Case report

Mixed neuroendocrine-non-neuroendocrine carcinoma (MiNEN) in gallbladder: a rare case report

Abstract

Introduction:
Mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs) of the gallbladder are exceptionally rare and diagnostically challenging tumors characterized by the coexistence of both neuroendocrine and non-neuroendocrine components, each comprising at least 30% of the tumor. Their clinical presentation often mimics benign gallbladder conditions, leading to delayed diagnosis and poor prognosis. This report aims to highlight a rare case of gallbladder MiNEN and review its diagnostic, therapeutic, and pathological features.

Case Report:
A 54-year-old male presented with upper abdominal discomfort and intermittent vomiting. Imaging revealed a hypodense gallbladder mass infiltrating liver segments 4B and 5. PET-CT confirmed metabolic activity consistent with malignancy. ~~Biopsy~~Pathology examination of biopsy specimen of the mass showed a tumor composed of 20% moderately differentiated adenocarcinoma (CK7, CK19, AE1/AE3 positive) and 80% high-grade small cell neuroendocrine carcinoma (chromogranin, synaptophysin positive) with a Ki-67 index >70%. Following four cycles of neoadjuvant cisplatin and etoposide chemotherapy, imaging showed marked tumor reduction and complete metabolic response. The patient subsequently underwent radical cholecystectomy with liver wedge resection and lymphadenectomy. Final pathology revealed minimal residual adenocarcinoma and no residual neuroendocrine carcinoma. Surgical margins and lymph nodes were free of disease (ypT3N0).

Discussion:
Gallbladder MiNENs are rare, often presenting with non-specific symptoms. Accurate preoperative diagnosis remains difficult, with histopathology and immunohistochemistry being essential. The neuroendocrine component often dictates tumor aggressiveness and response to therapy. In this case, neoadjuvant chemotherapy achieved tumor downstaging and enabled complete surgical resection. The negative TTF-1 and CDX2 helped confirm the primary biliary origin. Radical resection remains the mainstay of treatment, while the role of chemotherapy and somatostatin analogues continues to evolve.

Conclusion:
This case highlights the diagnostic complexity and therapeutic potential in managing gallbladder MiNENs. Early multimodal treatment, including neoadjuvant chemotherapy and radical surgery, may offer favorable outcomes. Greater clinical awareness and reporting of such cases are essential to develop standardized diagnostic and treatment protocols.

Introduction

Mixed neuroendocrine–non-neuroendocrine neoplasms (MiNENs) are rare and complex tumors that present significant challenges in diagnosis and treatment.[1] These neoplasms are characterized by the

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presence of both neuroendocrine and non-neuroendocrine elements—each comprising at least 30% of the tumor volume, as per the latest WHO classification [2]. Preoperative misdiagnosis is common, with MiNENs frequently mistaken for adenocarcinoma or high-grade neuroendocrine carcinoma [3]. European epidemiological data suggests an incidence of fewer than 0.01 cases per 100,000 individuals per year [4]. MiNENs are most commonly found in the appendix (60.3%), followed by the colorectal region (14.5%), while occurrences in the biliary tract are rare (1.6%), with the gallbladder accounting for nearly two-thirds of these biliary cases [5]. Neuroendocrine carcinomas (NECs) of the gallbladder represent approximately 4% of all malignant gallbladder tumors, and over one-third of these contain an adenocarcinoma component, classifying them as MiNENs [1].

Clinically, gallbladder MiNENs often mimic benign conditions such as cholelithiasis or present as non-specific gallbladder masses. Due to their subtle onset, early detection is difficult. These tumors usually progress rapidly and are associated with a poor prognosis.[4] Given the scarcity of reported cases and limited literature, this report aims to contribute valuable insights through a case study and comprehensive literature review, thereby supporting improved diagnostic and therapeutic approaches.

Case Presentation

A 54-year-old male presented with a one-month history of upper abdominal discomfort accompanied by intermittent episodes of vomiting. On physical examination, a hard, palpable mass measuring approximately 6x6 cm was detected in the gallbladder region. ~~Routine~~The results of his routine laboratory investigations, including tumor markers CEA and CA 19-9, were within normal ranges. Imaging with contrast-enhanced CT identified a 62x68x43 mm hypodense mass originating from the gallbladder fundus, infiltrating hepatic segments 4B and 5, and encasing the middle hepatic vein. These findings were corroborated by 18F-FDG PET-CT.

Histopathological evaluation of a CT-guided biopsy specimen of the mass revealed features consistent with a mixed neuroendocrine-non-neuroendocrine neoplasm. The non-neuroendocrine portion, accounting for 20% of the tumor, was confirmed as adenocarcinoma, with immunohistochemistry positive staining for CK7, CK19, and AE1/AE3. The remaining 80%, representing the neuroendocrine component, was identified as small cell carcinoma, exhibiting positivity for synaptophysin and chromogranin.

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Due to the locally advanced nature of the disease, the multidisciplinary tumor board recommended neoadjuvant chemotherapy. The patient received four cycles of cisplatin and etoposide. A follow-up CT scan performed three weeks post-treatment showed a significant reduction in tumor size to 36x36x13 mm, while PET-CT revealed a complete metabolic response in the gallbladder region.

Subsequently, the patient underwent radical surgery, including en bloc cholecystectomy and wedge resection of liver segments 4B and 5, along with complete lymphadenectomy of stations 8, 12, and 13.

Patient recovered well postoperatively, clear liquids started orally on postoperative day 1, mobilized on postoperative day 2, drain placed in right subhepatic space removed on day 5 and patient discharged on day 7.

~~Final~~His final histopathology report suggested 1x0.7x0.5cm residual tumour in the fundus and body of the gall bladder, residual adenocarcinoma was moderately differentiated while the neuroendocrine component had no residual disease.

The liver and the cystic duct margin were free of tumour, none of the lymph nodes ~~are~~were involved.

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Pathological stage: ypT3N0

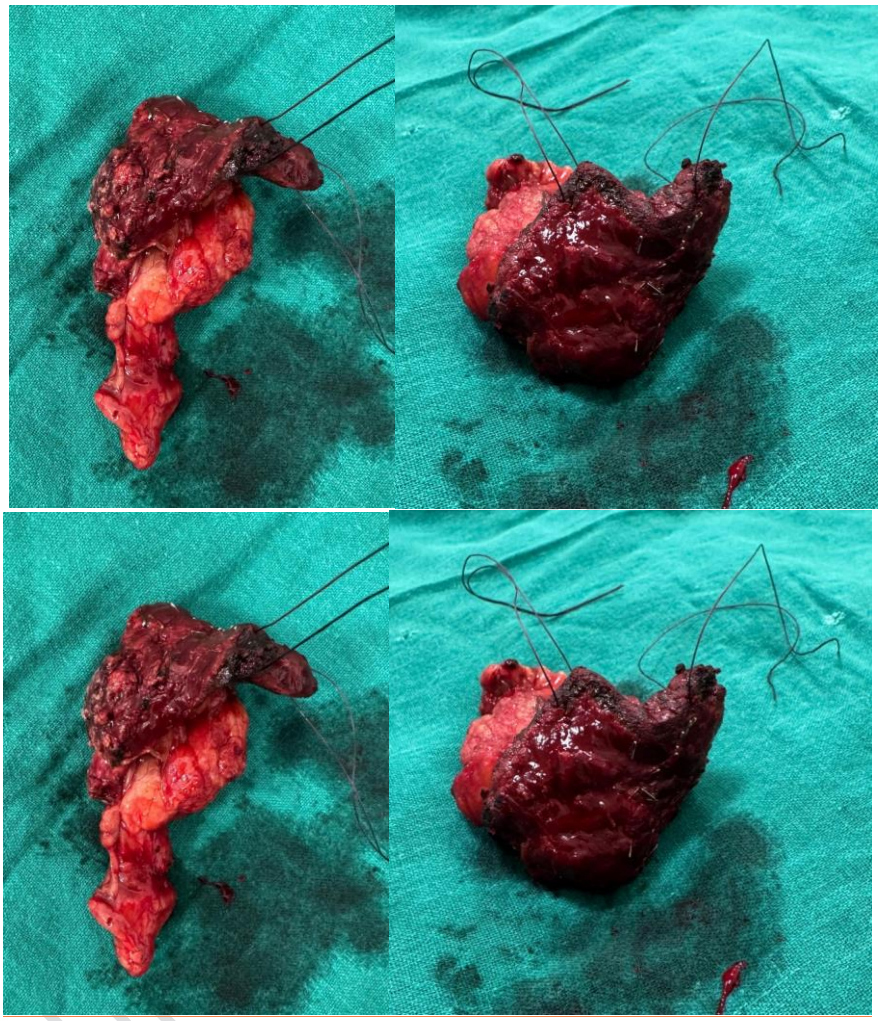


Figure 1 and 2 : specimen image – gall bladder with resected liver tissue

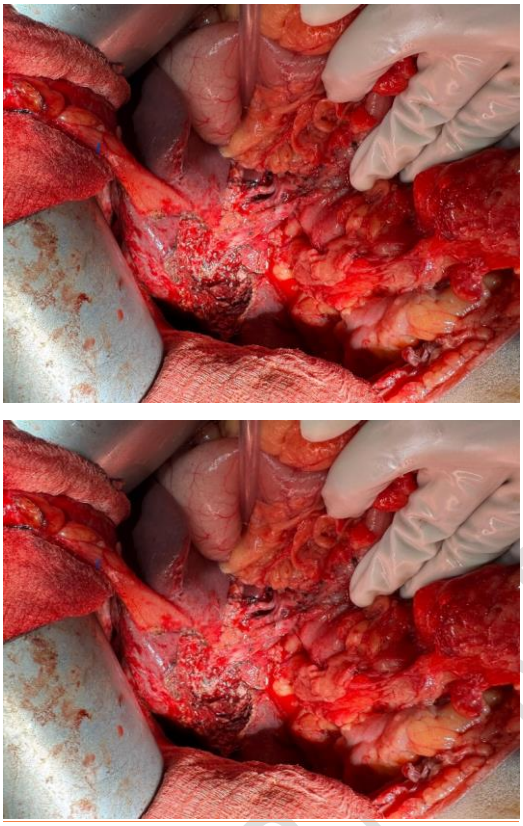
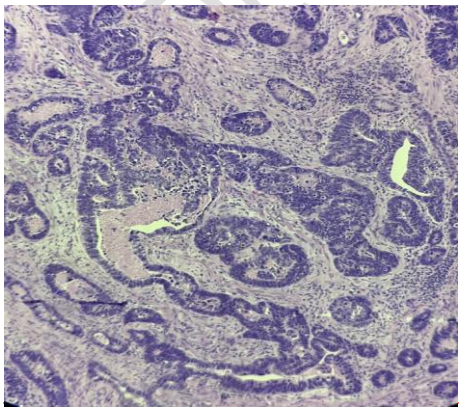


Figure 3: Post resection tumour bed



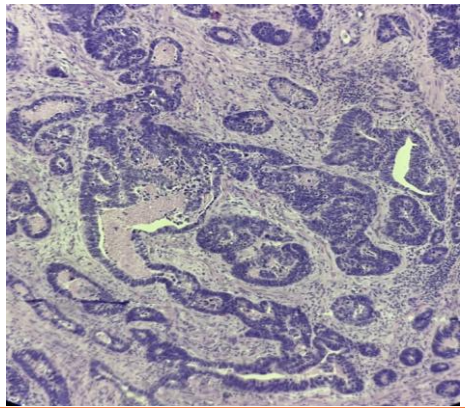
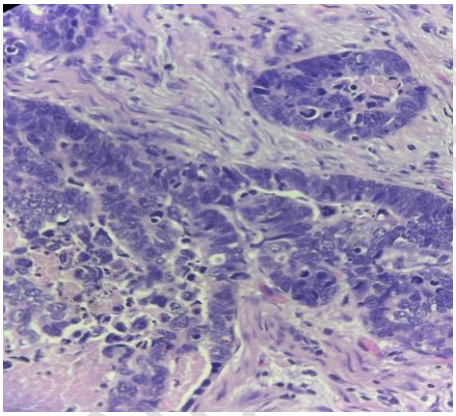


Figure 4: Histopathology image showing well-formed irregular glandular architecture consistent with adenocarcinoma and sheets and nests of small, round cells with scant cytoplasm and stippled chromatin with high mitotic activity consistent with neuroendocrine component.



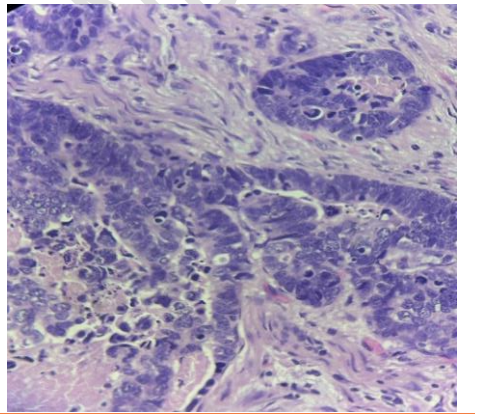


Figure 5: Histopathology image showing solid nests of tumor cells with salt pepper chromatin suggestive of neuroendocrine component. High mitotic activity and nuclear pleomorphism is consistent with high grade neuroendocrine carcinoma. Glandular structure consistent with adenocarcinoma.

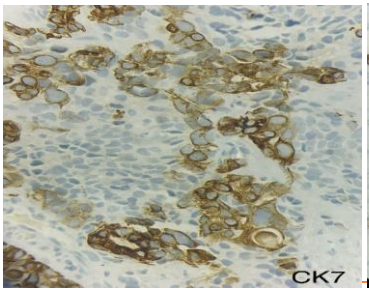


Figure 6: CK7 positive on IHC

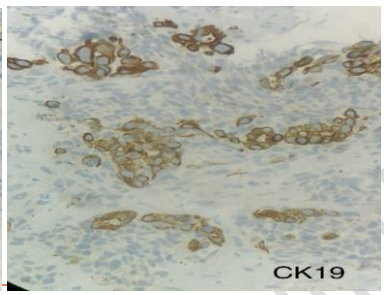
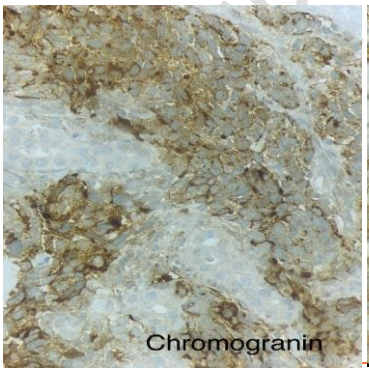
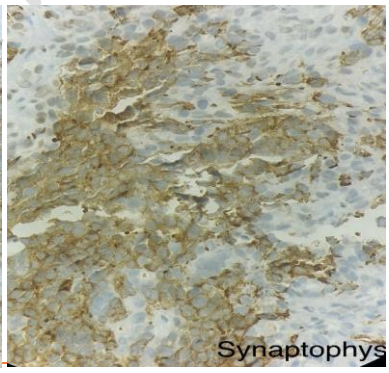
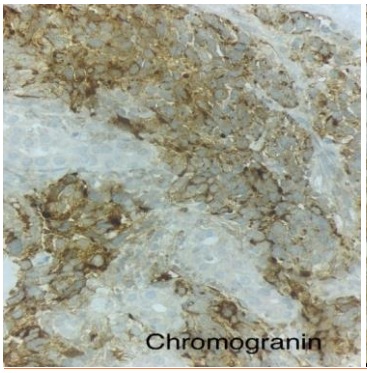


Figure 7: CK19 positive on IHC







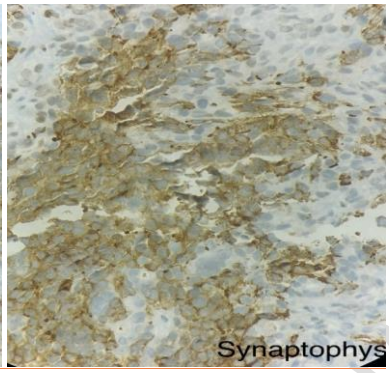
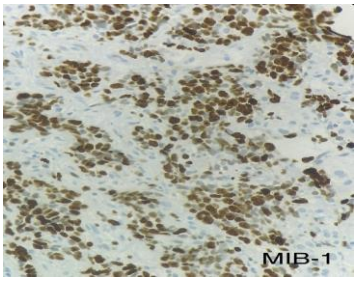


Figure 8: Chromogranin positive on IHC Figure 9: Synaptophysin positive on IHC



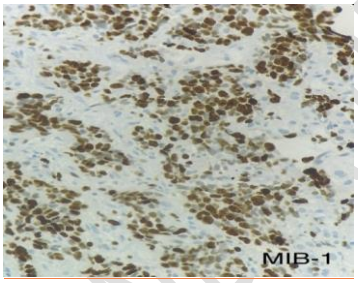


Figure 10: MIB-1 positive indicating proliferating cells

Discussion

Gallbladder MiNENs are exceedingly uncommon and are reported more frequently in women, with a male-to-female ratio of 0.22 [6]. Most individuals initially experience vague abdominal symptoms similar to those seen in gallstone disease, without signs of carcinoid syndrome. This absence is likely due to the confined release or non-production of neuroendocrine-secreted substances in early disease stages.[7]

Pathologically, MiNENs of the gallbladder generally form nodular or polypoid masses and may invade nearby structures, particularly the liver. While some present with wall thickening and tumor necrosis, histological evaluation is essential for definitive diagnosis. These tumors consist of neuroendocrine and non-neuroendocrine elements, each contributing at least 30% to the tumor mass.

Although adenocarcinoma is most commonly observed as the non-neuroendocrine element, rare histological combinations including squamous cell carcinoma, mucinous adenocarcinoma, and others have been documented [7,8]. In certain cases, both small and large cell neuroendocrine components may coexist with adenocarcinoma [9]. Their exact pathogenesis remains unclear, given the general absence of neuroendocrine cells in gallbladder mucosa, except in the neck region [10].

Studies suggest that gallbladder MiNENs are more prone to lymphatic (50.7%) and hepatic (34.3%) spread than pure NECs (15% and 17%, respectively) [11]. This aggressive behavior could be a result of synergistic malignancy between the two tumor components, though the grade of the neuroendocrine component often correlates with prognosis [12,13]. Interestingly, these dual components may metastasize independently, with synchronous liver metastases typically reflecting one histological subtype and metachronous lesions potentially involving the other [13,14].

Diagnostic imaging plays a central role in identifying MiNENs. Ultrasonography often reveals irregular, hypoechoic gallbladder masses with increased vascularity. CT and MRI frequently demonstrate strongly enhanced, irregular tumors, though differentiation from pure gallbladder carcinomas remains challenging [15,16]. In cases of gallbladder wall thickening, contrast-enhanced CT may show heterogeneous soft tissue in the fossa, while MRI might highlight cystic changes due to necrosis [17,18].

18F-FDG PET/CT has demonstrated high sensitivity and specificity in detecting gallbladder MiNENs, especially those with aggressive behavior [19,20]. However, it may miss well-differentiated tumors. Somatostatin receptor (SSR) imaging provides functional insights by identifying receptor expression on tumor surfaces. Modalities like 111In-octreotide-based scintigraphy or 68Ga-DOTA-NOC PET-CT have proven useful in localizing and staging neuroendocrine tumors [21].

Definitive diagnosis requires tissue sampling. CT- or ultrasound-guided fine-needle aspiration (FNA) and endoscopic ultrasound (EUS)-guided biopsies enhance diagnostic accuracy. EUS-FNA, in particular, has significantly improved sensitivity rates to as high as 90% [22,23,24]. However, biopsy is more effective as a confirmatory test rather than a tool for early diagnosis.

Surgical management mirrors that of advanced gallbladder carcinoma. Radical cholecystectomy with hepatic resection and lymphadenectomy remains the mainstay for early and localized disease [19]. Simple cholecystectomy may suffice for early-stage NETs (T1N0), while more advanced stages (pT2 or pT3) typically require extended resections [24,25].

Platinum-based chemotherapy, such as cisplatin and etoposide, is often employed in managing high-grade neuroendocrine components, particularly SCNEC and LCNEC [26]. Despite this, the response to adjuvant chemotherapy remains inconsistent, and many patients do not show prolonged survival. Data from multiple studies indicate that only a minority of patients undergo postoperative treatment, with mixed results regarding its efficacy [11,24].

Somatostatin analogues like octreotide and lanreotide have shown promise in reducing tumor progression and symptoms in receptor-positive tumors [24,27]. Some case reports also highlight successful conversion of unresectable MiNENs to operable status with neoadjuvant chemotherapy and somatostatin analogue therapy, suggesting potential benefit for long-term outcomes [24].

The authors should reflect upon the ensuing supporting additions and if they agree then the additions should be undertaken, but if they do not agree they can omit the suggested addition. Some clinicians would argue that despite post-operative radiology-image evidence of no a residual or metastatic lesion, some clinicians would argue that if there any microscopic metastasis within the liver or elsewhere, radiology-image in the form of PET/CT scan would to detect it and they would tend to suggest that molecular and cytogenetics studies should be undertaken to ascertain the immunotherapy medicament options that should be administered as adjuvant therapy to help the patient's immune profile to be enhanced which would then enable the immune cells of the patient to destroy the microscopic metastatic cells before they subsequently grow bigger. Other clinicians would argue that the treatment provided was adequate treatment based upon the understanding that there is no consensus opinion on utilisation of immunotherapy for such tumours.

Conclusion

Gallbladder MiNENs are a rare pathological entity, often presenting with vague symptoms that hinder early diagnosis. Advanced imaging techniques, including contrast-enhanced CT, MRI, and functional PET-CT scans, offer crucial diagnostic value. Tissue biopsy, though primarily confirmatory, also supports diagnosis when imaging findings are inconclusive. Treatment typically involves extensive surgical resection, and while chemotherapy and somatostatin analogues may offer benefits in selected cases, further studies are needed to define standardized treatment protocols and assess their prognostic value.

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