ISSN 2689-8268 | Volume 6

American Journal of Surgery and Clinical Case Reports

Case Report Open Access

Mixed Poorly-Differentiated Neuroendocrine Carcinoma and Well-Differentiated Neuroendocrine Tumor in the Extrahepatic Common Bile Duct: A Unique Rare Case

Young AR*, Amin A, Ram B, Sham S, Monika SA and Paterson J

Department of Pathology and Anatomical Sciences, University at Buffalo, Buffalo, NY, USA

***Corresponding author:**

Alecia R Young,
Department of Anatomic Pathology, Buffalo General Medical Center, 100 High St, Buffalo, NY, 14203, USA, E-mail: aleciayo@buffalo.edu

Received: 10 Apr 2023
Accepted: 08 May 2023
Published: 15 May 2023
J Short Name: AJSCCR

Keywords:

Neuroendocrine neoplasm; Well-differentiated neuroendocrine tumor; Poorly-differentiated neuroendocrine carcinoma; Common bile duct; Mixed

Citation:

Young AR. Mixed Poorly-Differentiated Neuroendocrine Carcinoma and Well-Differentiated Neuroendocrine Tumor in the Extrahepatic Common Bile Duct: A Unique Rare Case. Ame J Surg Clin Case Rep. 2023; 6(12): 1-6

1. Abstract

The World Health Organization classified neuroendocrine neoplasms of the digestive system into well-differentiated neuroendocrine tumor (NET) and poorly-differentiated neuroendocrine carcinoma (NEC) based on their unique morphological, clinical, epidemiological, histological, and prognostic differences. We present a case of an 80-year old female found to have a 31x22x21 mm mass in the perihilar common bile duct on CT scan. A tan-yellow mass within the common bile duct wall, extending into the surrounding fibroconnective tissue was noted on gross examination. Histologic examination revealed a well-circumscribed tumor with a biphasic appearance consisting of predominantly well-differentiated NET (approximately 80%) arranged in a trabecular architecture with round nuclei, finely granular chromatin, moderate cytoplasm, rare mitosis (6/2mm^2), and minor poorly differentiated NEC (approximately 20%) with markedly pleomorphic cells, necrosis, and abundant mitosis (40/2mm^2). Tumor cells in both morphologies showed immunoreactivity for AE1/AE3, CD56, synaptophysin and chromogranin. The Ki-67 proliferation index in the well-differentiated component was low (approximately 3-20%) and unequivocally high in the poorly-differentiated component (focally >50%). In the well-differentiated component, p53 staining was patchy and weak (wild-type), whereas it was negative (null-type) in the poorly-differentiated component. RB1 immunostaining showed weak staining in the well-differentiated component and diffusely strong staining in the poorly-differentiated component. The final diagnosis of mixed well-differentiated NET and poorly-differentiated NEC is made, which does not fit neatly into a specific category in the current classification of neuroendocrine neoplasms of the digestive system. Reporting more cases like this will be helpful for the revision of the current classification system.

2. Introduction

In 2018, the World Health Organization (WHO) established a standardized classification system for neuroendocrine neoplasms to reduce inconsistencies among various classification systems [1]. The WHO consensus conference at the International Agency for Research on Cancer (IARC) classified neuroendocrine neoplasms of the digestive system into well-differentiated neuroendocrine tumors (NET) and poorly differentiated neuroendocrine carcinomas (NEC) [2]. Although these entities share some immunohistochemical markers, they differ in many aspects, including morphological appearances, genetic mutations, and prognostic factors [1]. Thus, NET and NEC may not be closely related and may have different degrees of behavior, resulting in different staging systems [3].

Although neuroendocrine neoplasms can occur at any anatomical site in the body, those presenting in the extra hepatic biliary tract are rare and account for less than 1% of all gastrointestinal neuroendocrine neoplasms [4]. NEC typically presents with a glandular component and is classified as a mixed neuroendocrine and non-neuroendocrine neoplasm (MiNEN) [2]. However, it is highly unusual for NEC to contain a well-differentiated NET component [2]. Currently, there is no specific category in the classification of neuroendocrine neoplasms for such tumors.

In this report, we present the case of an 80-year-old woman with a mixed poorly-differentiated neuroendocrine carcinoma, large cell type, and well-differentiated neuroendocrine tumor, grade 2 in the extra hepatic common bile duct.

3. Case Presentation

The patient is an 80-year-old Caucasian female with a history of hiatal hernia, non-obstructing Schatzki ring, and appendectomy. She presented to the hospital with nausea, vomiting and jaundice. The abdominal ultrasound showed a solid mass with intrahepatic biliary ductal dilation and common bile duct dilation, raising concerns for malignant pancreatic carcinoma and gallbladder hydrops. A follow-up computed tomography scan showed a hyper-enhancing mass (31 x 22 x 21 mm) in the porta hepatis with intra and extrahepatic biliary ductal dilation, gallbladder hydrops without wall thickening, and dilation of the common bile duct. Upper endoscopic ultrasound (EUS) showed a round hypoechoic mass next to the proximal common bile duct measuring 32mm x 21mm. Endoscopic Retrograde Cholangiopancreatography (ERCP) confirmed an extrinsic impression to the middle third of the common bile duct causing severely narrowed stenosis, 20mm in length, and dilated intrahepatic and common hepatic duct. A fine needle aspiration of the periportal mass was performed for cytological examination during the EUS/ERCP procedure.

The fine needle aspiration revealed groups of neoplastic cells exhibiting trabecular and pseudo glandular growth patterns with moderate cytoplasm, round to oval nuclei, with finely granular chromatin. No necrosis or mitosis were detected. Subsequent immunohistochemical staining demonstrated that the neoplastic cells were positive for synaptophysin, chromogranin, CD56 and pancytokeratin, but negative for CK7. The Ki-67 nuclear index was less than 3%. Based on the immunoprofile and cytological characteristics, the diagnosis was consistent with a grade 1, well-differentiated neuroendocrine tumor.

The patient elected to undergo surgical exploratory laparotomy, cholecystectomy, choledochojejunostomy with Roux-en-Y jejunojejunostomy, and common bile duct resection. After surgery, the patient experienced delirium, tachycardia, hypotension, and increased bilious output from her drains on post-operative day two. A computed tomography scan revealed a significant amount of intra-abdominal fluid, and she underwent emergent surgery for abdominal washout and repair of the jejunalenterotomy. The patient was later discharged to a subacute rehabilitation facility without any further complications.

On gross examination of the surgical specimen, a well-circumscribed, tan-yellow, hemorrhagic soft mass was found within the wall of the common bile duct measuring 3 x 2.5 x 2 cm. The mass showed a nodular growth pattern growing into the wall, narrowing the lumen of the common bile duct, with focal extension beyond the common bile duct wall to the surrounding fibroconnective soft tissue. Histologically, the tumor showed a biphasic appearance consisting of approximately 80% well-differentiated tumor cells and 20% poorly-differentiated tumor cells (Figure 1 A-B). The well-differentiated component consisted of tumor cells arranged in a trabeculated and tubular architecture with round to oval nuclei, finely granular chromatin, moderate cytoplasm, and rare mitosis ($6/2mm^2$) (Figure 1 C-D). The poorly-differentiated component showed tumor cells with marked pleomorphism, highly atypical nuclei, prominent nucleoli, and moderate cytoplasm with a high nuclear/cytoplasmic ratio (Figure 1 E-F). Abundant mitosis ($40/2mm^2$), necrosis, and increased apoptosis were also present.

The tumor cells showed immunoreactivity for AE1/AE3, CD56, synaptophysin, and chromogranin in both morphologic components (Figure 2 A-D). The Ki-67 proliferation index was low in the well-differentiated component and high in the poorly-differentiated component (Figure 2 E-F). P53 immunostain showed patchy and weak (wild-type) staining in the well-differentiated component, while it was negative (null-type) in the poorly-differentiated component (Figure 3 A-B). RB1 immunostaining showed weak staining in the well-differentiated component and diffuse strong staining in the poorly-differentiated component (Figure 3 C-D). The final diagnosis was reported as mixed poorly-differentiated neuroendocrine carcinoma, large cell type, and well-differentiated neuroendocrine tumor, grade 2 of the common bile duct with perineural invasion and invasion into the surrounding connective tissue. The pathologic stage classification according to AJCC eight edition was pT2a pN0 pM not applicable.

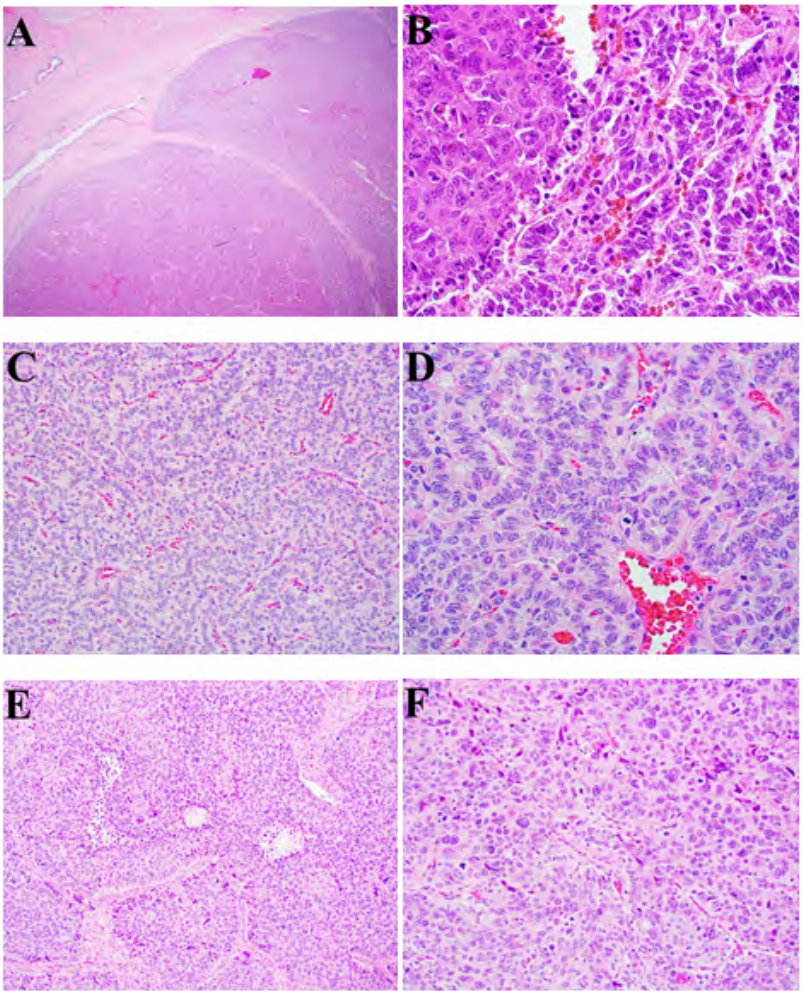

Figure 1: A) Well-circumscribed tumor mass. B) Tumor cells with a biphasic appearance consisting of a well-differentiated component (right side) and a poorly-differentiated component (left side). C) Low magnification view showing well-differentiated tumor cells arranged in a trabecular and tubular pattern. D) High magnification view of well-differentiated tumor cells with round to oval nuclei, finely granular chromatin, moderate cytoplasm, and rare mitotic figures. E) Low magnification view of poorly-differentiated tumor cells with pleomorphic large cells and necrosis. F) High magnification view of poorly-differentiated tumor cells with atypical nuclei, prominent nucleoli, high nuclear/cytoplasmic ratio, and numerous mitotic figures.

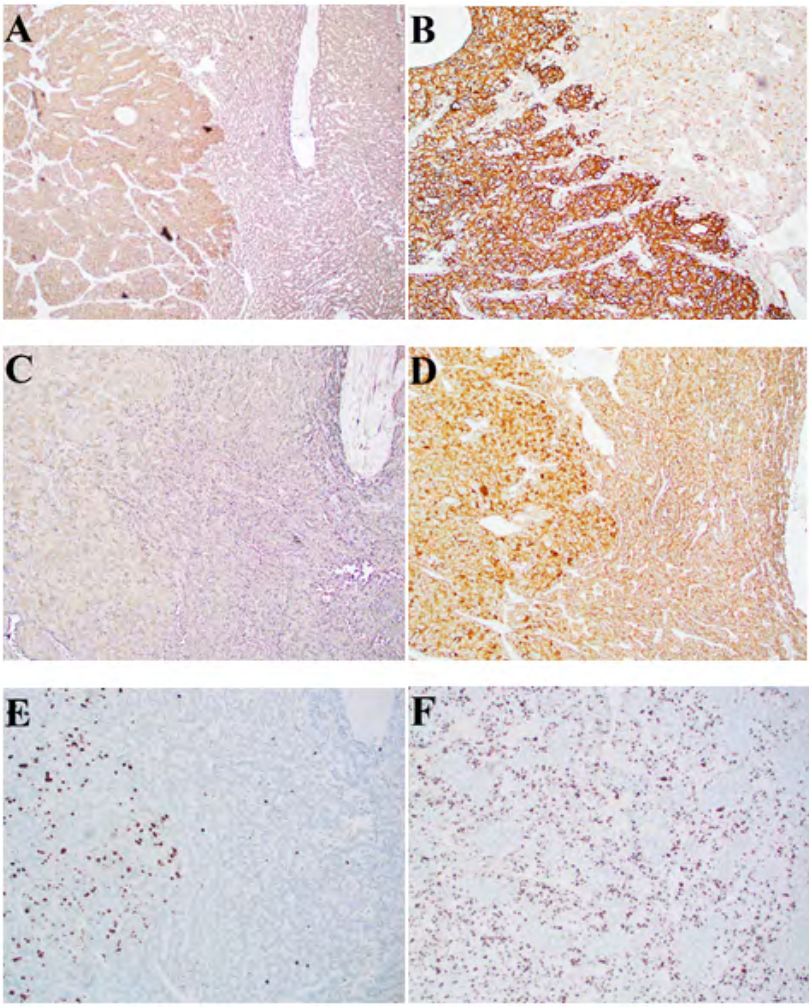

Figure 2: Tumor cells display A) Positive AE1/AE3. B) Positive CD56. C) Positive Chromogranin A. D) Positive Synaptophysin. E) Low Ki-67 in the well-differentiated component (right side) and high Ki-67 in the poorly differentiated component (left side). F) High Ki-67 of the poorly-differentiated component.

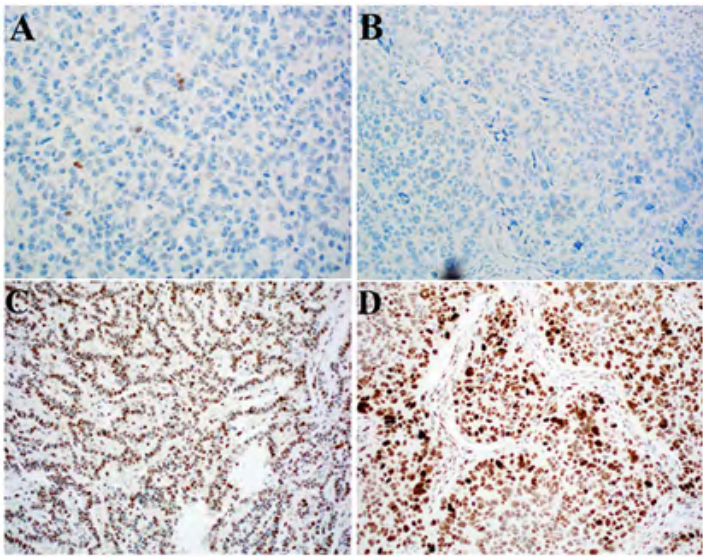

Figure 3: A) Patchy and weak P53 in the well-differentiated component. B) Negative P53 in the poorly-differentiated component. C) Weak scattered RB1 in the well-differentiated component. D) Diffusely strong RB1 in the poorly-differentiated component.

4. Discussion

The classification of neuroendocrine neoplasms of the digestive system includes three main categories: well-differentiated neuroendocrine tumors (NETs), poorly-differentiated neuroendocrine carcinoma (NECs) and mixed neuroendocrine and non-neuroendocrine neoplasm (MiNEN) [1, 2]. Well-differentiated NETs are further graded as G1, G2, or G3 based on proliferative activity determined by mitotic count and the Ki-67 proliferation index [1,2]. Poorly-differentiated NECs consist of small cell carcinoma (SCNEC) and large cell carcinoma (LCNEC) based on cytomorphology [1,2]. MiNEN is a conceptual category of neoplasms in which a neuroendocrine neoplasm is combined with a non-neuroendocrine neoplasm, each of which is morphologically and immunohistochemically recognizable as a discrete component and constitutes ≥30% of the neoplasm [1,9]. In 2018, the neuroendocrine neoplasm classification was revised to differentiate between NETs and NECs, as they differ in morphology, aggressiveness, clinical presentation, medical genetics, and therapeutic approaches despite their similarities in immunoreactivity with neuroendocrine markers [2].

Neuroendocrine neoplasms can develop in any anatomical site, with some areas such as the lungs, gastrointestinal tract, and pancreas being more common than others [4]. In the extra hepatic biliary tract, NETs account for only 0.2 to 2% of all bile duct cancers and less than 1% of all well-differentiated neuroendocrine tumors of the gastrointestinal system [7,8]. Conversely, NECs represent less than 2% of all identified tumors in the extrahepatic biliary tract [3].

Several studies have reported that the common hepatic duct and distal common bile duct are the most frequent sites of NET in the biliary tract (19.2%), followed by the middle of the common bile duct (17.9%), cystic duct (16.7%), and proximal common bile duct (11.5%) [5, 6, 7]. A literature review was conducted to identify cases of NET, pure NEC, and mixed adeno-neuroendocrine carcinoma in the extrahepatic biliary tract, common bile duct, or cystic duct. Of the identified cases, there were 50 cases of NET, 23 cases of pure NEC, and 14 cases of mixed adeno-neuroendocrine carcinoma. However, no case has been reported in which the tumor consists of both NET and NEC.

Well-differentiated NETs are characterized by uniform monomorphic cells with round nuclei, inconspicuous nucleoli, and finely granular cytoplasm arranged in a cord or trabecular pattern [1]. On immunohistochemistry, these tumors are positive for neuroendocrine markers such as synaptophysin, chromogranin and CD56 [1]. Based on mitotic count or Ki-67 proliferation index, well-differentiated NETs are graded as G1, G2, or G3 [1,2]. In this case, the well-differentiated NET component showed a mitotic count of 6 mitoses per 2mm^2 and a Ki-67 proliferation index of 3 - 20%, indicating that it is graded as G2, an intermediate grade. Our patient had a minor component composed of tumor cells that were morphologically distinct from the well-differentiated component showing highly pleomorphic cells, atypical nuclei, prominent nucleoli, and a high nuclear cytoplasmic ratio, associated with abundant necrosis, apoptosis, and mitosis. This poorly-differentiated component exhibits >40 mitosis per 2mm^2 and a Ki-67 proliferation index focally >50%. These features are more characteristic of LCNEC lending support to a mixed poorly-differentiated NEC and well-differentiated NET. In contrast, poorly-differentiated NECs are considered high-grade by definition [1,2]. They have a mitotic count of >20 mitoses per 2mm^2 and a Ki-67 proliferation index of >20% [1,2]. SCNEC have small fusiform nuclei with finely granular chromatin, scant cytoplasm, and nuclear molding, whereas LCNEC have larger round nuclei with prominent nucleoli and moderate amounts of cytoplasm [1].

Recent genomic data provides further evidence that NETs and NECs are unrelated, in addition to their morphological differences [10]. Mutations in MEN1, DAXX, and ATRX are frequently found in NETs, while TP53 and RB1 mutations are more commonly observed in NECs, particularly in pancreatic neuroendocrine neoplasms [10]. NET grading can vary within an individual tumor at presentation or between primary and metastatic sites during disease progression [1,2]. A NET may contain both low- and high-grade components, which suggest that the high-grade component is also a part of the well-differentiated neoplasm [1]. On the other hand, NECs are believed to arise from precursor lesions that typically give rise to non-neuroendocrine carcinomas, such as adenomas in the colorectum or squamous dysplasia in the esophagus [1]. Therefore, NECs are staged similarly to non-neuroendocrine carcinomas of the respective organ system [4]. MiNENs, mixed neoplasms with both neuroendocrine and non-neuroendocrine components comprising at least 30% of the tumor, are classified as a separate category [1,9]. Our case is unique because it does not fit neatly into any category of the current classification of neuroendocrine neoplasms of the digestive system.

According to a review of the Surveillance, Epidemiology and End Results (SEER) database of the U.S. National Cancer Institute, patients with NET in the gallbladder have a 10-year survival rate of 36%, while those with NET in the extrahepatic biliary tract have a 10-year survival rate of 80% [4]. However, patients with NEC have a much poorer prognosis with an average survival rate of less than one year after diagnosis and higher rates of recurrence and distant metastasis [4,8]. A study by Park et al. reported a patient with LCNEC recurring seven months after surgical excision, with the patient passing away five months after recurrence [11]. While platinum-containing regimens appear to have some efficacy based on anecdotal reports, further research is needed to establish their effectiveness [10]

5. Conclusion

In summary, our case highlights the unique presentation of a mixed NET and NEC tumor, showcasing the distinct morphological and immunohistochemical differences between the well-differentiated and poorly- differentiated components. Such mixed neoplasms are exceedingly rare, and this case serves to expand our understanding of the heterogeneity within neuroendocrine neoplasms. The differences in genetic mutations and prognosis between NET and NEC emphasize the importance of accurate diagnosis and appropriate management for optimal patient outcomes. Overall, this case underscores the significance of careful histopathological evaluation and immunohistochemical staining for the diagnosis and management of neuroendocrine neoplasms. Reporting more cases such as this will be helpful for the revision of the current classification system.

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