RESEARCH PAPER

Proptosis as the First Manifestation of a Metastatic High-Grade Neuroendocrine Neoplasm of Unknown Primary: A Case Report

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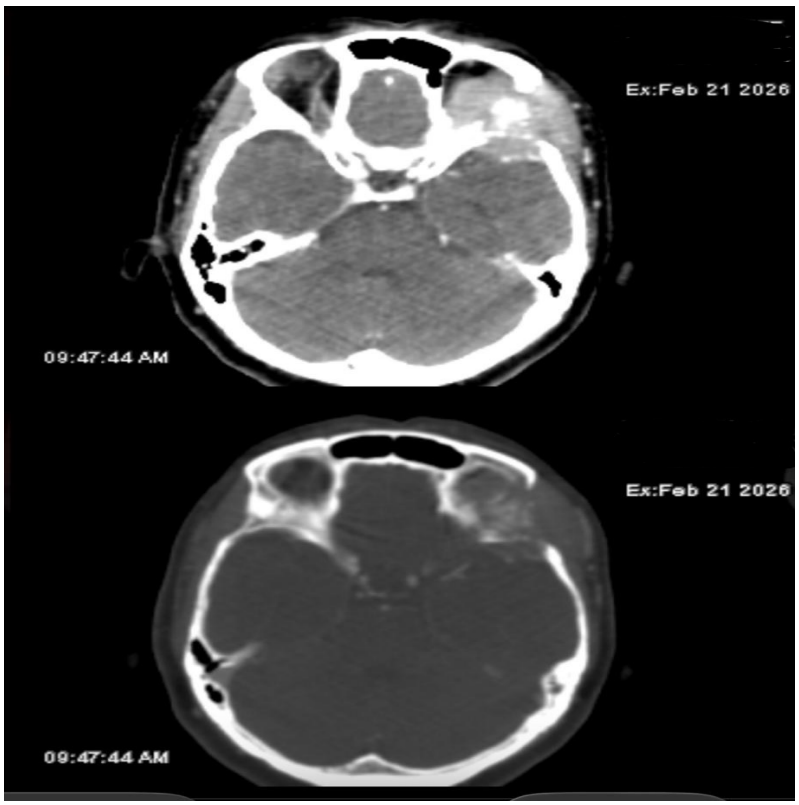
Received: 13th Dec, 2025; Revised: 8th Feb 2026; Accepted: 10th Feb, 2026; Available Online: 28th Feb, 2026

ABSTRACT

Neuroendocrine Neoplasm (NEN) of unknown primary are rare, and presentation with orbital metastasis is exceedingly uncommon. High-grade NENs lacking somatostatin receptor expression pose diagnostic and therapeutic challenges.

We report a 55-year-old female with no prior comorbidities, presenting with progressive restriction of left sided extraocular movements for four months, followed by one month of periorbital swelling and proptosis. CT Brain showed a homogenous enhancing soft tissue mass centred along the left lateral orbital wall involving the adjacent frontal and sphenoid bones with lytic changes and mild periostea reaction with posterior and superior intracranial extension.



Suspecting neoplastic aetiology, whole body ^{18}F-FDG PET/CT was done and the orbital mass exhibited FDG avidity with SUV max of 12.01. Additionally, the scan revealed FDG avid ill defined heterogeneously enhancing lesion in the segment VII of the liver, measuring about 2.1 x 1.9cm, along with FDG avid enlarged confluent and discrete lymph nodes in the periportal, portocaval and paraaortic regions, largest measuring 4.1 x 2.7cm with mild necrotic changes.

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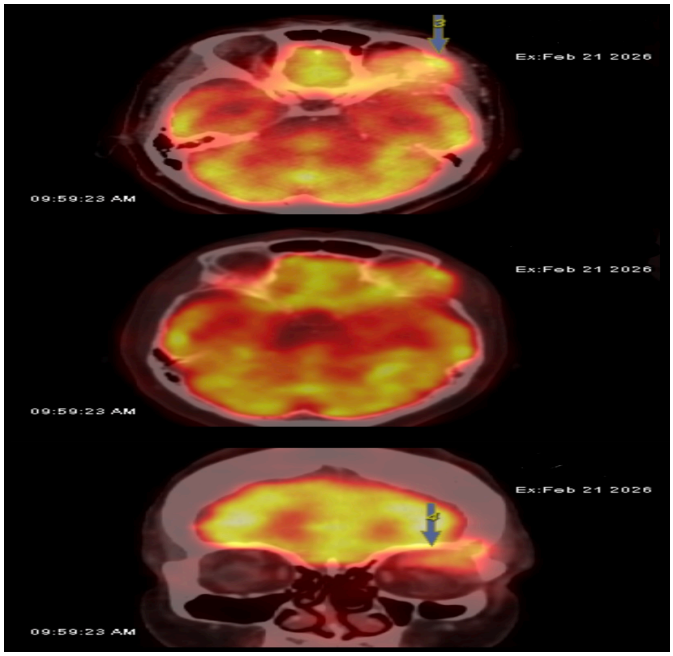


Notably, whole body imaging revealed no other abnormalities with no lesions or FDG uptake in the lungs, pancreas, gastrointestinal tract or elsewhere in the hepatobiliary system.

Biopsy of the orbital lesion showed cores of fibrocollagenous and bone fragments infiltrated by tumor clusters, nests, and ribbons of round-to-ovoid moderately pleomorphic nuclei, dispersed chromatin, moderate eosinophilic cytoplasm, and foci of necrosis. Biopsy of the liver lesion showed cores of liver parenchyma infiltrated by morphologically identical cells, confirming common etiological origin.

Immunohistochemistry demonstrated strong positivity for synaptophysin, chromogranin, and CK19, weak-to-moderate CK7 expression, and negativity for CK20 and Glypican-3. The Ki-67 proliferation index was >80%, consistent with a high-grade tumor. Serum tumor markers (AFP, CEA, CA 125, CA 15-3, CA 19-9, LDH) were within normal limits. ^{68}Ga-DOTATATE PET/CT showed no uptake in any of the lesions, indicating absence of somatostatin receptor expression. Overall, these imaging and Histological findings indicated a metastatic, high grade neuroendocrine neoplasm of undetermined primary site.

Management: The patient is planned for systemic chemotherapy with cisplatin and etoposide. Next-Generation Sequencing (NGS) is underway to identify molecular targets for potential immunotherapy.

Conclusion: This case illustrates a rare high-grade DOTATATE-negative NET presenting with orbital and hepatic metastases. It highlights the diagnostic complexity, need for multimodal evaluation, and the importance of histopathology, immunohistochemistry, and molecular profiling in guiding management when conventional imaging and receptor-directed therapies are uninformative

Keywords: Neuroendocrine neoplasm, poorly differentiated, metastatic, Somatostatin, Synaptophysin, Chromogranin

How to cite this article: Gaur G, Vinatha MC, Gurucharan, Shobana, Proptosis as the First Manifestation of a Metastatic High-Grade Neuroendocrine Neoplasm of Unknown Primary: A Case Report..Int J Drug Deliv Technol. 2026; 16(2): 761-764; DOI: 10.25258/ijddt.16.2.81

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Neuroendocrine Neoplasm (NENs) are a diverse group of neoplasms that originate from specialized neuroendocrine cells found throughout the body, most frequently in the gastrointestinal tract, pancreas, and lungs. These tumors display a broad spectrum of clinical behaviors, from slow-growing, well-differentiated forms to highly aggressive poorly differentiated carcinomas. Diagnosis typically relies on identifying neuroendocrine markers such as chromogranin A and synaptophysin, and many NENs express somatostatin receptors that can be targeted both diagnostically and therapeutically. Over recent decades, reported incidences of NETs have risen, reflecting improvements in imaging, pathology techniques, and clinical recognition rather than a true epidemic of disease.

Despite advances in diagnostic technologies, a proportion of patients present with metastatic neuroendocrine disease without an identifiable primary tumor. These cases are designated as **Neuroendocrine Neoplasm of unknown primary (NEN-UP)**. Although relatively uncommon, NET-UP represents a significant clinical challenge; studies estimate that approximately one-tenth of patients with

metastatic NETs have no detectable primary site after initial evaluation.

In most instances of NET-UP, the liver serves as the first recognized location of disease, often prompting further investigation. Conventional imaging methods such as contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) may not reliably visualize small or deeply situated primary tumors, especially within the small bowel or pancreas. Functional imaging modalities that exploit somatostatin receptor expression — particularly ^{68}Gallium-labeled somatostatin analogue PET/CT scans — have markedly enhanced the ability to detect previously unseen primary lesions. These newer PET-based approaches have demonstrated higher sensitivity and specificity compared with earlier techniques, such as ^{111}Indium-octreotide scintigraphy, and have changed the diagnostic landscape for NET-UP.

Identifying the site of origin in NETs is clinically important because it can influence therapeutic decisions, prognostication, and surgical planning. Treatment options such as somatostatin analogues or peptide receptor radionuclide therapy are guided not only by tumor grade but also by receptor status and, ideally, the organ of origin. However, in NET-UP the primary site frequently remains elusive, underscoring the importance of conducting thorough diagnostic evaluations that combine advanced imaging modalities, careful histopathologic analysis, and a multidisciplinary approach. Continued reporting and evaluation of NET-UP cases help clarify their clinical behavior and enhance understanding of optimal management strategies.

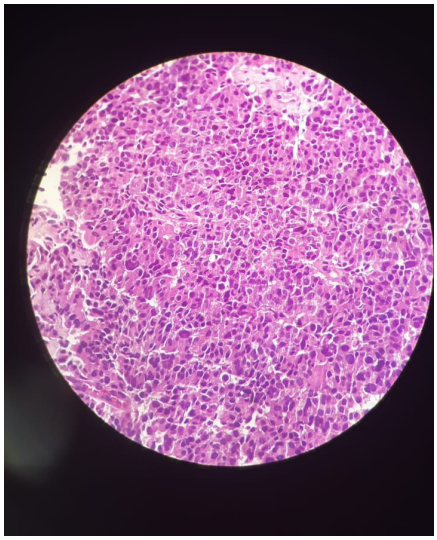
Case Presentation

A 55-year-old female with no prior medical comorbidities presented with a **four-month history of progressive restriction of extraocular movements**, initially affecting her right eye. Over the following month, she developed **periorbital swelling** that progressed to **proptosis**, prompting ophthalmological evaluation. She denied systemic symptoms such as fever, weight loss, flushing, diarrhea, or hormonal manifestations.

Clinical Examination:
On examination, the patient had **right-sided proptosis**, periorbital edema, and restricted ocular motility in all directions. Visual acuity was preserved. No palpable lymphadenopathy or hepatosplenomegaly was noted. Vital signs were within normal limits.

Investigations:
Laboratory studies revealed normal serum tumor markers, including **AFP, CEA, CA 125, CA 15-3, CA 19-9, and LDH**. Liver function tests and complete blood counts were unremarkable.
^{18}F-FDG PET/CT demonstrated **metabolically active lesions** in the **orbit, liver, and periportal/peripancreatic lymph nodes**, with no clear primary tumor identified. ^{68}Ga-DOTATATE PET/CT revealed **no somatostatin receptor uptake** in any lesion.

Histopathology:
Biopsies of the orbital and liver lesions showed multiple cores of grey-white soft tissue (largest 1 cm). Sections demonstrated **clusters, nests, ribbons, and small fused acinar structures** composed of cuboidal cells with **round-to-ovoid, moderately pleomorphic nuclei, dispersed chromatin, moderate eosinophilic cytoplasm, and foci of necrosis**. Orbital tissue also contained fibrocollagenous tissue and bone fragments with **prominent osteoblastic rimming**. Liver parenchyma displayed mild macro- and microvesicular steatosis and moderate portal inflammation.



Immunohistochemistry:
Strongly positive: synaptophysin, chromogranin, CK19
Weak-to-moderate: CK7
Negative: CK20, Glypican-3
Ki-67 index: >80%, confirming high-grade neuroendocrine neoplasm.

Discussion

While NETs generally exhibit an indolent clinical course, high-grade neuroendocrine neoplasms demonstrate aggressive behavior and early metastatic potential. Occult primary NETs, where metastatic disease is present without identification of a primary tumor, represent a distinct diagnostic subset—accounting for approximately 10–15% of metastatic NET cases.[1, 2] The current case adds to this cohort and underscores multiple diagnostic and therapeutic challenges.

Orbital metastasis from NETs is exceedingly rare. A review of the literature reveals only isolated case reports describing orbital involvement as the initial manifestation of neuroendocrine disease. Most reported orbital NET metastases arise from well-differentiated, somatostatin receptor–positive tumors identified via ^{68}Ga-DOTATATE PET/CT. [2, 3]
In contrast, our patient presented with high-grade metastatic disease affecting the orbit and liver, and notably

demonstrated **absent uptake on ^{68}Ga-DOTATATE imaging**, indicating lack of somatostatin receptor expression. This distinction is significant, as negative somatostatin receptor imaging eliminates eligibility for peptide receptor radionuclide therapy (PRRT), a cornerstone of treatment for receptor-positive NETs.

Histopathologically, the tumor exhibited features consistent with a neuroendocrine phenotype, with strong positivity for synaptophysin and chromogranin and a markedly elevated Ki-67 index (>80%), consistent with a high-grade neoplasm. These findings align with criteria for high-grade neuroendocrine carcinomas as per WHO classification.[3]

The absence of site-specific markers (e.g., CK20 or Glypican-3) and negative tumor markers (AFP, CEA, CA 125, CA 19-9) further complicated primary site identification. Although immunohistochemistry panels such as TTF-1, CDX2, and PAX8 may offer clues to the tissue of origin, their expression is not universally definitive, particularly in poorly differentiated neoplasms.

A key differentiator in this case is the combination of orbital metastasis as the presenting feature, high proliferative index, and **lack of somatostatin receptor expression** on advanced imaging. Few reports have documented NETs that are both DOTATATE-negative and present with orbital metastases, making this case an educational example of an uncommon clinical phenotype. [4,5,6]

This underscores the necessity for clinicians to consider high-grade NETs in the differential diagnosis of orbital masses, even when traditional imaging fails to localize a primary site.

From a management standpoint, the absence of receptor expression redirects treatment away from PRRT toward **platinum-based chemotherapy,** in this case cisplatin and etoposide, which remains the standard for high-grade neuroendocrine carcinoma. Concurrent next-generation sequencing may reveal actionable molecular alterations amenable to immunotherapy or targeted agents, an evolving area in NET management.

CONCLUSION

This case highlights a rare presentation of a high-grade neuroendocrine tumor of unknown primary manifesting with orbital and hepatic metastases, negative somatostatin receptor imaging, and an elevated Ki-67 proliferation index. It underscores the importance of maintaining a broad differential diagnosis when evaluating orbital masses and the critical role of histopathology and immunohistochemistry in establishing the diagnosis when imaging and serum markers are inconclusive. High-grade, receptor-negative NETs necessitate systemic chemotherapy, while next-generation molecular profiling may reveal additional therapeutic targets, including immunotherapy. It should be recognized that occult NETs can present atypically, and a **multidisciplinary, multimodal diagnostic and management approach** is essential to optimize patient outcomes

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