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Case Report

Coexistence of Cholangiocarcinoma and Poorly Differentiated Neuroendocrine Carcinoma in the Gallbladder: A Rare Case Report

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ABSTRACT

Gallbladder cancer arising from the epithelial cells lining the bile ducts within gall bladder is known as cholangiocarcinoma of gall bladder. It is one of rarest and aggressive malignancies. This cancer is divided into different types depending on the location and histologic characteristics. Of these, high-grade neuroendocrine carcinoma is a very aggressive subtype. This rare subtype is much more high-grade and neuroendocrine than other neuroendocrine tumour, which comes with a quite unique set of challenges in terms of diagnosis and treatment. We report a case of an 83 years elderly female diagnosed as poorly differentiated neuroendocrine carcinoma of the gall bladder was presented to our department. The patient presentation is characterized by its severity and rapid progress, reflecting a common feature of this aggressive subtype. The rarity and high-grade nature of poorly differentiated neuroendocrine carcinoma complicate treatment and prognosis, highlighting the need for specialized medical attention and tailored therapeutic approaches. This case underscores the importance of considering this rare variant in the differential diagnosis of gall bladder malignancies, particularly in elderly patients presenting with advanced symptoms.

Keywords: Cholangiocarcinoma, Poorly differentiated neuroendocrine carcinoma, Mixed Adenoneuroendocrine carcinoma, Rare malignancy, Case report.

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INTRODUCTION

The most common gallbladder neoplasm is papillary adenocarcinoma, accounting for 98% of cases. Mixed Neuroendocrine Non-neuroendocrine Neoplasms (MINENs) represent an aggressive subtype of MINEN. MINENs are rare gastro-entero-pancreatic tract cancers with aggressive biological behaviour and a poor prognosis. The non-neuroendocrine component is often of adenocarcinoma histology. MINENs are often treated like pure neuroendocrine carcinomas or adenocarcinomas due to lack of clinical trials. However, little is known about their molecular aberrations and pathogenesis. Current studies suggest a common monoclonal origin of the two components, involving mutations in tumour-associated genes and microsatellite instability as potential drivers.[1]

Mixed Adeno-Neuroendocrine Carcinoma (MANEC) is a rare pathological diagnosis recognized by the World Health Organisation in 2010. MANECs are difficult to diagnose due to their heterogeneity and require at least 30% of each tumour component. It is characterized by significant histological heterogeneity and simultaneous presence of adeno-carcinomatous and neuroendocrine differentiation. They typically appear in the colon, appendix, rectum, or stomach and are rarely found in the biliary tract, pancreas, or gallbladder. Colorectal MANEC is an uncommon malignant tumour, but its true prevalence is not precisely defined.[2]

Bile duct cancer, also known as cholangiocarcinoma, is a rare disease involving malignant cells in the bile ducts, a network of tubes connecting the liver, gallbladder and small intestine. The liver collects bile, which is then stored in the gallbladder and released during digestion, passing through the cystic duct to the common bile duct and into the small intestine.[3] Its incidence varies globally, with higher rates reported in Southeast Asia, particularly in countries like Thailand due to liver fluke infection (Opisthorchis viverrini).[4] Primary Neuroendocrine Tumours (NETs) of the gallbladder are rare, accounting for 0.5% of all

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NETs and 2.1% of all gallbladder cancers. They are more common in females (68%) and their presentation ranges from 25-85 years, peaking in ages 75-79. The current WHO classification divides NETs into categories like small cell neuroendocrine carcinoma, large cell neuroendocrine carcinoma, mixed adeno-neuroendocrine carcinoma and tubular carcinoid.[5]

Clinical symptoms of mixed neuroendocrine carcinoma of gall bladder are non-specific such as epigastric or right hypochondrium pain, nausea and vomiting. However asymptomatic cases are also being reported. The median overall survival of patients receiving first-line chemotherapy with gemcitabine and cisplatin is believed to be less than a year.[5] Antibodies against Programmed cell Death-1 (PD-1) and Programmed cell Death Ligand-1 (PDL1) have shown great success in treating various malignancies. In ongoing clinical trials, the combination of immunotherapy and targeted medications is being evaluated as a possible treatment option for CCA. Recent studies have shown promising antitumour activity in various cancer types, such as recurrent or metastatic nasopharyngeal carcinoma and advanced biliary tract cancer. Conversion therapy, which involves lowering unresectable tumour volume via interdisciplinary systematic treatment, is widely used in hepatocellular carcinoma and can achieve complete pathological necrosis.[6]

CASE PRESENTATION

An 83-year-old female patient, known case of hypertension and coronary artery disease for which percutaneous transluminal coronary angioplasty and stenting were done, she was on medication for the same- aspirin 75 mg once daily. She had a chief complaint of back pain for one month. Currently, she was being evaluated for suspected Gallbladder (GB) Cancer. She was detected to have mass in GB fossa extending into the adjacent liver and with large periportal and aortocaval lymph nodes.

A whole-body PET CT (Positron Emission Tomography-Computed Tomography) SCAN revealed Fluorodeoxyglucose (FDG) avid (SUV max 9) heterogeneously enhancing ill-defined hypodense lesion measuring 1.9x3.3x3.1 cm (APxTRxCC) is seen involving the segments IVb and V of the liver. The lesion is seen closely abutting the adjacent enhancing and thickened gall bladder fundus wall (maximum thickness-11 mm) showing no significant FDG uptake. Minimal retraction of overlying capsule was noted. No portal vein invasion or Intrahepatic Biliary tract Dilatation (IHBRD) was seen. Focal FDG avid (SUV max 9) enhancing centimetre sized ill-defined lesion was seen close to the peritoneal side of the body of the gall bladder and common bile duct. A faintly FDG avid (SUV max 3) aortocaval lymph node measuring 1.3x1.0 cm was also seen at the level of L2 vertebra.

EUS-guided biopsy was done Figure 1, which revealed a hypoechoic mass lesion was seen encasing the Common Hepatic Duct (CHD) extending from the hilum till the suprapancreatic portion of pancreas; Intrapancreatic portion of Common Bile Duct (CBD) appeared normal; Ecstatic dilatation of CBD notes; The lesion was found to be involving the GB wall; FNB was taken from the lesion using the acquire FNB needle. This report was suggestive of malignant growth.

Since EUS- guided biopsy was inconclusive, she was admitted for liver biopsy. Liver biopsy revealed Moderately Differentiated (grade II) Cholangiocarcinoma/Gallbladder (GB) Adenocarcinoma and poorly differentiated neuroendocrine carcinoma consistent with mixed adenoneuroendocrine carcinoma. Her serum Carcinoembryogenic Antigen (CEA)-19.8 ng/mL, SERUM CA 125 -23.6 ng/mL and SERUM CA 19-9 -3409 U/mL were estimated.

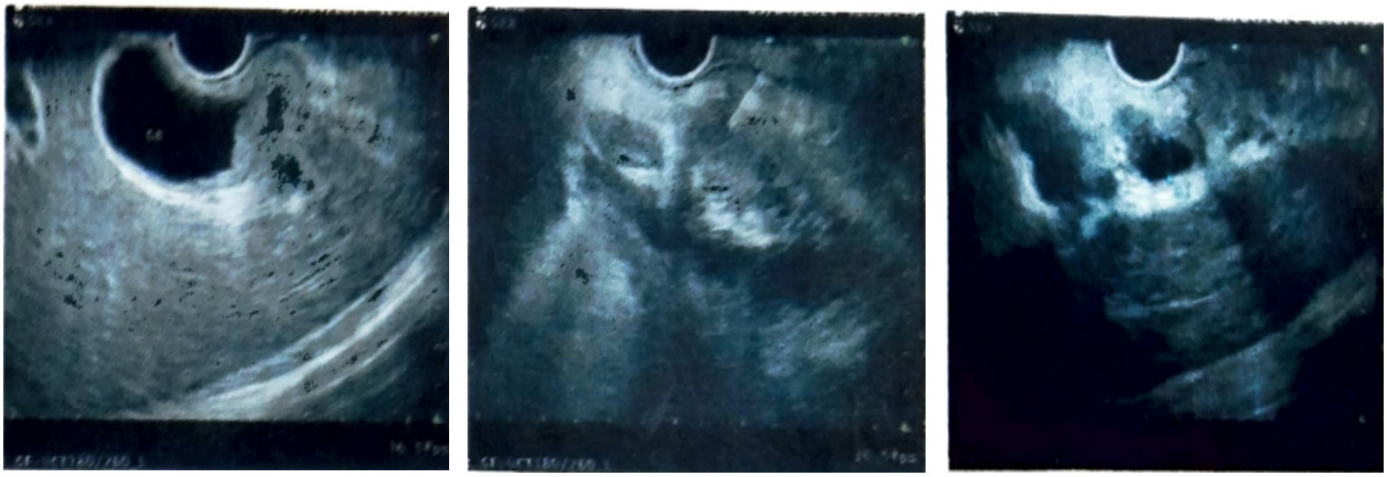

Figure 1: Endoscopic Ultrasound-Fine Needle Biopsy (Fnb) Report.

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The malignant epithelial component showed strong membranous positivity for CK-7 with CK-20 positivity, negative for CD-56, synaptophysin, chromogranin and has a Ki-67 index of 30%, indicating cholangiocarcinoma/gall bladder adenocarcinoma.

The undifferentiated tumour cells showed strong positivity for CD-56 patchy weak cytoplasmic positivity for synaptophysin, negative for CK-7, CK-20, chromogranin and has a Ki-67 index of 70%, indicating neuroendocrine carcinoma.

It showed a strong expression of Mismatch Repair (MMR) proteins in immunohistochemistry, akin to Microsatellite Instability (MSI)-Low or Microsatellite Instability (MSI)-stable status. She was positive for Her2neu proteins.

After complete evaluation by medical oncologists, she was planned for Palliative Chemotherapy+Targeted therapy. Baseline investigations were done and were under normal limits. Currently treated with GEMOX regimen (Gemcitabine 800 mg+Oxaliplatin 80 mg) and Trastuzumab 360 mg.

The patient showed initial symptomatic improvement and stabilization of disease progression in response to the GEMOX regimen (Gemcitabine 800 mg+Oxaliplatin 80 mg+Trastuzumab 360 mg). To maximize therapy results and preserve quality of life, constant monitoring of treatment efficacy and side effects is required. In order to manage her complex disease and provide individualized care and support throughout her treatment path, multidisciplinary collaboration is still essential.

DISCUSSION

In our patient the diagnosis of moderately differentiated (Grade II) cholangiocarcinoma/gall bladder adenocarcinoma and poorly differentiated neuroendocrine carcinoma consistent with mixed adenoneuroendocrine carcinoma was made through liver biopsy. Cholangiocarcinoma is a malignant neoplasm of the biliary tree, with three types: mass forming, periductal infiltrating and intraductal growing. Risk factors include inflammatory bowel disease, biliary parasites and choledochal cysts. The most common site of involvement is the Klatskin or hilar cholangiocarcinoma (50%-60%), followed by the extrahepatic duct (30-35%) and the least common site is intrahepatic (10%). It has also been reported that chronic liver disease, older age, diabetes, certain inherited conditions also contribute as predisposing factor for the disease condition.[7]

The early diagnosis of cholangiocarcinoma is difficult. Imaging modalities like transabdominal ultrasound, computed tomography and magnetic resonance imaging are crucial for detecting tumours and guiding biopsy procedures in Cholangiocarcinoma (CCA) is suggested. Extrahepatic CCA exhibits abrupt changes in ductal diameter and Endoscopic Ultrasound (EUS) and Endoscopic Retrograde Cholangiopancreatography (ERCP) are recommended for evaluation. Tissue is obtained through EUS-FNA or ERCP and therapeutic intervention is performed with ERCP. Serum tumour markers like cancer antigen 19-9 and carcinoembryonic antigen can also aid in diagnosis.[8] EUS-guided biopsy revealed that the lesion was found to be involving the GB wall; FNB was taken from the lesion using the acquire FNB needle. This report was suggestive of malignant growth. Her serum Carcinoembryogenic Antigen (CEA)-19.8 ng/mL, SERUM CA 125-23.6 ng/mL and SERUM CA 19-9-3409 U/mL were estimated. The biopsy report and cancer antigen 19-9 helped to diagnose our patient condition. Cholangiocarcinoma can lead to complications, including intrahepatic metastases, liver failure, cholangitis, liver atrophy, cirrhosis and deconditioning. In addition, biliary obstruction due to mass-like lesions can cause cholangitis, liver atrophy, cirrhosis considerable deconditioning. Distant metastatic disease can occur, as can local intraperitoneal spread.[9]

The World Health Organization (WHO) Grading for Neuroendocrine Tumour establishes 3 degrees of tumour differentiation: G1 (mitotic count <2 per 10 HPF and/or a Ki-67 index ≤2%); G2 (mitotic count 2-20 per 10 HPF and/or Ki-67 index of 3-20%); and G3 (mitotic count >20 per 10 HPF and/or Ki-67 index >20%).[10] In our case neuroendocrine portion presented a Ki-67 index of 70%, which would make it a neuroendocrine neoplasm of third grade or low differentiation according to WHO classification., moreover the adenocarcinoma portion was classified as Grade 3; therefore, poor prognosis is expected.

CONCLUSION

Finding the most effective standard practice is still hampered by the scarcity of gMANEC. That being said a malignant illness should be suspected in patients presenting unusual clinical signs and symptoms similar to cholecystitis. But our asymptomatic which lead to the delay in the diagnosis of the disease. Unfortunately, gMANEC is a histopathological diagnosis that is typically verified by the expression of CgA and SynA. Neoadjuvant therapy can be advantageous in pre-operative diagnosis, complete surgical resection is the cornerstone of therapeutic management. Regrettably our patient's clinical conditions only led to palliative care with chemotherapy and targeted therapy.

In conclusion, further research into gMANEC is essential to optimise diagnostic and therapeutic strategies, ultimately improving patient prognosis. Increased literature and clinical trials are imperative to advance our knowledge and enhance treatment outcomes for this complex neoplasm.

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AUTHOR'S CONTRIBUTION

PB and DR collected the full details of the case, wrote and prepared the final draft of the manuscript. DS performed a critical review of the manuscript. BH helped to draft the manuscript. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

ABBREVIATIONS

MINEN: Mixed Neuroendocrine Non-Neuroendocrine Neoplasms; **MANEC:** Mixed Adeno-Neuroendocrine Carcinoma; **NETs:** Neuroendocrine Tumours; **PD-1:** Programmed Cell Death-1; **CCA:** Cholangiocarcinoma; **GB:** Gallbladder; **PET CT:** Positron Emission Tomography-Computed Tomography; **FDG:** Fluorodeoxyglucose; **SUV:** Standardised Uptake Value; **APxTRxCC:** Anteroposterior x Transverse x Craniocaudal; **IHBRD:** Intrahepatic Biliary Tract Dilatation; **CHD:** Common Hepatic Duct; **CBD:** Common Bile Duct; **FNB:** Fine Needle Biopsy; **EUS:** Endoscopic Ultrasound; **CA:** Cancer Antigen; **CEA:** Carcinoembryogenic Antigen; **MMR:** Mismatch repair; **MSI:** Microsatellite Instability; **GEMOX:** Gemcitabine+Oxaliplatin; **ERCP:** Endoscopic Retrograde Cholangiopancreatography; **CgA:** Chromogranin; SynA- Synaptophysin.

SUMMARY

This case report discusses an 83-year-old female diagnosed with a rare and aggressive mixed neuroendocrine carcinoma of the gallbladder, comprising both cholangiocarcinoma and poorly differentiated neuroendocrine carcinoma. Initially presenting with back pain, imaging revealed a mass in the gallbladder fossa extending into the liver. A liver biopsy confirmed the diagnosis. The patient's treatment involved a combination of chemotherapy (GEMOX regimen) and targeted therapy (Trastuzumab), which showed initial stabilization of the disease. The report highlights the challenges in diagnosing and treating such rare malignancies, emphasizing the need for multidisciplinary care and further research to improve outcomes. Due to the rarity and aggressive nature of this cancer, early diagnosis and tailored therapeutic approaches are critical, but the prognosis remains poor. The case underscores the importance of considering this rare variant in differential diagnoses, especially in elderly patients with atypical presentations.

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