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Gallbladder Adenosquamous Carcinoma in the Setting of a Pancreatic Head Mass and Bile Duct Abnormalities: A Diagnostic Challenge

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Abstract

Adenosquamous carcinoma (ASC) of the gallbladder is a rare and aggressive malignancy. Its diagnosis can be challenging when pancreatic and bile duct lesions coexist, particularly when tissue samples are limited. We report the case of a 61-year-old woman presenting with a pancreatic head mass, biliary dilatation, and a gallbladder wall lesion. Surgical exploration revealed abnormalities involving the gallbladder, pancreatic head, and common bile duct. Histopathological examination established the diagnosis of gallbladder ASC, characterized by a poorly differentiated glandular component and a squamous component representing more than 40% of the tumor. The pancreatic biopsy showed a poorly differentiated carcinoma without an identifiable squamous component, whereas the bile duct biopsy contained only scattered atypical epithelial cells. Immunohistochemistry supported the diagnosis of gallbladder ASC, but the limited pancreatic and bile duct samples and incomplete comparative immunohistochemical analyses prevented definitive determination of the relationship between the lesions. This case highlights the importance of integrating morphological, immunohistochemical, radiological, and operative findings while acknowledging the limitations of tissue sampling when evaluating potentially related pancreatobiliary lesions.

Categories: General Surgery, Pathology
Keywords: adenosquamous carcinoma, bile duct, diagnostic challenge, gallbladder, immunohistochemistry, pancreatic head mass

Introduction

Gallbladder carcinoma is an aggressive malignancy of the biliary tract, with adenocarcinoma representing the predominant histological subtype. Adenosquamous carcinoma (ASC), characterized by the coexistence of glandular and squamous differentiation, is uncommon. In a population-based study, adenosquamous and squamous carcinomas together accounted for 4.6% of selected gallbladder carcinomas and were associated with poorer survival than conventional adenocarcinoma [1]. Clinical presentation is often non-specific, with abdominal pain and manifestations of biliary obstruction [2].

The presence of squamous differentiation is important for accurate histopathological classification [3] and has been associated with aggressive tumor behavior [4]. Immunohistochemical markers such as p63 and p40 help identify squamous differentiation, particularly in poorly differentiated carcinomas. A recent clinicopathological and molecular study of 25 gallbladder ASC cases demonstrated frequent p63 and p40 expression and highlighted the predominance of locally advanced disease at diagnosis [5].

Establishing the primary site may be particularly challenging when gallbladder carcinoma coexists with a pancreatic head mass and bile duct abnormalities. Such findings raise several possibilities, including direct tumor extension, secondary involvement, or synchronous primary malignancies. Distinguishing between these scenarios is important for tumor classification, staging, and clinical management. However, limited tissue sampling and incomplete comparative immunohistochemical or molecular investigations may prevent a definitive determination of the relationship between the lesions.

We report a case of gallbladder ASC associated with a pancreatic head mass and bile duct abnormalities. This case highlights the diagnostic challenge of determining the relationship between these lesions when the available pathological material does not permit comprehensive comparative assessment.

Case Presentation

Clinical and radiological findings

A 61-year-old woman presented with abdominal pain and deterioration of her general condition. Initial

abdominal ultrasonography revealed a gallbladder wall lesion and a nodular pancreatic head mass associated with dilatation of the common bile duct and intrahepatic bile ducts. Subsequent magnetic resonance imaging (MRI) confirmed the pancreatic head lesion and associated hepatobiliary abnormalities.

Computed tomography (CT), performed as part of the preoperative assessment, described a pancreatic head lesion considered resectable, marked biliary dilatation, a hepatic lesion suspicious for metastasis, and a hepatic hilar lymph node. Pulmonary micronodules were also reported. Although ultrasonography identified a gallbladder wall lesion, the available CT report did not specifically describe a gallbladder mass. The reason for this discrepancy could not be established from the available radiological reports.

Preoperative laboratory results, including liver function tests, bilirubin levels, and tumor markers, were not available for review. The axial and sagittal CT images are presented in Figures *1*, *2*, respectively.

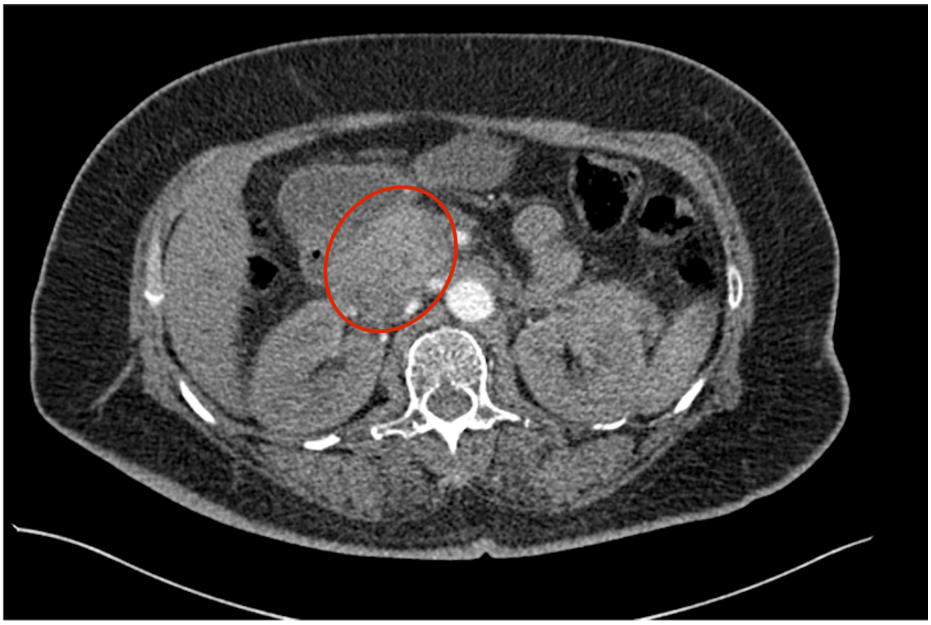


FIGURE 1: Axial abdominal CT showing the pancreatic head lesion

Contrast-enhanced abdominal computed tomography (CT), axial section. The red circle highlights the pancreatic head lesion identified during the preoperative assessment.

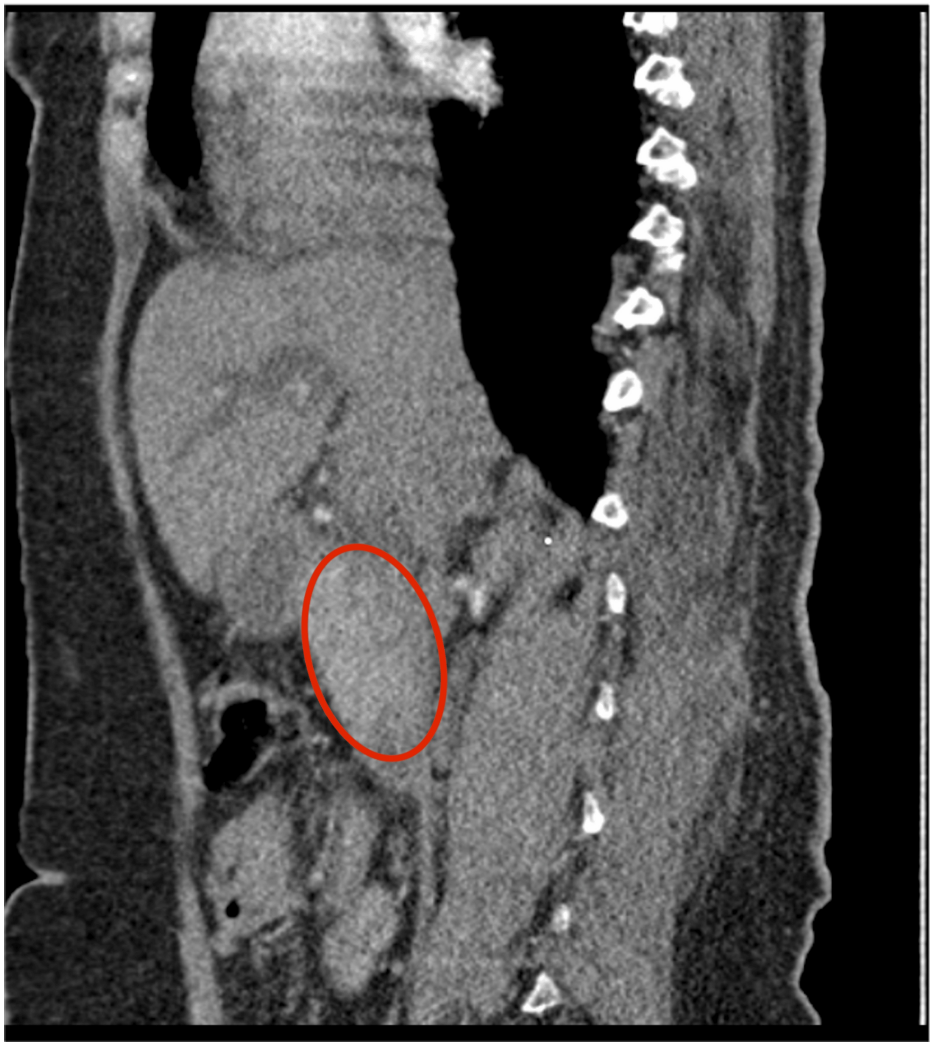


FIGURE 2: Sagittal abdominal CT reconstruction showing the pancreatic head lesion

Sagittal multiplanar reconstruction of the contrast-enhanced abdominal computed tomography (CT) scan. The red circle highlights the pancreatic head lesion identified during the preoperative assessment.

Operative findings and management

Surgical exploration was initially undertaken for the pancreatic head mass, which had been considered resectable on preoperative imaging. Intraoperatively, a 3 × 4 cm pancreatic head mass was identified, with fixation to the posterior plane, and was considered unresectable. Consequently, pancreatic resection was not performed, and pancreatic biopsies were obtained.

The gallbladder fundus was markedly thickened and appeared to invade the adjacent hepatic tissue. The common bile duct was markedly dilated, measuring approximately 3 cm, with areas of wall thickening. No separate hepatic metastasis or peritoneal carcinomatosis was identified during surgical exploration.

Retrograde cholecystectomy with resection of adjacent hepatic parenchyma was performed, together with bile duct biopsies. A choledochoduodenal bypass was also carried out to provide biliary drainage in the setting of marked common bile duct dilatation. The precise rationale for the extended gallbladder resection was not documented in the available operative records.

Histopathological findings

Gross examination of the gallbladder revealed a firm, beige, exophytic mass measuring 5 × 3 × 2.8 cm, located in the fundus. The adjacent hepatic tissue appeared infiltrated.

Microscopically, the gallbladder tumor was an infiltrating carcinoma composed of two distinct epithelial

components. The glandular component showed poorly differentiated adenocarcinomatous features, with glands, trabeculae, and small clusters of atypical cells. The squamous component represented more than 40% of the tumor, as estimated microscopically after complete histological sampling of the tumor and examination of all corresponding slides. It consisted of polygonal cells with dyskeratosis and well-formed keratin pearls (Figures *3*, *4*).

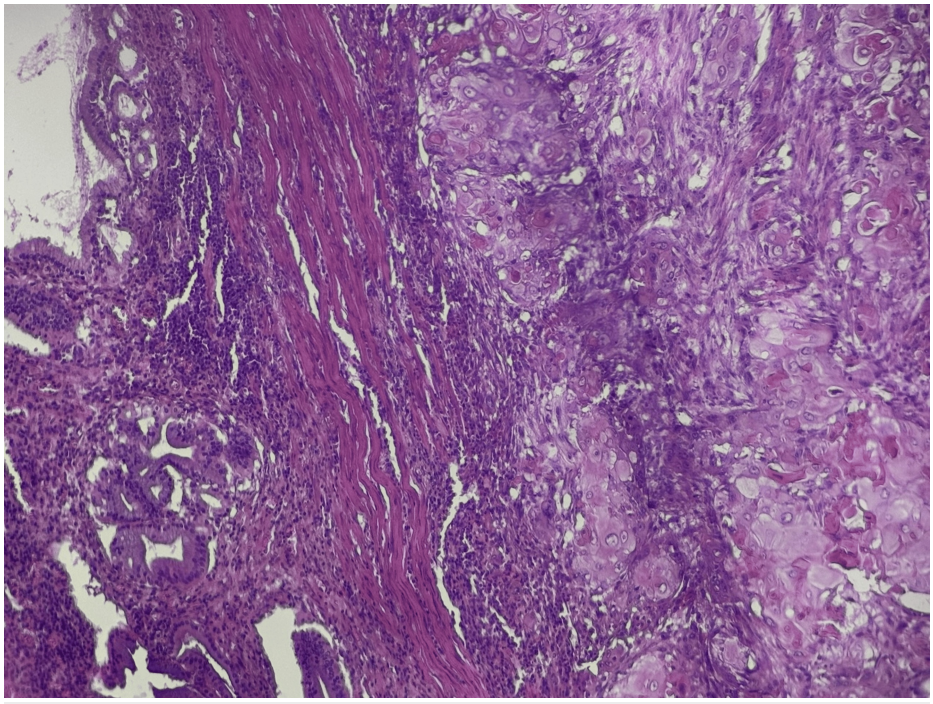


FIGURE 3: Histopathological features of gallbladder adenosquamous carcinoma

Hematoxylin and eosin (H&E) staining showing infiltration of the gallbladder wall by carcinoma with squamous differentiation (×20).

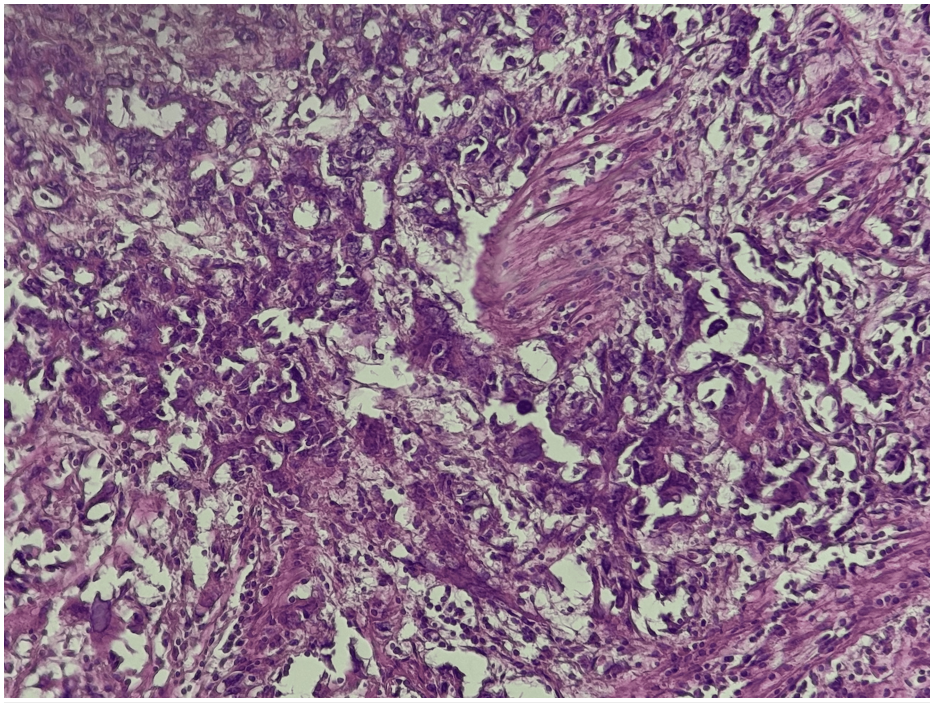


FIGURE 4: Glandular and squamous components of gallbladder adenosquamous carcinoma

Hematoxylin and eosin (H&E) staining demonstrating the coexistence of glandular and squamous differentiation in gallbladder adenosquamous carcinoma (×20).

The tumor was associated with a fibroinflammatory stroma, perineural invasion, and lymphovascular tumor emboli. Tumor necrosis was estimated at approximately 10%. The carcinoma infiltrated the full thickness of the gallbladder wall and extended directly into the adjacent hepatic parenchyma. The cystic duct margin was free of tumor, whereas the hepatic resection margin was involved. No precursor epithelial lesion or dysplasia was identified in the examined gallbladder sections.

According to the American Joint Committee on Cancer (AJCC) eighth edition TNM classification for gallbladder carcinoma, the tumor was classified as pT3 because of direct invasion into the adjacent hepatic parenchyma. No regional lymph nodes were submitted for histological examination; therefore, the pathological nodal category was pNX. A pathological distant metastasis category was not assigned.

The pancreatic biopsy showed an infiltrating poorly differentiated carcinoma arranged in glands, trabeculae, and isolated cells. The tumor was associated with a fibroinflammatory stroma and perineural invasion. No lymphovascular tumor emboli or squamous component was identified in the examined biopsy sections. However, the limited biopsy material did not allow a comprehensive assessment of tumor heterogeneity, and the absence of a squamous component does not exclude its presence elsewhere in the lesion.

Compared with the recognizable adenocarcinomatous component of the gallbladder tumor, the pancreatic carcinoma showed less distinct glandular differentiation. No mucin production was identified in either lesion on the examined histological sections. Both lesions exhibited a fibroinflammatory stroma and perineural invasion, whereas lymphovascular tumor emboli were identified only in the gallbladder specimen. Although some architectural and stromal features overlapped, the limited pancreatic biopsy and poor tumor differentiation prevented a reliable assessment of morphological similarity and did not permit a definitive determination of the relationship between the two lesions.

The bile duct biopsy consisted predominantly of crushed, inflamed fibroadipose tissue containing scattered atypical epithelial cells. Their limited representation precluded definitive morphological characterization and did not allow a definitive diagnosis of carcinoma in this sample.

Unlike the gallbladder resection specimen, the pancreatic and bile duct biopsies provided limited tissue for comparative assessment. Tissue exhaustion prevented completion of the immunohistochemical panel, further restricting the evaluation of the relationship between the lesions.

Immunohistochemical findings

Immunohistochemistry was performed using an automated platform (OMNIS, Agilent, Santa Clara, CA, USA). The antibodies included p63 (clone 4A4, Dako), CK7 (clone OV-TL 12/30, Dako), CK19 (clone RCK108, Dako), MUC1 (clone MH1), and pan-cytokeratin AE1/AE3 (Dako). CK20 was unavailable in our laboratory.

In the gallbladder tumor, p63 showed moderate nuclear expression in the squamous component, whereas CK7 and CK19 showed moderate, diffuse cytoplasmic expression in the glandular component. MUC1 was negative. The representative immunohistochemical findings are illustrated in Figures *5*, *6*.

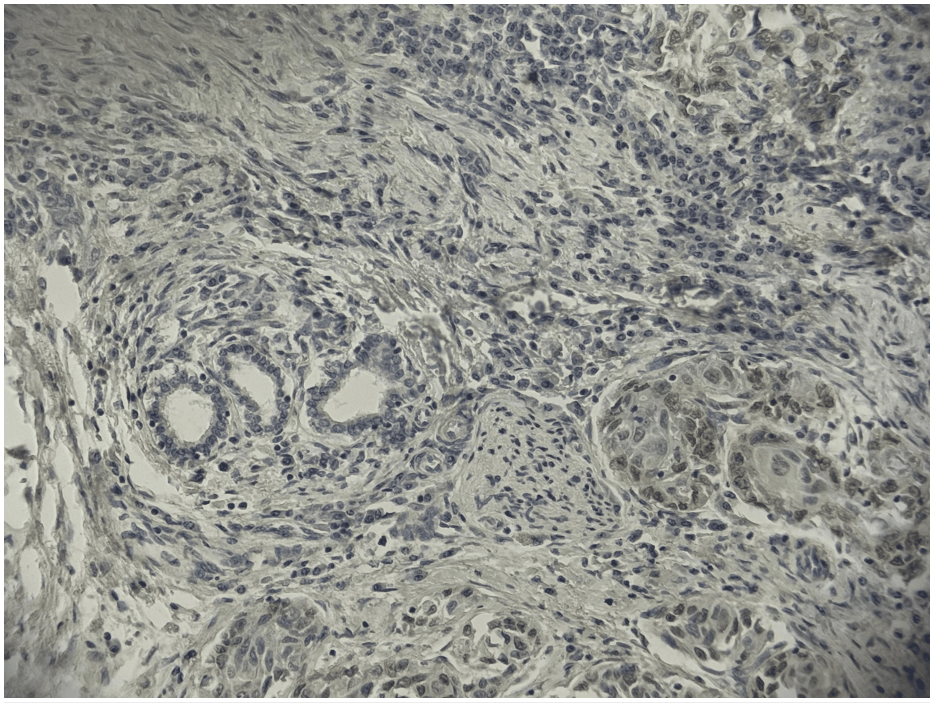


FIGURE 5: Nuclear p63 expression in the squamous component of gallbladder adenosquamous carcinoma

Immunohistochemical staining for p63 demonstrating nuclear positivity in the squamous tumor cells of gallbladder adenosquamous carcinoma (×10).



FIGURE 6: CK7 expression in the glandular component of gallbladder adenosquamous carcinoma

Immunohistochemical staining for CK7 demonstrating cytoplasmic positivity in the glandular tumor cells of gallbladder adenosquamous carcinoma (×10).

The pancreatic tumor cells showed moderate cytoplasmic expression of CK7. In the bile duct biopsy, the atypical epithelial cells expressed pan-cytokeratin (AE1/AE3), whereas CD45 highlighted reactive lymphoid cells. CK19 and MUC1 were non-contributory in both the pancreatic and bile duct biopsies because of tissue exhaustion.

The comparative histopathological and immunohistochemical findings of the gallbladder, pancreatic, and bile duct specimens are summarized in Table *1*.

Feature	Gallbladder	Pancreatic biopsy	Bile duct biopsy
Histological diagnosis	Adenosquamous carcinoma	Poorly differentiated carcinoma	Scattered atypical epithelial cells
Architecture	Glandular and squamous components	Glands, trabeculae, isolated cells	Isolated atypical cells
Squamous component	>40%	Not identified	Not assessable
Stroma	Fibroinflammatory	Fibroinflammatory	Inflamed fibroadipose tissue
Perineural invasion	Present	Present	Not identified
Lymphovascular invasion	Present	Not identified	Not identified
CK7	Positive	Positive	Not tested
CK19	Positive	Non-contributory	Non-contributory
p63	Positive in squamous component	Not tested	Not tested
MUC1	Negative	Non-contributory	Non-contributory
AE1/AE3	Not tested	Not tested	Positive in atypical epithelial cells
CD45	Not tested	Not tested	Positive in reactive lymphoid cells
CK20	Unavailable	Unavailable	Not tested

TABLE 1: Comparative histopathological and immunohistochemical findings in the gallbladder, pancreatic, and bile duct specimens

Non-contributory: insufficient residual tissue for reliable immunohistochemical interpretation. Not tested: immunohistochemical staining was not performed. Unavailable: the antibody was not available in the laboratory. The absence of a histological finding in a limited biopsy does not exclude its presence elsewhere in the lesion.

MUC1 negativity in the gallbladder tumor did not exclude ASC, as its expression may vary among pancreatobiliary carcinomas. Since MUC1 assessment was non-contributory in both the pancreatic and bile duct biopsies because of tissue exhaustion, this marker could not be used for a meaningful comparison between the lesions.

Overall, the immunohistochemical findings supported the diagnosis of gallbladder ASC but did not establish whether the pancreatic lesion represented direct extension, secondary involvement, or a separate primary tumor. The bile duct sample was too limited to resolve its relationship to the other lesions.

Final pathological interpretation

Histopathological and immunohistochemical findings established the diagnosis of poorly differentiated gallbladder ASC with direct invasion of the adjacent hepatic parenchyma. The pancreatic biopsy confirmed a poorly differentiated carcinoma, whereas the bile duct biopsy contained atypical epithelial cells insufficient for a definitive diagnosis of carcinoma. The available findings did not establish whether the pancreatic carcinoma was related to the gallbladder tumor or represented a separate primary malignancy. The relationship of the bile duct abnormalities to these lesions also remained unresolved.

Discussion

The diagnostic challenge of determining tumor origin

The main diagnostic challenge in this case was determining the relationship between the gallbladder ASC, the pancreatic head carcinoma, and the bile duct abnormalities. Although the gallbladder resection specimen established the diagnosis of ASC, the available findings did not establish whether the pancreatic lesion represented an independent primary tumor or secondary involvement.

The anatomical distribution of the lesions provides important clues. The gallbladder carcinoma was centered in the fundus, with direct invasion of the adjacent hepatic parenchyma and a tumor-free cystic duct margin. In contrast, the pancreatic head mass was associated with marked dilatation of the common bile duct. These findings suggest that the pancreatic head lesion may have contributed to the biliary obstruction, although the precise mechanism could not be definitively established. Furthermore, the anatomical distance between the gallbladder fundus and the pancreatic head, together with the uninvolved cystic duct margin, makes direct contiguous extension between these sites less likely, although it cannot be entirely excluded.

The hepatic lesion initially considered suspicious for metastasis on CT was not identified as a separate metastatic lesion during surgery. Histological examination demonstrated tumor infiltration of the hepatic parenchyma adjacent to the gallbladder, supporting direct local invasion at this site. However, the relationship between this finding and the radiologically described hepatic lesion cannot be established with certainty.

The pancreatic biopsy demonstrated poorly differentiated carcinoma without an identifiable squamous component. Although this finding does not exclude secondary involvement by gallbladder ASC, it also does not establish a common origin. The bile duct biopsy contained only scattered atypical epithelial cells and was insufficient for definitive tumor classification.

Considering the anatomical distribution and available pathological findings, two independent primary tumors, namely, gallbladder ASC and pancreatic carcinoma, represent a plausible explanation. However, the absence of comprehensive morphological, immunohistochemical, and molecular comparison prevents confirmation of this hypothesis. The possibility of secondary tumor involvement therefore remains unresolved.

This case emphasizes the importance of integrating anatomical topography with histopathological findings when evaluating multiple pancreatobiliary lesions. While the diagnosis of gallbladder ASC is established, the precise relationship between the gallbladder and pancreatic carcinomas cannot be definitively determined from the available evidence.

Contribution and limitations of immunohistochemistry

Immunohistochemistry supported the morphological diagnosis of ASC in the gallbladder. Nuclear p63 expression highlighted the squamous component, whereas CK7 and CK19 expression supported the epithelial differentiation of the glandular component. p63 is a useful marker of squamous or basal differentiation in the appropriate morphological context, but its expression is not specific for anatomical origin [6].

CK7 expression in the pancreatic carcinoma and pan-cytokeratin (AE1/AE3) expression in the atypical bile duct cells confirmed their epithelial differentiation but did not establish their anatomical origin or a common origin with the gallbladder tumor. This limitation is particularly relevant because CK7 expression overlaps among carcinomas of the pancreas, gallbladder, and extrahepatic biliary tract and cannot reliably establish the site of origin in this anatomical region [7]. The absence of interpretable CK19 and MUC1 results in the limited pancreatic and bile duct samples further restricted the immunohistochemical assessment. The available immunohistochemical work-up was insufficient to determine the relationship between the lesions. Additional comparative markers, including p63/p40, p53, and SMAD4, could have provided further diagnostic information, although their findings would require interpretation alongside morphology and anatomical distribution. SMAD4 immunohistochemistry was unavailable in our laboratory, and molecular analyses were not performed.

A more comprehensive comparison of representative tissue samples might have helped clarify whether the lesions shared a common origin or represented independent primary tumors. Nevertheless, the available findings do not permit a definitive conclusion regarding their relationship. This case therefore illustrates the importance of integrating morphology, immunohistochemistry, imaging, and operative findings while recognizing the limitations of the investigations performed.

Aggressive local behavior and surgical implications

The gallbladder tumor displayed several adverse pathological features, including a size of 5 cm, poor differentiation, full-thickness wall invasion, extension into adjacent hepatic tissue, perineural and lymphovascular invasion, and an involved hepatic resection margin. These findings illustrate the locally aggressive behavior reported in gallbladder ASC [1,4].

Because this histological subtype is rare, evidence guiding treatment is limited and largely derived from retrospective studies and case reports. Complete resection, when feasible, remains an important consideration in localized disease, but the optimal management of advanced ASC is not well established [8-10].

In this patient, the pancreatic head mass was found to be fixed to the posterior plane during surgical exploration and was considered unresectable. Consequently, pancreatic biopsies were obtained instead of pancreaticoduodenectomy, and biliary drainage was achieved by choledochoduodenal bypass. Detailed postoperative clinical records and complete information regarding subsequent treatment and clinical outcomes were unavailable for review. Therefore, the long-term outcome and response to treatment could not be assessed.

Limitations

This case report has several limitations. The limited pancreatic and bile duct biopsy samples restricted comprehensive morphological and immunohistochemical comparison. Tissue exhaustion prevented completion of some immunohistochemical analyses, while SMAD4 was unavailable in our laboratory. Additional comparative immunohistochemical and molecular studies were not performed. Consequently, the relationship between the gallbladder, pancreatic, and bile duct lesions could not be definitively established.

Postoperative clinical information was limited, and the available records did not permit a reliable assessment of postoperative complications, improvement in biliary obstruction, subsequent disease progression, or survival. This incomplete clinical follow-up further limited the assessment of patient outcome.

Conclusions

Gallbladder ASC may coexist with a pancreatic head mass and bile duct abnormalities, creating diagnostic uncertainty regarding the relationship between these lesions. In the present case, histopathological and immunohistochemical examination established the diagnosis of gallbladder ASC, whereas the origin and relationship of the pancreatic and bile duct lesions remained unresolved because of limited biopsy material and incomplete comparative analyses. Careful integration of imaging, operative findings, morphology, and immunohistochemistry is essential to avoid overinterpreting the available evidence. When the relationship between lesions cannot be established, diagnostic conclusions should clearly distinguish confirmed pathological findings from unresolved questions of tumor origin.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Maria Dref, Anas Fakhri

Acquisition, analysis, or interpretation of data: Maria Dref, Hind Rachidi, Anas Fakhri, Hanane Rais

Drafting of the manuscript: Maria Dref

Critical review of the manuscript for important intellectual content: Maria Dref, Hind Rachidi, Anas Fakhri, Hanane Rais

Supervision: Maria Dref, Hind Rachidi, Anas Fakhri, Hanane Rais

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. **AI use statement:** The authors used ChatGPT (OpenAI, San Francisco, CA, USA) as follows: language polishing in entire manuscript. ChatGPT was used solely for language editing. After using this tool, the authors reviewed and edited the content as needed. The authors confirm that they have reviewed and verified all AI-assisted content and take full responsibility for the work. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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