

## Case Report

# Neuroendocrine Tumor of the Gallbladder, a Rare Incidental Finding

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### Abstract

#### Background

Neuroendocrine tumors are a rare finding in the gallbladder. The incidence of this entity in the gallbladder is roughly 1.13 cases per 100,000 in the US, with a steady increase in the last decade. Gallbladder neuroendocrine tumors are generally asymptomatic; the majority of cases have been reported as incidental findings in specimens, resected due to secondary symptomatology, such as chronic cholecystitis. Treatment strategies are limited, in part due to the often advanced stage in which this disease presents. Furthermore, there is a restricted utility of diagnostic tools for early detection; these factors contribute to the poor prognosis of this disease process.

#### Case Summary

We describe a case of a gallbladder carcinoid tumor, incidentally found in a 78-year-old male patient who presented to the emergency room complaining of chronic intermittent right upper quadrant pain, accompanied by nausea and vomiting. A positive murphy sign was elicited on physical examination, which was otherwise unremarkable. An abdominal ultrasound showed an otherwise normal-appearing gallbladder except for a "floating polyp" with no suspicious radiologic features. A diagnosis of chronic cholecystitis was presumed, and the patient was taken to the operative room for laparoscopic cholecystectomy. Microscopic evaluation of the gallbladder specimen yielded a diagnosis of a well-differentiated neuroendocrine tumor and complex cholesterol polyps, in a setting of chronic cholecystitis.

#### Conclusions

Neuroendocrine tumors of the gallbladder, a rare entity, are generally asymptomatic, with most cases diagnosed incidentally in gallbladder specimen resected for reasons other than suspected malignancy. Chronic inflammatory processes are seen to be related to the development of metaplasia and possibly the development of tumors of the neuroendocrine lineage. Based on a review of literature, we have found that no specific treatment approach, beyond surgical resection, is in place to manage patients with this condition. Formation of an expert committee to review and discuss guidelines for appropriate clinical monitoring, as well as consideration of a multi-site prospective registry is suggested.

#### Keywords

neuroendocrine tumors; gallbladder; carcinoid tumor; osseous metaplasia; inflammation; cell transformation, neoplastic; gallbladder neoplasms

#### Introduction

More than ten different types of neuroendocrine cells are present throughout the gastrointestinal (GI) tract. Among these various cell types, enterochromaffin cells are thought to be the precursor of neuroendocrine tumors (NETs). These highly specialized cells, despite their widespread distribution in the GI tract, are usually not present in the gallbladder.<sup>1</sup> NETs

are routinely diagnosed in the gastrointestinal and respiratory tract and are considered a rare finding in the gallbladder, with an incidence of approximately 1.13 cases per 100,000.<sup>2</sup> The mechanism for neoplastic transformation is still not well understood; however, it is hypothesized that there is a correlation between metaplasia and NETs in long-standing inflammatory processes such as chronic cholecysti

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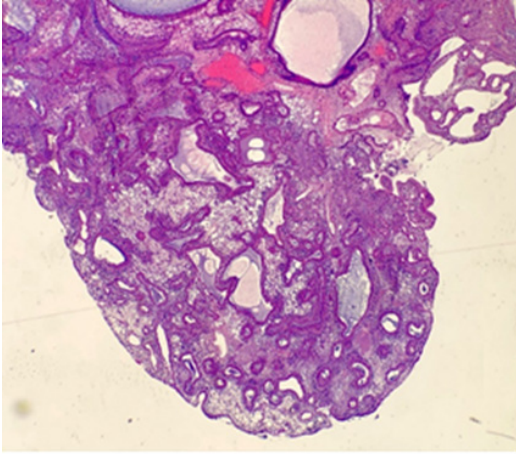
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**Figure 1.** Complex cholesterol polyp. H&E (10X original magnification) Image provided by the authors.

tis.<sup>3,4</sup> (**Figures 1 and 2**) NETs can arise anywhere within the gallbladder, with no tendency for a specific anatomical site. Clinical manifestation is non-specific and is usually related to symptoms of a secondary pathologic process such as chronic cholecystitis.<sup>5</sup> Classification is based on histological features and mitotic activity of tumor cells, and is grouped in two broad categories: well-differentiated (with better prognosis in most cases), and poorly differentiated (characteristically aggressive and with poor prognosis). The well-differentiated type accounts for a minority of cases with a slight incidental rise in recent years due to the improvement of diagnostic methods, as well as more awareness among pathologists regarding this lesion. Prognosis is based on factors like tumor size, the grade of differentiation, presence of angio-invasion and local spread to adjacent structures (liver) or regional lymph nodes.<sup>5</sup> There is no standardization in the management of these cases, with therapeutic decisions taken based upon personal experience, as well as the general approach to gallbladder tumors others than NETs.

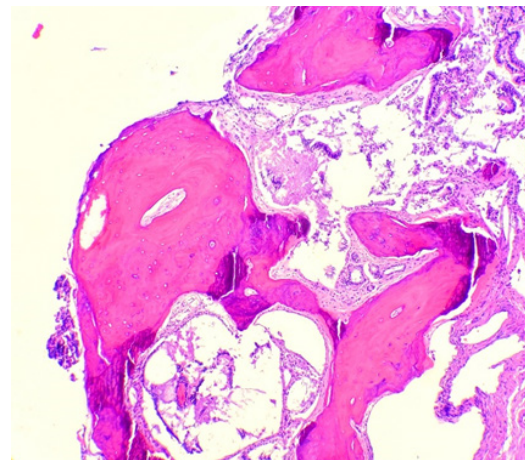
### Case Presentation

We describe a case of a gallbladder carcinoid tumor, incidentally found in a 78-year-old male patient who came to the emergency room (ER) complaining of chronic, intermittent, right upper-quadrant pain, accompanied by nausea and vomiting. Physical examination was non-contributory, except for a positive murphy sign. Medical history was significant for gout

and essential hypertension, for which he was getting the appropriate treatment. On further assessment, the abdominal ultrasound showed an otherwise normal-appearing gallbladder, except for a “floating polyp” with no suspicious radiologic features. Laboratory analysis showed mildly elevated AST and BUN, and decreased GFR, but was otherwise unremarkable. A clinical diagnosis of chronic acalculous cholecystitis and gallbladder polyp was made. A decision was taken to proceed with surgical intervention, and laparoscopic cholecystectomy was performed.

Histological examination of the gallbladder specimen showed a 2-millimeter lesion, located within the gallbladder wall, about 1 millimeter from the serosa surface. Microscopic evaluation revealed a round-to-oval, well-circumscribed proliferation of monotonous neoplastic cells arranged in cords and nests. The neoplastic cells had a central ovoid nucleus, with stippled chromatin and inconspicuous nucleoli. The immunohistochemical profile was relatively uniform, with immune-reactivity for chromogranin and synaptophysin, and an absence of sub-tentacular cells (S100 negative). These classical morphological features, along with the uniform staining pattern, confirmed the neuroendocrine lineage of the lesional cells.

The final diagnosis was rendered as neuroendocrine tumor of the gallbladder, in the settings of chronic cholecystitis and complex cholesterol polyps. After surgical intervention, the patient

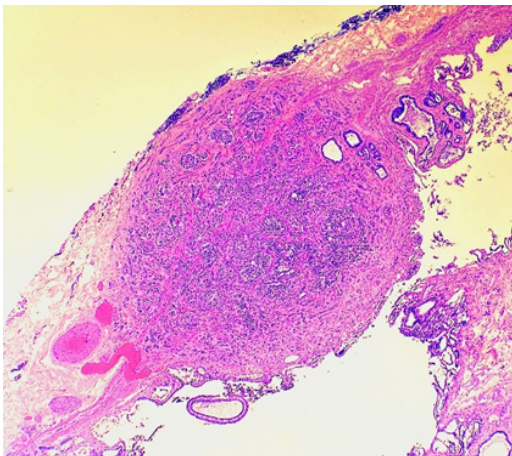


**Figure 2.** Gallbladder mucosal polyp with osseous metaplasia, in a setting of chronic cholecystitis. H&E (10X original magnification) Image provided by the authors.

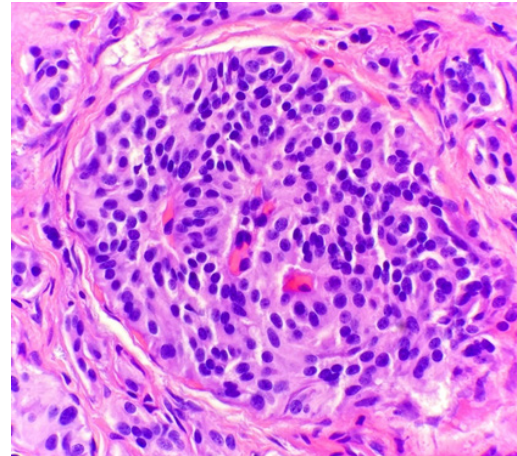
was discharged with instructions to follow-up on the pathology results in the outpatient setting. After a negative PET-CT and almost one year follow up, he has been declared free of disease.

## Discussion

Neuroendocrine tumor of the gallbladder is an extremely rare diagnosis. The clinical presentation is non-specific and overlaps with other types of gallbladder malignancies, especially adenocarcinomas. In recent years, the incidence of this pathologic process has been increasing at a steady rate. This may be explained by improved sensitivity of the diagnostic radiological tools and increased awareness among pathologists. Radiologic findings, such as a heterogeneous or hypo-attenuating mass (which shows variable degrees of enhancement), circumferential homogenous thickening or an intraluminal polypoid mass, are not reliable in distinguishing NETs from other forms of gallbladder tumors. In advanced cases, direct liver involvement (present in up to 44% of the cases) by the tumor can be evident in the liver segments contiguous with the gallbladder bed (segments 4 and 5). Metastases can occur even in microscopic lesions and appear to have no relationship with tumor size, grade of differentiation and proliferation indices. The most common site for metastases is the hilar lymph nodes and liver (segments other than 4 and 5), with about 80% of cases with metastases



**Figure 3.** Focal cellular proliferation of cells with salt-and-pepper chromatin forming nests and cords in the gallbladder wall, infiltrating muscularis mucosa and approaching serosa surface H&E. (4x original magnification) Image provided by the authors.

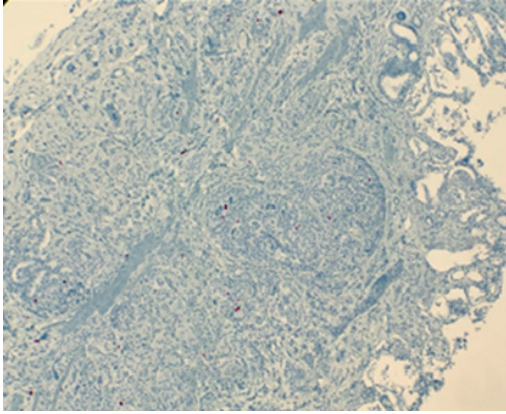


**Figure 4.** High power image of the neoplastic cells showing salt and pepper chromatin. No mitotic activity was identified. Neoplastic cells are organized mainly in nest-like structures. H&E (40X original magnification) Image provided by the authors.

presenting with an enlarged lymph node on CT images.<sup>6,7</sup>

Histologically, gallbladder NETs resemble their homologous counterparts throughout the gastrointestinal tract, with the cytological architecture depending on the grade of differentiation. The well-differentiated lesions are generally composed of small, uniform cells with low variability in size and shape, organized in nests, cords, trabecular and glandular patterns. (Figures 3 and 4) Tumor cells in the poorly differentiated type are large and pleomorphic with prominent nucleoli and a variable amount of cytoplasm. Necrosis and mitotic activity are salient findings in the latter. Though an independent factor, metastases and angio-invasion are more common in poorly differentiated cases.

The World Health Organization (WHO) classifies neuroendocrine neoplasias into two main subcategories based on grade of differentiation: well-differentiated type and poorly differentiated type. The well-differentiated type is further classified into grades (G1, G2, and G3) based on mitotic rate and proliferation indices. The low-grade subtype (G1) typically has a low mitotic rate and proliferation index (Figure 5), less than 2 mitosis/high-power field (HPF), and less than 2 percent proliferation rate, respectively. Historically, this was considered a benign condition with uncertain malignant potential;



**Figure 5.** Immunohistochemistry: Ki67 demonstrating a proliferative index of about 1%. (40x original magnification) Image provided by the authors.

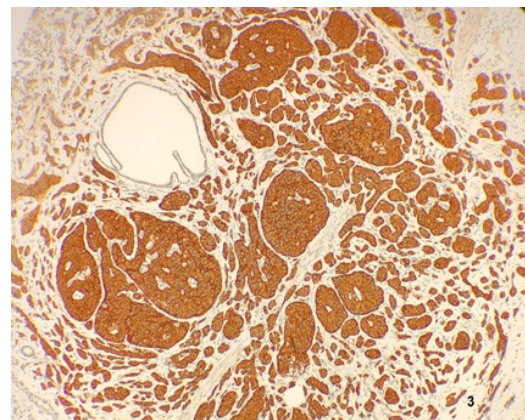
however, its metastatic potential is now well recognized, even in microscopic lesions. The intermediate grade (G2) in this category is defined by a mitotic rate between 2-20/HPF and a proliferation rate that does not surpass 20%. The grade 3 (G3) or high-grade type has some overlapping features with the poorly differentiated neuroendocrine carcinoma (NEC), such as a Ki67 more than 20%, but typically less than 50% and more than 20 mitotic figures per 10 HPF; however, the clinical and genetic differences help make them distinguishable.<sup>8</sup> Mutations in the MEN1, DAXX and ATRX genes define the well-differentiated NETs, while NECs usually have TP53 or RB1 gene mutations.

The diagnosis of a neuroendocrine tumor of the gallbladder is exclusively made by histologic examination. Immunohistochemistry profile for NETs has some variabilities and these tumors can be immunoreactive to a variety of immuno-stains, including synaptophysin (**Figure 6**), chromogranin (**Figure 7**), CD56, neuron-specific enolase (NSE), pan-cytokeratin (AE1/AE3) and CK7. Synaptophysin results in positive staining in up to 90% of the cases, while chromogranin results in positive staining in up to 85% of the cases. The use of these two neuroendocrine markers in combination often yields positive results in up to 95% of cases.

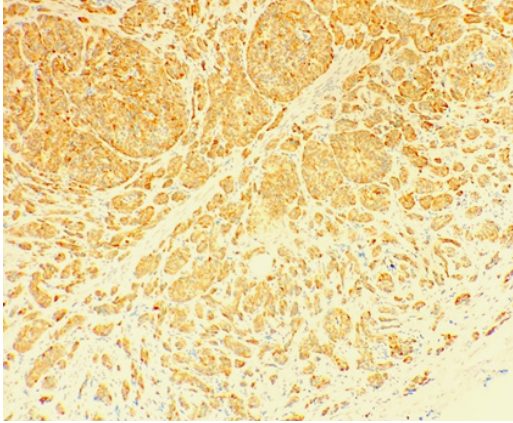
The differential diagnosis for NETs of the gallbladder can be very broad, depending upon the grade of differentiation and the architectural patterns of the lesion. Gangliocytic paragangliomas (GP) are a rare entity with multiple

overlapping structural, cytologic and immunohistochemical features similar to NETs. The epithelioid cell types are typically arranged in nests, trabeculae or papillary structures. Immunohistochemically, these lesions show reactivity to S-100 and NSE, the ganglion cells are positive for synaptophysin and up to 50% positivity for cytokeratin, making the differential diagnosis even more difficult. Glomus tumor is another entity that represents a diagnostic challenge in the differential diagnosis of NETs. These tumors are multinodular with strands of smooth muscle dissecting in between the nodules. The nodules are composed of solid sheets of cells that typically surround a blood vessel. Cells comprising these nodules are round with a sharply defined border and evenly distributed chromatin. On immunohistochemistry, these cells are positive for calponin and smooth muscle actin, but typically lack immunoreactivity for neuroendocrine markers.

Treatment options for NETs of the gallbladder are limited by the advanced stage in which almost all cases present, and the lack of data that supports a particular approach. Current practices are based on personal experiences and the consensus from other types of gallbladder tumors. Surgical resection (when possible) with gallbladder bed cauterization is seen to be adequate for low-grade tumors without serosa or contiguous involvement of liver parenchyma. In advanced cases with metastases to liver parenchyma (contiguous spread or distant metastases) or regional lymph nodes, surgical resection of the gallbladder (if possible) followed by chemotherapy is seen to be the



**Figure 6.** Immunohistochemistry: Strong immunoreactivity for synaptophysin. (20x original magnification) Image provided by the authors.



**Figure 7.** Immunohistochemistry: Diffused immunoreactivity for chromogranin. (20X original magnification) Image provided by the authors.

best approach; albeit there is lack of sufficient statistical evidence to support this approach.<sup>5,9</sup> There are multiple chemotherapy agents used in the treatment of tumors of neuroendocrine origin; among them, the most frequently used are cisplatin and carboplatin. The combination of chemotherapeutic agents are more often used than a single agent. Cisplatin and carboplatin are combined with gemcitabine and etoposide, with some studies reporting a tumor regression of up to 67% using this strategy.

The prognosis of this disease is highly variable, depending upon the stage in which the patient presents, the degree of differentiation and proliferation indices of the tumor. Typically, well-differentiated lesions, confined to the gallbladder's wall and without systemic metastasis, have an excellent prognosis. However, the poorly differentiated type typically presents in more advanced stages, with local spread and systemic metastasis. These cases count for the majority of gallbladder NET-related fatalities.

## Conclusion

Neuroendocrine tumors of the gallbladder are generally asymptomatic, with the majority of cases diagnosed incidentally in the gallbladder's specimen, resected for reasons other than suspected malignancy. Chronic inflammatory processes are related to the development of metaplasia and posteriorly the development of tumors of the neuroendocrine lineage. Based on a review of the literature, we have found that no specific treatment approach is in place

to manage patients with this disease process. Multi-center studies could help to further elucidate the pathogenesis, behavior and treatment strategies for neuroendocrine neoplasia of the gallbladder.

## Conflicts of Interest

The authors declare they have no conflicts of interest.

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## References

1. Matsuo S, Shinozaki T, Yamaguchi S, et al. Small-cell carcinoma of the gallbladder: report of a case. *Surg Today*. 2000;30(1):89-93. <https://doi.org/10.1007/PL00010056>
2. Ayabe RI, Wach M, Ruff S, et al. Primary Gallbladder Neuroendocrine Tumors: Insights into a Rare Histology Using a Large National Database. *Ann Surg Oncol*. 2019;26(11):3577-3585. <https://doi.org/10.1245/s10434-019-07440-6>
3. Chuang SS, Lin CN, Chu CH, Chen FF. Small cell carcinoma of the gallbladder: report of two cases. *Pathol Oncol Res*. 1999;5(3):235-238. <https://doi.org/10.1053/paor.1999.0216>
4. Kuwabara H, Uda H. Small cell carcinoma of the gall-bladder with intestinal metaplastic epithelium. *Pathol Int*. 1998;48(4):303-306. <https://doi.org/10.1111/j.1440-1827.1998.tb03910.x>
5. Eltawil KM, Gustafsson BI, Kidd M, Modlin IM. Neuroendocrine tumors of the gallbladder: an evaluation and reassessment of management strategy. *J Clin Gastroenterol*. 2010;44(10):687-695. [https://journals.lww.com/jcge/Fulltext/2010/11000/Neuroendocrine\\_Tumors\\_of\\_the\\_Gallbladder\\_An.12.aspx](https://journals.lww.com/jcge/Fulltext/2010/11000/Neuroendocrine_Tumors_of_the_Gallbladder_An.12.aspx)
6. Faraoun SA, Guerrache Y, Dautry R, et al. Computed Tomographic Features of Primary Small Cell Neuroendocrine Tumors of the Gallbladder.

*J Comput Assist Tomogr.* 2018;42(5):707-713.

<https://doi.org/10.1097/RCT.0000000000000753>

7. El Fattach H, Guerrache Y, Eveno C, et al. Primary neuroendocrine tumors of the gallbladder: Ultrasonographic and MDCT features with pathologic correlation. *Diagn Interv Imaging.* 2015;96(5):499-502. <https://doi.org/10.1016/j.diii.2014.11.027>
8. Komminoth P, Arnold R, Capella C, Klimstra DS, Kloppel G. Neuroendocrine neoplasms of the gallbladder and extrahepatic bile ducts. In: Bosman FT, Carneiro F, Hruban RH, Theise HD, editors. *WHO Classification of Tumours of the Digestive System.* Lyon: International Agency for Research on Cancer; 2010:274–276.
9. Liu W, Chen W, He X, Qu Q, Hong T, Li B. Cholecystectomy with gallbladder bed cauterization might be sufficient for T1bN0M0 neuroendocrine carcinoma of gallbladders: Cases report and literature review. *Medicine (Baltimore).* 2017;96(47):e8778. <https://doi.org/10.1097/MD.00000000000008778>
10. Smith JL, Davis BR. Neuroendocrine tumor of the gallbladder treated with neoadjuvant chemotherapy and surgery. *Am Surg.* 2014;80(3):318-320.