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(CASE REPORT)

A case of neuroendocrine tumor with multiple metastatic hepatic lesions and an unknown primary site

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Abstract

Introduction: Neuroendocrine neoplasms (NEN) are typically characterized by an indolent and slow-growing nature. Due to their gradual progression, these tumors are often detected incidentally, presenting as metastatic deposits rather than primary masses. Neuroendocrine tumors (NET) with an unknown primary origin are relatively common in clinical practice, accounting for approximately 12–22% of NEN cases. In such instances, biopsy plays a crucial role, enabling pathologists to determine the tumor type and, where possible, the site of the primary tumor through histopathological analysis. The classification of NETs is based on their histological differentiation and grading. Low-grade, well-differentiated tumors tend to follow a more indolent course, while high-grade, poorly differentiated neoplasms exhibit rapid growth and aggressive behavior. This classification is closely linked to the clinical presentation and prognostic outcomes of the patients.

Presentation of the Case: A 74-year-old female hospitalized at the internal medicine service due to difficulty in breathing during minor physical exertion, thoracic-abdominal discomfort, leg edema, after exclusion of pulmonary thromboembolism with pulmonary angio-CT and acute coronary syndrome in the emergency department. Abdominal ultrasound raised the suspicion of a cholecystic tumor with multiple hepatic metastases. Subsequent examinations with contrast CT and MRI abdomen, EGD, and colonoscopy resulted in multiple secondary hepatic lesions and cholecystic calculi. CT-guided biopsy and immunohistochemical analysis of the liver mass identified poorly differentiated small cell carcinoma with positive staining for PanCK, Chromogranin, CD56, and a Ki67 proliferation index of 70%. After extensive examinations were unable to determine the primary origin of the tumor, oncological assessment recommended chemotherapy with cisplatin and etoposide for the treatment of stage IV small cell neuroendocrine tumor of unknown primary origin with liver metastasis. Considering the advanced stage of the disease, the patient opted for palliative care.

Conclusion: In cases of neuroendocrine tumors with well-differentiated cells, more detailed diagnostic examinations are performed to find the primary site, to perform surgical intervention, or to start systemic therapy depending on location. The location of the primary site is also important in determining the prognosis of neoplasia. In the case of poorly differentiated neoplasms, detailed diagnostic investigations to identify the primary source do not affect the prognosis of the disease.

Keywords: Gallbladder; Hepatic; Metastasis; Neuroendocrine

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1. Introduction

Neuroendocrine neoplasms (NENs) are rare tumors that originate from cells with a neuroendocrine phenotype. They constitute only 0.5-1% of all malignancies, with an estimated incidence of 2-4 per 100,000 and a higher prevalence in females [1]. NENs occur almost everywhere in the body, but most commonly in the Gastro-Intestinal tract, pancreas, and the lungs, causing a range of symptoms leading to their detection [2,3]. Nonetheless, there are instances where NENs present as metastatic deposits, whose primary tumor is occult or clinically undetectable. These neoplasms are referred to as NEN of Unknown Primary Site and comprise 12-22% of all NENs [4]. The primary tumor site plays a crucial role in determining both treatment options and prognosis. However, when the primary site cannot be definitively identified, treatment strategies are guided by tumor differentiation and grading.

The updated WHO classification system (2022) identifies two distinct groups based on genetic features, morphology, and clinical behavior. Well-differentiated neuroendocrine neoplasms (NENs) are classified as neuroendocrine tumors (NET G1, G2, G3), while poorly differentiated neoplasms are categorized as neuroendocrine carcinomas (NEC, G3), which are further subdivided into small cell and large cell carcinomas [5]. The first group of tumors has a more indolent course, while the latter presents rapidly and more aggressively, closely associated with clinical presentation and prognosis. This case report presents our experience with this rare type of neoplasm and our challenges in determining the site of origin.

2. Presentation of the case

A 74-year-old female presented to our emergency department complaining of difficulty breathing during minor exertion, chest pain, abdominal discomfort, nausea, fatigue, weakness and leg swelling for nearly two months, worsening progressively. She had a medical history of hypertension and type 2 diabetes mellitus. After excluding pulmonary thromboembolism and acute coronary syndrome in the emergency room, the patient was admitted to the internal medicine department with a diagnosis of right-sided heart failure.

On physical examination, there was inspected peripheral edema and skin pallor; nontender abdomen on palpation, although there was noted a mild discomfort in the right upper quadrant; pulmonary wheezing on auscultation. Blood tests showed elevated levels of NTproBNP (3215 pg/mL), Fibrinogen (446 mg/dL), D- dimer (3,31 ug/mL), CRP (5.73 mg/dL), LDH (461 U/mL); full blood count revealed hypochromic microcytic anemia (RBC 3.01 x 10^6; Hgb 8.4 g/dL; HCT 26.1%; MCV 86.6 μm^3); other values (liver function, urea and creatinine, electrolytes, albumin, total protein) were within normal ranges.

Echocardiogram showed normal left ventricle size and ejection fraction; dilated right ventricle and right atrium; mild tricuspid regurgitation; PsPA 80 mmHg; no pericardial effusion. A routine abdominal ultrasound revealed an enlarged liver with multiple hepatic nodules, suggestive of secondary lesions; irregular wall thickness of the gallbladder near the fundus, as well as a calculus 25 mm in diameter (Fig. 1).

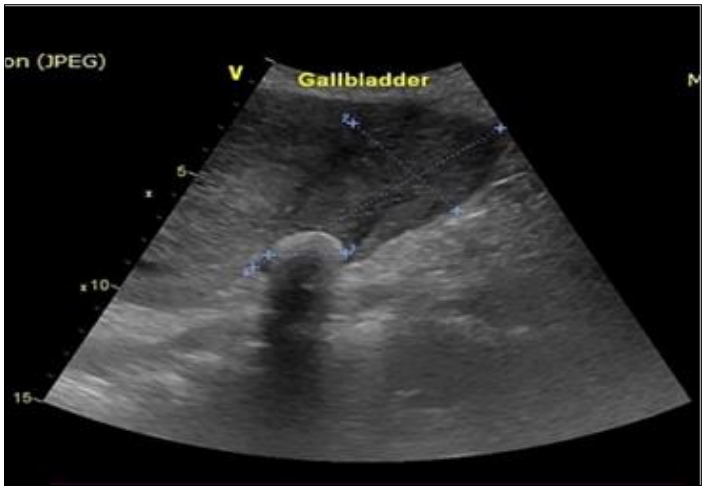


Figure 1 Gallbladder ultrasound showing irregular wall thickness and a calculus near the gallbladder neck

Abdominal ultrasound raised the suspicion of gallbladder cancer with multiple hepatic metastases. Subsequently, the patient underwent further investigations, including a total body CT scan with IV contrast, which revealed an enlarged liver with multiple diffuse heterogeneous lesions exhibiting peripheral enhancement, irregular thickening of the gallbladder fundus wall, and thrombosis of the left branch of the portal vein. Abdominal MRI also revealed multiple hepatic tumor lesions up to 90 mm in diameter (Fig. 2); gallbladder calculi (Fig.3); dilated cystic duct; images suggesting Mirizzi Syndrome.

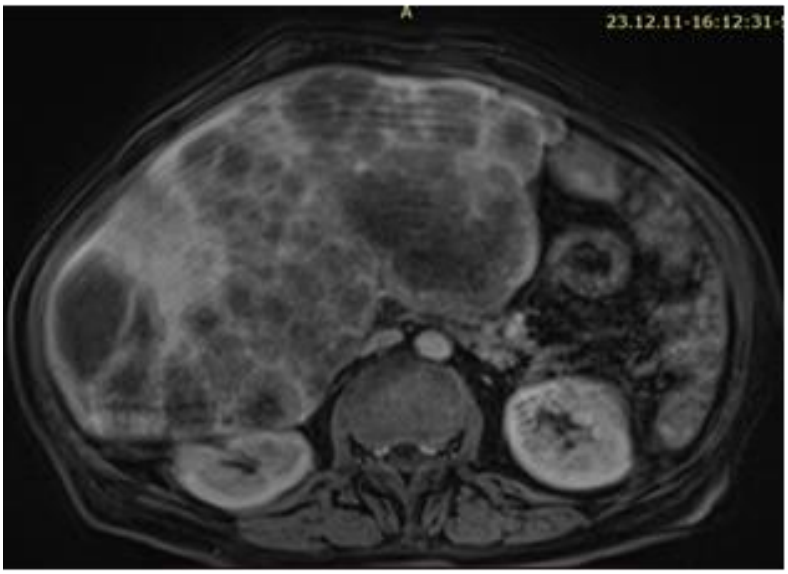


Figure 2 Multiple hepatic tumour lesions in MRI

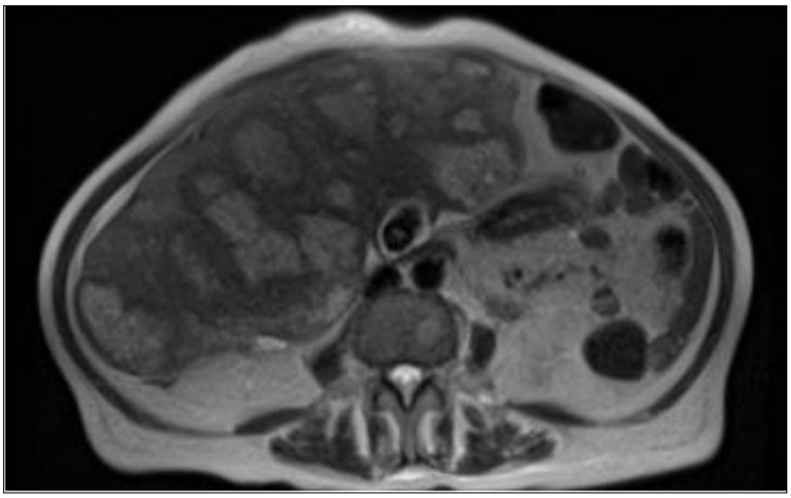
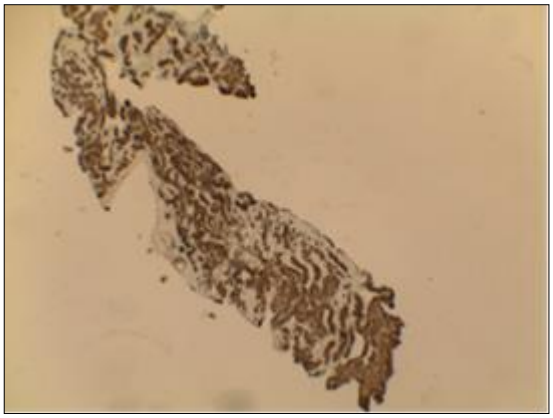
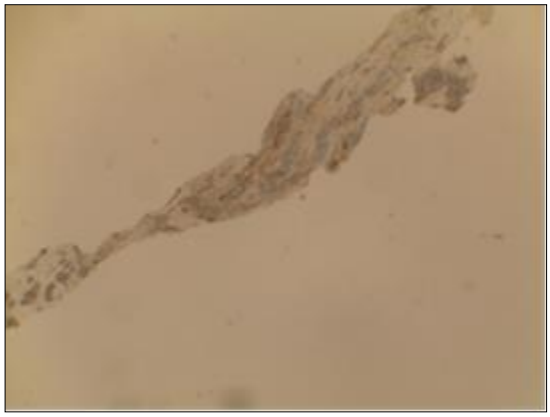


Figure 3 MRI image of gallbladder calculi

At this point, all the imaging data suggest gallbladder cancer with liver metastasis. To confirm the diagnosis, a CT-guided biopsy of the liver lesions was performed. Histopathological examination and immunohistochemical staining revealed infiltration of neuroendocrine carcinoma (NEC), which, according to the new WHO classification system, is a poorly differentiated neoplasm. The tumor cells were positive for Chromogranin A (Fig.4), PanCK (Fig.5), CD56, which confirms neuroendocrine origin; negative for HSA, CDX-2, CK7, CK20, CEA, TTF1, HMB45, Vimentin. Ki67 revealed a proliferative index of 70%.

Figures 4 and 5 Chromogranin A and Pankeratin positive stain

Our challenge, so far, has been to determine the primary site to help us guide the treatment decisions. The patient underwent EGD and colonoscopy to find a possible site in the GI tract, but the results were negative for neoplasm.

Given the aforementioned imaging and endoscopic data, the location of the primary site remained questionable, so our only guide was the tumor histology. Unlike in NETs, immunohistochemistry plays a more limited role in determining the site of origin for NECs. TTF-1 would suggest visceral origin, while CK20 would suggest cutaneous origin, but both of these markers are negative in our case. Except for in situ hybridization for HR-HPV (associated with anogenital and occasionally head and neck origins), there are currently no reliable markers to differentiate between sites of origin in visceral NEC [6].

After managing the actual heart condition, the patient was evaluated by the oncology team. Since all the performed examinations were not able to identify a primary source of the tumor, they recommended chemotherapy treatment with platinum-based agents and etoposide (recommended chemotherapy regimen for stage IV small cell NET of unknown primary site with liver metastasis [7,8]. Considering the advanced stage of the disease, the patient chose palliative treatment.

3. Discussion

When a neuroendocrine tumor of unknown primary is diagnosed, identifying the origin of the neoplasm is crucial to help guide the treatment decisions. If the primary site remains unidentified after a thorough evaluation, treatment is typically based on the tumor's histology [9]. In instances of well-differentiated neuroendocrine tumors, the site of origin holds considerable prognostic and therapeutic significance [10]. On the other hand, in cases of poorly differentiated neuroendocrine neoplasms, detailed diagnostic investigations to identify the primary source do not affect the prognosis of the disease and should be treated similarly to small cell lung cancer, including platinum-based chemotherapy with etoposide [9].

However, other treatment options are available. Firstly, checkpoint inhibitor therapy has proven to be highly effective in Merkel cell carcinoma but only moderately so in visceral NECs and has quickly become the first-line treatment for this tumor type. [6,11]. Secondly, extrapulmonary visceral NECs are increasingly managed with regimens effective in site-specific non-neuroendocrine carcinomas (e.g., FOLFOX, FOLFIRI for GEP-NECs) or with emerging treatment protocols such as platinum/irinotecan and CAPTEM. [6,12]. Another useful index that plays a role in prognosis and treatment decisions is Ki-67. Ki67 immunohistochemistry may also be relevant for NECs, where higher proliferation indices are linked to poorer prognosis, improved responses to platinum-based chemotherapy, and diminished effectiveness of temozolomide-based treatments [6,13].

However, in our clinical case, it was not possible to determine the exact tumor origin. Given that a higher Ki67 index is associated with a better response to platinum-based agents, chemotherapy with cisplatin and etoposide was recommended for the patient.

Further studies with other chemotherapeutic and novel agents need to be done to achieve better treatment outcomes. Until then the standard treatment remains platinum in combination with etoposide, which provides a modest survival benefit.

4. Conclusion

In cases of neuroendocrine tumors, more detailed diagnostic examinations are performed to find the primary site, to perform surgical intervention, or start systemic therapy depending on location. In the case of poorly differentiated neoplasms, detailed diagnostic investigations to identify the primary source do not affect the prognosis of the disease.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no conflict of interest.

Statement of ethical approval

The study was designed in compliance with the ethical guidelines of the 1975 Declaration of Helsinki. Informed consent was obtained.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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References

[1] TAAL BG, VISSER O. Epidemiology of neuroendocrine tumours. Neuroendocrinology. 2004;80 Suppl 1:3-7. doi:10.1159/000080731

[2] SCHIMMACK S, SVEJDA B, LAWRENCE B, KIDD M, MODLIN IM. The diversity and commonalities of gastroenteropancreatic neuroendocrine tumors. Langenbecks Arch Surg. 2011;396(3):273-298. doi:10.1007/s00423-011-0739-1.

[3] KLÖPPEL G. Neuroendocrine Neoplasms: Dichotomy, Origin and Classifications. Visc Med. 2017 Oct;33(5):324-330. doi: 10.1159/000481390. Epub 2017 Oct 16. PMID: 29177160; PMCID: PMC5697503.

[4] DASARI A, SHEN C, HALPERIN D, ZHAO B, ZHOU S, XU Y, SHIH T, YAO JC. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol. 2017 Oct 1;3(10):1335-1342. doi: 10.1001/jamaoncol.2017.0589. PMID: 28448665; PMCID: PMC5824320.

[5] BUCHSTAB O, KNÖSEL T. AKTUELLE WHO-Klassifikation (2022) neuroendokriner Neoplasien [Current WHO classification (2022) of neuroendocrine neoplasms]. Radiologie (Heidelb). 2024 Jul;64(7):531-535. German. doi: 10.1007/s00117-024-01295-z. Epub 2024 Apr 15. PMID: 38622292.

[6] BELLIZZI AM. Immunohistochemistry in the diagnosis and classification of neuroendocrine neoplasms: what can brown do for you? Hum Pathol. 2020 Feb;96:8-33. doi: 10.1016/j.humpath.2019.12.002. Epub 2019 Dec 17. PMID: 31857137; PMCID: PMC7177196.

[7] SPIGEL DR, HAINSWORTH JD, GRECO FA. Neuroendocrine carcinoma of unknown primary site. Semin Oncol. 2009 Feb;36(1):52-9. doi: 10.1053/j.seminoncol.2008.10.003. PMID: 19179188.

[8] HAINSWORTH JD, GRECO FA. Neuroendocrine Carcinoma of Unknown Primary Site. In: Kufe DW, Pollock RE, Weichselbaum RR, et al., editors. Holland-Frei Cancer Medicine. 6th edition. Hamilton (ON): BC Decker; 2003. Available from: https://www.ncbi.nlm.nih.gov/books/NBK14036/

[9] POLISH A, VERGO MT, AGULNIK M. Management of Neuroendocrine Tumors of Unknown Origin. J Natl Compr Canc Netw. 2011;9(12):1397-1402. doi:10.6004/jnccn.2011.0118

[10] BELLIZZI AM. Assigning site of origin in metastatic neuroendocrine neoplasms: a clinically significant application of diagnostic immunohistochemistry. Adv Anat Pathol. 2013 Sep;20(5):285-314. doi: 10.1097/PAP.0b013e3182a2dc67. PMID: 23939147.

[11] SCHMULTS CD, BLITZBLAU R, AASI SZ, et al. NCCN Guidelines® Insights: Merkel Cell Carcinoma, Version 1.2024. J Natl Compr Canc Netw. 2024;22(1D):e240002. doi:10.6004/jnccn.2024.0002.

[12] GARCIA-CARBONERO R, SORBYE H, BAUDIN E, et al. ENETS consensus guidelines for high-grade Gastroenteropancreatic neuroendocrine tumors and neuroendocrine carcinomas. Neuroendocrinology 2016;103(2):186–94.

[13] SORBYE H, WELIN S, LANGER SW, VESTERMARK LW, HOLT N, OSTERLUND P, et.al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. Ann Oncol. 2013 Jan;24(1):152-60. doi: 10.1093/annonc/mds276. Epub 2012 Sep 11. PMID: 22967994.