not be definitively excluded.

Pathologic classification and primary-site uncertainty

Precise terminology is particularly important for neuroendocrine neoplasms. Well-differentiated NETs and poorly differentiated NECs are biologically distinct entities rather than interchangeable labels. Histologic morphology, proliferative activity, necrosis, and immunohistochemical findings can contribute to this distinction and, in metastatic neuroendocrine neoplasms, may also assist with determining a likely site of origin [1,2,5].

The liver biopsy in this case was interpreted as high-grade NEC, small-cell type, and was confirmed on outside review. Neuroendocrine neoplasms commonly present in liver biopsies as metastatic tumors with an initially uncertain primary site, and immunohistochemistry can contribute both to classification and evaluation of origin [5].

The subsequent thoracic findings favored a pulmonary origin. A right middle-lobe lesion accompanied by bulky mediastinal and hilar adenopathy provided a clinically coherent primary site for a small-cell NEC associated with extensive liver and skeletal metastases. Nevertheless, the pulmonary lesion and mediastinal nodes were not biopsied in the available records. The distinction between a probable and a proven pulmonary primary is important because the presence of liver metastasis itself does not determine the anatomic origin of the tumor [6]. The diagnosis should therefore retain this uncertainty rather than retrospectively converting a strong clinical inference into a pathologically established fact. The records available to us did not document the Ki-67 proliferation index, the mitotic rate, or the full immunohistochemistry panel, including synaptophysin, chromogranin, and thyroid transcription factor 1 (TTF-1). For that reason, the tumor grade and the primary site could not be confirmed with complete certainty.

Competing diagnoses and diagnostic reassessment

Several diagnoses reasonably competed with malignant hepatic infiltration during the patient's initial evaluation. Retained choledocholithiasis was important to consider because of abdominal pain, hyperbilirubinemia, and elevated alkaline phosphatase. Repeated MRCP examinations without choledocholithiasis or biliary dilation progressively reduced the likelihood of persistent mechanical obstruction. Recent cholecystectomy also made postoperative biliary complications relevant, but computed tomography did not demonstrate an abscess or biloma.

The importance of these competing diagnoses is that they were not irrational diagnostic errors. Each was plausible from portions of the available clinical information. The diagnostic challenge was recognizing when no single explanation adequately accounted for the entire clinical course.

This distinction is central to the case. Diagnostic reassessment should not be limited to situations in which the original diagnosis proves incorrect. Reassessment is equally important when an established diagnosis is genuine but fails to account for persistent or progressive findings. In this patient, tissue obtained during treatment of documented gallbladder disease revealed a concurrent metastatic malignancy that ultimately better explained the persistent cholestasis, abnormal hepatic morphology, and clinical deterioration.

Clinical course and goals of care

The rapid progression after diagnosis was consistent with the aggressive behavior expected of high-grade small-cell NEC rather than the prolonged natural history associated with many well-differentiated NETs. Despite systemic therapy, the patient developed progressive thoracic, hepatic, and osseous disease accompanied by substantial symptom burden and declining function.

Palliative care was integrated during cancer-directed treatment for symptom management and later facilitated reassessment of goals as the balance between treatment benefit and burden changed. Ultimately, the patient's decision to transition to hospice reflected progressive disease, worsening hepatic dysfunction, treatment-related morbidity, and declining functional reserve.

Conclusions

This case describes metastatic high-grade NEC, small-cell type, unexpectedly diagnosed on liver biopsy obtained during cholecystectomy for independently documented gallbladder disease. Persistent symptoms and cholestatic liver abnormalities despite treatment of the gallbladder disease, together with repeated absence of mechanical biliary obstruction, indicated that the initial diagnosis did not fully explain the clinical course. Subsequent staging established disseminated hepatic, thoracic, and skeletal disease, with the overall clinicopathologic pattern favoring, but not pathologically proving, a pulmonary primary.

The central diagnostic lesson is that a correct diagnosis may still be an incomplete diagnosis. When the subsequent clinical trajectory does not match the expected response to appropriate treatment, the discrepancy itself is diagnostic information and should prompt reconsideration of concurrent or alternative disease.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Ikken Aisin

Acquisition, analysis, or interpretation of data: Ikken Aisin

Drafting of the manuscript: Ikken Aisin

Critical review of the manuscript for important intellectual content: Ikken Aisin

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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