

Poorly Cohesive Cell Carcinoma of the Gallbladder: A Rare Case with Literature Review

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Abstract

Case Report

Poorly cohesive carcinoma of the gallbladder is a very rare, often incidental finding. We present a 67-year-old woman with a clinical diagnosis of chronic calculous cholecystitis who underwent elective laparoscopic cholecystectomy. Histopathology revealed a poorly cohesive carcinoma with focal abortive glandular formation, arising in a background of biliary intraepithelial neoplasia (BilIN), ranging from low to high grade. The tumor infiltrated the serosa and perivesical adipose tissue, with lymphovascular and perineural invasion and a focally positive resection margin. According to AJCC 8th edition, the findings were pT3, pNx, pMx, L1, Pn1, G3, R1, with a conditional stage IIIA (if pN0, pM0). Immunohistochemistry showed mutant-type p53 expression, negative HER2, and PD-L1 TPS <1. Molecular analysis showed no activating KRAS/NRAS mutations (exons 2, 3, 4), no BRAF p.V600E/K mutation, and no microsatellite instability. The patient was suitable for adjuvant oncological therapy and died approximately 20 months after the histopathological diagnosis, a longer survival than in several of the reported cases. We also review similar cases from the literature.

Keywords: poorly cohesive carcinoma, gallbladder, cholecystitis, biliary intraepithelial neoplasia, signet-ring cell carcinoma, p53, immunohistochemistry.

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INTRODUCTION

Poorly cohesive carcinomas, with or without signet ring cells, are defined in the gastrointestinal tract, particularly in the stomach. They are characterized by individual cells (poorly cohesive cells) and cord-like patterns forming a diffuse infiltrative growth in which the cells dissect through the tissue planes, leaving underlying structures such as the musculature intact and resulting grossly in a linitis plastica pattern. As many as 8% of conventional biliary-type carcinomas in the gallbladder exhibit a focal component of this pattern. Tumors composed predominantly of this pattern occur rarely. They are more frequent in women and clinically show a behavior more aggressive than that of ordinary gallbladder carcinoma [1]. The prognosis of gallbladder adenocarcinoma is generally very poor and correlates well with stage of disease at presentation. Prognosis is excellent, with nearly 100% survival, for CIS (Tis) or tumors confined to the gallbladder wall (T1) that are found incidentally at cholecystectomy, provided that the resection margins are negative. If the tumor infiltrates the serosa, further resection including liver resection and

regional lymphadenectomy is indicated. Radical resection in T2 tumors has resulted in 5-year survival of 61% to 70% [2,3]. Tumors with a polypoid growth pattern have a better survival than infiltrative tumors [4]. Here we describe a poorly cohesive cell carcinoma of the gallbladder arising in a background of BilIN in a 67-year-old woman, present its histopathological, immunohistochemical, and molecular features, and compare it with previously published cases.

CASE REPORT

Study area: Department of Pathology, City Hospital 8th September, Skopje, North Macedonia. [Written informed consent for publication of this case and the accompanying images was obtained from the patient's next of kin. The study was conducted in accordance with the Declaration of Helsinki and the institutional policies of City Hospital 8th September, Skopje]

We present a case of a 67-year-old female patient with a clinical diagnosis of chronic calculous

inflammation of the gallbladder who underwent an elective laparoscopic cholecystectomy. In the pathology department, the submitted surgical specimen consisted of an opened, emptied gallbladder measuring 4.5×4 cm, with a wall thickness of 0.4 cm. On gross inspection, the serosal surface showed a prominent vasculature pattern. The mucosal surface was ulcerated and eroded. On cross section, the wall was fibrotic with gray-white thickening. For histopathological examination, five tissue sections were initially embedded in two paraffin blocks; in a second sampling, the entire gallbladder was submitted in nine paraffin blocks. Microscopic examination demonstrated a fibrotic gallbladder wall with almost complete ulceration and denudation of the mucosa. In the remaining preserved mucosa, there were changes consistent with biliary intraepithelial neoplasia (BillIN), ranging from low grade to high grade (Figure 1A,B). In

the deeper parts of the wall, there was multifocal infiltration by a malignant neoplasm composed of atypical, poorly cohesive cells with an infiltrative growth pattern. Tumor cells were oval to round with scant eosinophilic cytoplasm and atypical hyperchromatic nuclei. In a smaller portion of the tumor, there was an attempt to form abortive glandular structures. The carcinoma infiltrated the serosa and surrounding adipose tissue (pT3). A moderate lymphocytic inflammatory infiltrate was present transmurally and around the tumor. A focal neoplastic infiltrate was identified at the surgical resection margin. Tumor emboli were present within small lymphovascular spaces (pL1), and perineural spread of the tumor was present (Figure 2A,B). The characteristics according to the AJCC 8th edition for gallbladder carcinoma were pT3, pNx, pMx, L1, Pn1, G3, R1, stage IIIA (conditional stage if pN0, pM0).

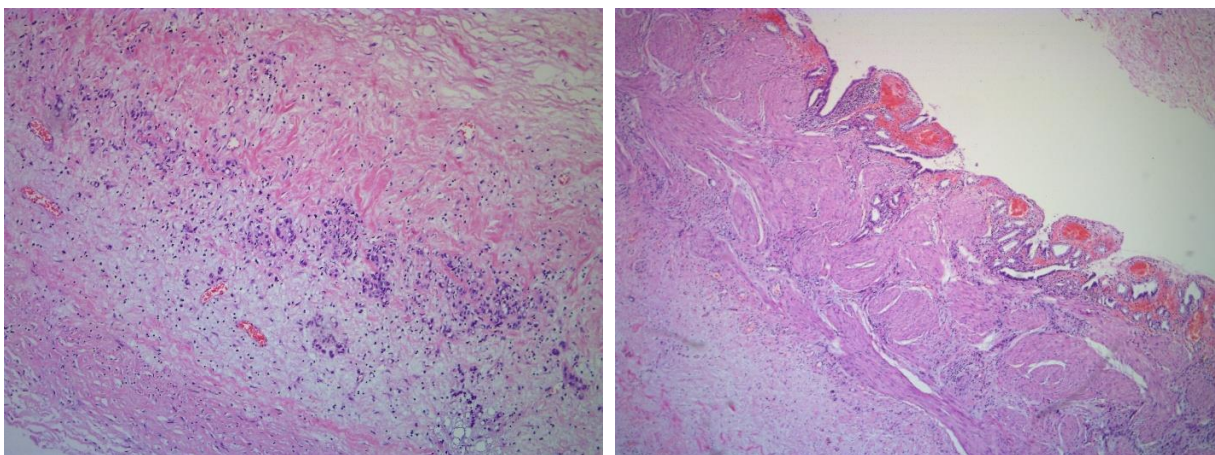


Figure 1. Histopathological findings. (A) Gallbladder wall with erosive changes of the surface mucosa and low-grade dysplasia (H&E, $\times 40$). (B) Deeper parts of the wall with clusters and individual atypical epithelial cells (H&E, $\times 400$).

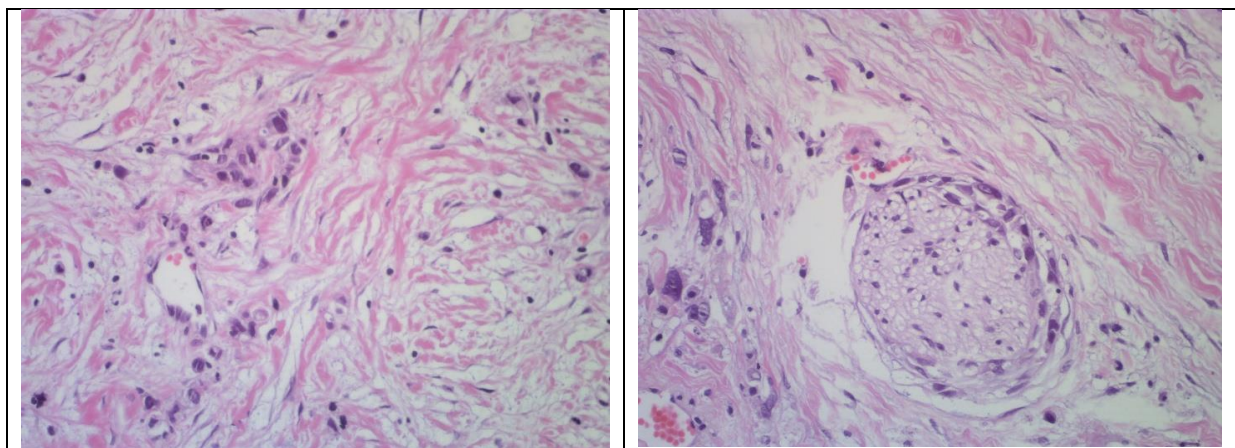


Figure 2. (A) Atypical malignant infiltrative cells at higher magnification. (B) Tumor cells showing perineural infiltration (H&E, $\times 200$).

Additional immunohistochemical staining was performed to assess the proliferative activity and p53 status of the tumor. Ki-67 showed positive nuclei in discohesive single malignant cells, particularly within the fibrous stroma infiltrated by the tumor (Figure 3A).

In p53 staining, the tumor cells showed a mutant-type (overexpression) pattern, with clusters of cells showing strong nuclear positivity in approximately 80% of tumor cells (Figure 3B).

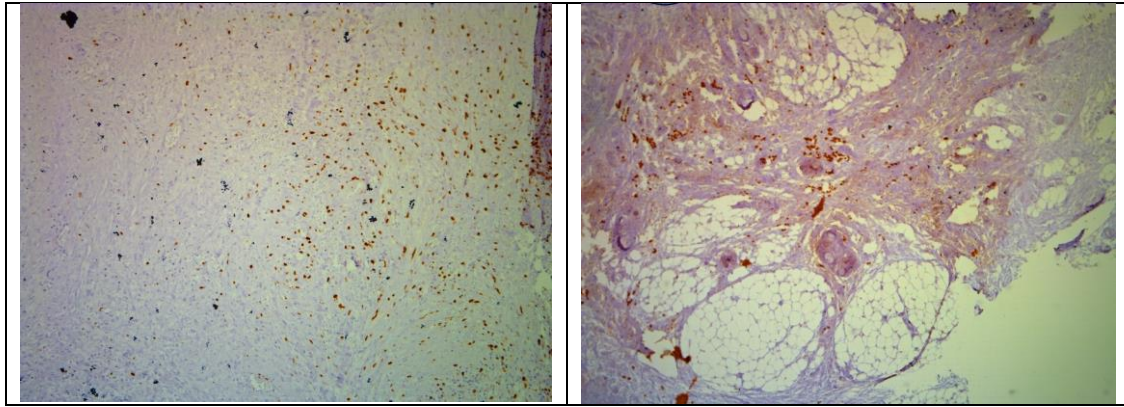


Figure 3. Immunohistochemistry. (A) Ki-67 immunostaining showing nuclear positivity with heterogeneous distribution in the malignant discohesive cells (×10). (B) p53 immunostaining showing strong nuclear positivity in approximately 80% of tumor cells, consistent with a mutant-type (overexpression) pattern (×10).

For adjuvant chemotherapy and immunotherapy, molecular analysis of the paraffin-embedded tumor tissue was performed for microsatellite instability (MSI) and for the BRAF p.V600E mutation in exon 15 of the BRAF gene, using fluorescent allele-specific PCR analysis and capillary electrophoresis on an automated DNA analyzer. The results showed absence of an activating BRAF p.V600E/K mutation and absence of microsatellite instability. Additional molecular testing for mutations in exons 2, 3, and 4 of the KRAS and NRAS genes showed absence of activating mutations. Immunohistochemical detection of HER2 protein expression and PD-L1 was also performed on the tissue samples. HER2 was negative, and PD-L1 immunohistochemistry showed positive expression in rare single tumor-infiltrating immune cells, TPS <1. Postoperatively, the patient's condition was good and she received adjuvant oncological therapy. She died approximately 20 months after the histopathological diagnosis.

DISCUSSION

In this case, we report a malignant epithelial carcinoma of the gallbladder characterized by poorly cohesive morphology. The tumor infiltrated all layers of the gallbladder wall, while the adjacent mucosa exhibited both dysplastic and metaplastic alterations. Clinically, the presence of gallstones supported the hypothesis that chronic inflammation may have driven the sequence of metaplasia and dysplasia, ultimately culminating in carcinoma. This presentation aligns with the inflammation–metaplasia–dysplasia pathway of gallbladder carcinogenesis [5].

Gallbladder carcinomas with a poorly cohesive or signet-ring component are exceptionally rare, and their clinicopathological profile is still poorly defined. Our PubMed search found only isolated case reports. Most of the cases we identified are summarized in Table 1.

Table 1. Reported cases of poorly cohesive / signet-ring cell carcinoma of the gallbladder

Ref.	Year	Patient	Presentation	Key pathology	Outcome
6	2008	76, M	Not stated	Signet-ring cell carcinoma	Radical surgery + 5-FU; died within 3 months
7	2010	86, F	Not stated	Signet-ring cell carcinoma; differential diagnosis discussed	Not stated
8	2010	32, M	Not stated	Signet-ring cell carcinoma; celiac lymph node metastasis	Radical surgery + chemotherapy; died 2 months postoperatively
9	2019	46, M	Acute cholecystitis	Linitis plastica-like wall; signet-ring cells plus neuroendocrine-like component	Nodal, peritoneal and liver metastases; chemotherapy; no progression at 4 months
10	2026	70, M	Fever, abdominal pain	Advanced poorly differentiated carcinoma with focal poorly cohesive/signet-ring features; peritoneal nodules	Rapid peritoneal progression; died within 2 months
11	2026	70s, F	Incidental nodule on screening ultrasound	Multifocal ICPN with a 6 mm invasive poorly cohesive component, focal signet-ring cells	Not stated
This case		67, F	Chronic calculous cholecystitis	pT3, G3, R1, L1, Pn1; BillIN background	Adjuvant therapy; died at about 20 months

Several themes emerge from these reports. First, the clinical presentation is nonspecific. Several tumors

were found in patients treated for presumed cholecystitis or gallstone disease [9], and one was found incidentally

on screening imaging [11], which supports submitting and thoroughly sampling every cholecystectomy specimen. Second, the tumor often arises in or beside a preinvasive lesion. In the ICPN case [11] and in our patient, a poorly cohesive invasive component was associated with flat or papillary intraepithelial neoplasia, which suggests a link to the biliary precursor pathway. Third, the diagnosis can be difficult. Signet-ring and discohesive cells overlap with other entities, so immunohistochemistry was needed to exclude a gastric primary, goblet cell adenocarcinoma, or a neuroendocrine neoplasm [7,9,11].

The prognosis in most reports was poor, with death within 2 to 3 months of diagnosis or surgery [6,8,10], even in a young patient treated radically [8]. A population-based Hong Kong study of gallbladder cancer found incidentally during cholecystectomy for acute cholecystitis reported a median survival of only 5 months and a 5-year survival of 20.8% [12]. That cohort was predominantly conventional adenocarcinoma (90.5%), so it is only an indirect comparison. The one exception was a patient with an indolent early course, with no progression at 4 months [9], although follow-up there was short. Our patient survived about 20 months despite pT3 disease, lymphovascular and perineural invasion, and a positive margin. This is longer than most reported cases, although a single case cannot show whether this reflects tumor biology, adjuvant therapy, or other factors. The tumor lacked actionable alterations (KRAS/NRAS and BRAF wild-type, MSS, HER2-negative, PD-L1 TPS <1), which limits targeted and immunotherapy options. The lack of data on the adjuvant regimen is a limitation of this report.

CONCLUSION

Our patient had a poorly cohesive carcinoma of the gallbladder arising in a background of BiIN, with no actionable molecular alterations, and survived about 20 months after diagnosis. From reviewing the online database, only a few cases of poorly cohesive carcinoma of the gallbladder have been reported. This entity is extremely rare, so it is very important that it is not missed during routine histopathological examination. Patients mainly present clinically with symptoms of gallbladder inflammation. Unfortunately, the overall prognosis of gallbladder cancer is poor. There is an urgent need for further research to help improve the prognosis of this tumor.

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