

Gallbladder Adenosquamous Cancer With Situs Inversus Totalis: A Case Report and Literature Review

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Case report

Keywords: Situs inversus totalis, Gallbladder adenosquamous carcinoma

Posted Date: March 5th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-261819/v1>

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Abstract

Background: Situs inversus totalis (SIT) is a rare genetic congenital disease, characterized by complete right-left inversion of all the internal organs. We herein describe a meaningful case which was diagnosed as gallbladder adenosquamous carcinoma, a rare histology type of gallbladder cancer, with SIT.

Case presentation: A 59-year-old Chinese woman was admitted for persistent epigastric distention and intermittent abdominal pain. The abdominal CT scan revealed a huge mass at the gallbladder bottom, involving the adjacent transverse colon and liver. En-bloc radical resection of the gallbladder cancer, including partial colectomy and hepatectomy with regional node dissection, followed by colocolostomy and Roux-en-Y choledochojejunostomy, was successfully performed. Pathology analysis indicated an adenosquamous carcinoma with positive adenocarcinoma marker (CK7, CK19) and squamous carcinoma markers (CK5/6, P63).

Conclusion: The SIT anomaly might increase the risk of malignancies by sharing genome mutations, suggesting the importance of surveillance in the SIT settings.

Background

Situs inversus totalis (SIT) is a rare genetic predisposition in which the organs in the chest and abdomen are positioned in a mirror manner from their normal location to the other side of the body. The incidence of SIT is approximately 1/8000 to 1/25,000 in live births^{1,2}. Although the exact etiology of SIT is still unclear, several mutations, such as DNAH11 and Nme7, are closely related to SIT^{3,4}. SIT does not seriously affect most organ functions and usually shows no significant symptoms, except some patients with ciliary dyskinesia might present obvious mobility dysfunction⁵. Therefore, SIT is found occasionally in routine imaging studies in most circumstances.

Due to the altered anatomical position of the vessels and organs in the SIT setting, anatomical dissection and surgical resection proposed greater technical challenges to the surgeons⁶. Only a few cases of successful surgical treatments in SIT patients of esophageal cancer, pancreatic cancer, or ovarian cancer have been previously reported⁷⁻⁹. To our knowledge, there has been no surgical report of SIT combined with gallbladder cancer. Herein, we first describe a successful case of radical resection of gallbladder cancer in a SIT patient.

Case Presentation

A 59-year-old Chinese woman was admitted to our hospital due to persistent epigastric distention and intermittent abdominal pain for 10 days. The patient had a 10-year history of gallbladder stones. Physical examination revealed right upper abdomen tenderness. All the tumor markers were in normal ranges. Initial chest X-ray found a mirror-image dextrocardia (**Fig. 1A**), and further computed tomography (CT)

revealed a complete, right-to-left reverse transposition of the organs in the thoracic cavity and the abdomen (**Fig. 1B & 1C**), confirming her congenital anomaly of SIT.

A contrasted CT scan revealed a 6.3 cm×4.5 cm mass at the gallbladder bottom, with involvement of the transverse colon and the left lateral liver (**Fig. 2A & 2B**). No other distant metastasis or lymph node enlargement was observed. The initial diagnosis was gallbladder cancer at stage IIIA (cT3N0M0) according to the AJCC staging guideline¹⁰. Multiple vascular variations were also seen in addition to the right-to-left reversal anomaly (**Fig. 2C**). Specifically, the celiac trunk divided into the splenic artery and the left gastric artery, while the common hepatic artery originates from the superior mesenteric artery. The polysplenia syndrome is defined as the existence of multiple spleens similar in size, usually numbering between two and six, which is different from the accessory spleen¹¹. Until now, it is not clear whether there is a relationship between polysplenia syndrome and SIT. The coexistence of polysplenia syndrome is common in SIT, for instance in our case.

The multidisciplinary board considered the clinical diagnosis of resectable gallbladder cancer with SIT, and suggested surgical resection. En-bloc radical resection of the gallbladder cancer, including partial colonectomy and hepatectomy with regional node dissection, followed by colocolostomy and Roux-en-Y choledochojejunostomy, was successfully performed. The whole operation took around 5 hours, and the estimated blood loss was 100mL. Gross anatomy showed multiple gallstones in the gallbladder and a huge tumor at the gallbladder bottom, invading the transverse colon and the liver (**Fig. 3A & 3B**). Final pathology revealed a moderately differentiated adenosquamous carcinoma of the gallbladder, invading the submucosa of the transverse colon (**Fig. 3C & 3D**), further confirmed by immunohistochemical staining showing positive P63, P53, CK5/6, CK19, CK7, CK20, and CDX2, and negative ERBR expressions (**Fig 4**). All the 10 dissected lymph nodes were negative. The pathological stage of this patient is pT3N0M0. The patient recovered well after surgery. Two months post the surgical procedure, she started adjuvant gemcitabine plus cisplatin regimen. She received 5 cycles of chemotherapy and was free of recurrence at 5 months post operation.

Discussion And Conclusions

The exact etiology of SIT still remains unclear, majorly caused by gene mutations and chromosomal abnormalities^{3, 12}. As SIT itself does not seriously affect the function of organs, most patients will not have any abnormal feeling and it is generally only found during radiological examinations. However, the incidence of cardiovascular, hepatobiliary, and spleen malformations, accompanied by anomalies of abdominal vessels origination or distribution, markedly increases in SIT patients^{13, 14}. In our case, two major anatomical malformations were presented. One malformation was the vascular variation. In regular circumstances, celiac trunk divides into common hepatic artery, splenic artery, and left gastric artery. On the contrary in this patient, the celiac trunk only divides to splenic artery and left gastric artery, while the common hepatic artery originates from the superior mesenteric artery. The other malformation was the polysplenia syndrome, where three spleens with a similar size were presented. Polysplenia

syndrome is often associated with multiple visceral and vascular abnormalities¹⁵. These two malformations brought higher risks of intraoperative complications associated with incomprehension of the anatomical variations.

Notably, malignancy is also a potential outcome of SIT since the two diseases might share certain mutations in several signaling pathways. The DNAH11 (axonemal heavy chain dynein type 11) gene mutations were found to cause SIT in mice, which was further confirmed in SIT patients¹⁴. Meanwhile, the DNAH11 mutations are also associated with esophageal squamous cell carcinoma, ovarian cancer, and breast cancer^{16,17}. Another DNAH family member DNAH5, another SIT-related gene, was found to be mutated in several malignancies¹⁸⁻²⁰. Inversin, whose mutations cause an autosomal recessive cystic disorder characterized by SIT, functions as a molecular switch between Wnt signaling pathways²¹, as the Wnt pathways has close relationship with carcinogenesis including development of gallbladder cancer^{22,23}. Therefore, it is possible that the mutations in SIT results in malignancy. However, no specific shared mutation has been verified between SIT and malignancy yet.

Previous studies have demonstrated that SIT patients might develop malignancies like esophageal cancer, pancreatic cancer, and ovarian cancer. In our case, we showed that gallbladder carcinoma, a highly malignant disease with poor prognosis²⁴, could also be an unfortunate outcome of SIT. Specifically, our pathology diagnosis is adenosquamous carcinoma, a relatively rare type among all the pathological conditions of gallbladder malignancies^{25,26}, especially in a SIT setting. In comparison to adenocarcinoma, adenosquamous carcinoma is likely to have a more advanced stage with rapid progression and declined prognosis²⁷. Optimistically, the survival data of resectable adenosquamous gallbladder cancer is comparable to gallbladder adenocarcinoma after successful radical surgical resection^{28,29}. Therefore, radical resection is the preferred curative approach for this patient and similar cases^{30,31}.

In conclusion, a SIT patient who developed a rare gallbladder adenosquamous carcinoma received a successful en-bloc surgical resection with no intraoperative vascular injuries. Proper imaging assessments, along with multidisciplinary cooperation, helps detailed evaluation of the visceral malformations, which eventually facilitates surgery success. The high-risk SIT populations should receive regular surveillance to improve early detection and long-term survival in case the malignancies occur.

Abbreviations

SIT: Situs inversus totalis; CK7: Cytokeratin 7; CK19: Cytokeratin 19, CK5/6: Cytokeratin 5/6

CT: Computed tomography

Declarations

1. **Ethics approval and consent to participate:** Ethics approval and consent was approved by Ethics Committee of First Affiliated Hospital, Zhejiang University School of Medicine.
2. **Consent for publication:** Patient consent form had signed by patient.
3. **Competing interests:** There is no any competing interests.
4. **Funding:** This work was supported by financially by the National Natural Science Foundation of China (81972207, 81830089), the Key Program of Medical Scientific Research Foundation of Zhejiang Province (2019C03019), the National High Technology Research and Development Program 863 of China (SS2015AA020405), and Zhejiang Provincial Natural Science Foundation (LY18H160026).
5. **Authors' contributions:** TL and QH contributed to the conception of the study. JH analyzed and interpreted the patient data regarding situs inversus totalis and gallbladder adenosquamous carcinoma. HY performed the histological examination of the tumor. MW, XZ, SS, FZ, and RQ treated the patient and helped perform the analysis with constructive discussions.
6. **Acknowledgements:** We are very grateful to the patient for her support of clinical data collection.
7. **Availability of data and materials:** All data generated or analysed during this study are included in this article.

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Figures

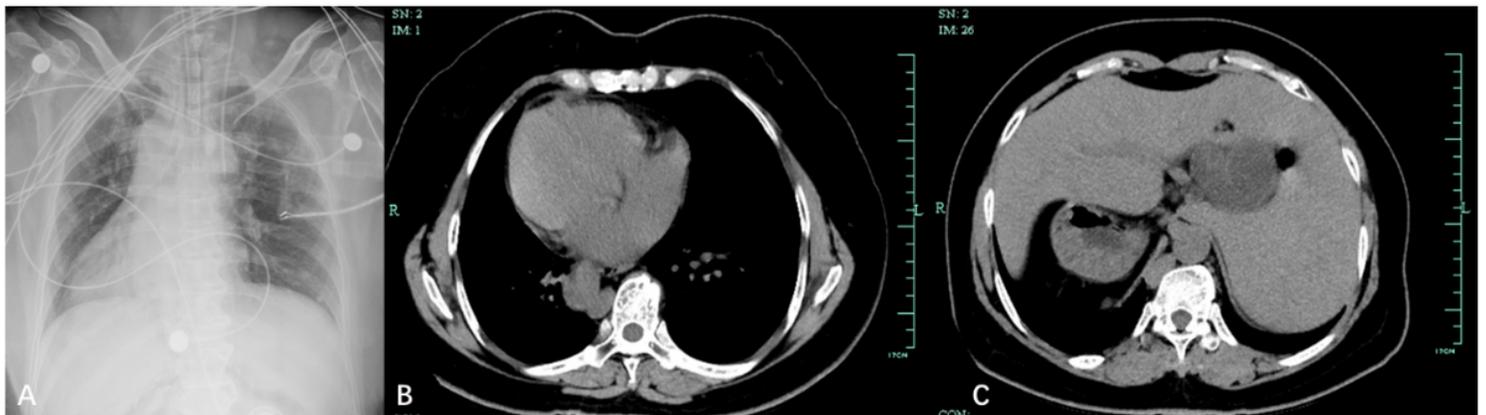


Figure 1

Radiology studies revealed SIT anomaly. (A) Dextrocardia in the chest X-ray image, right-to-left reverse transposition in (B) thoracic and (C) abdominal computed tomography (CT) images.

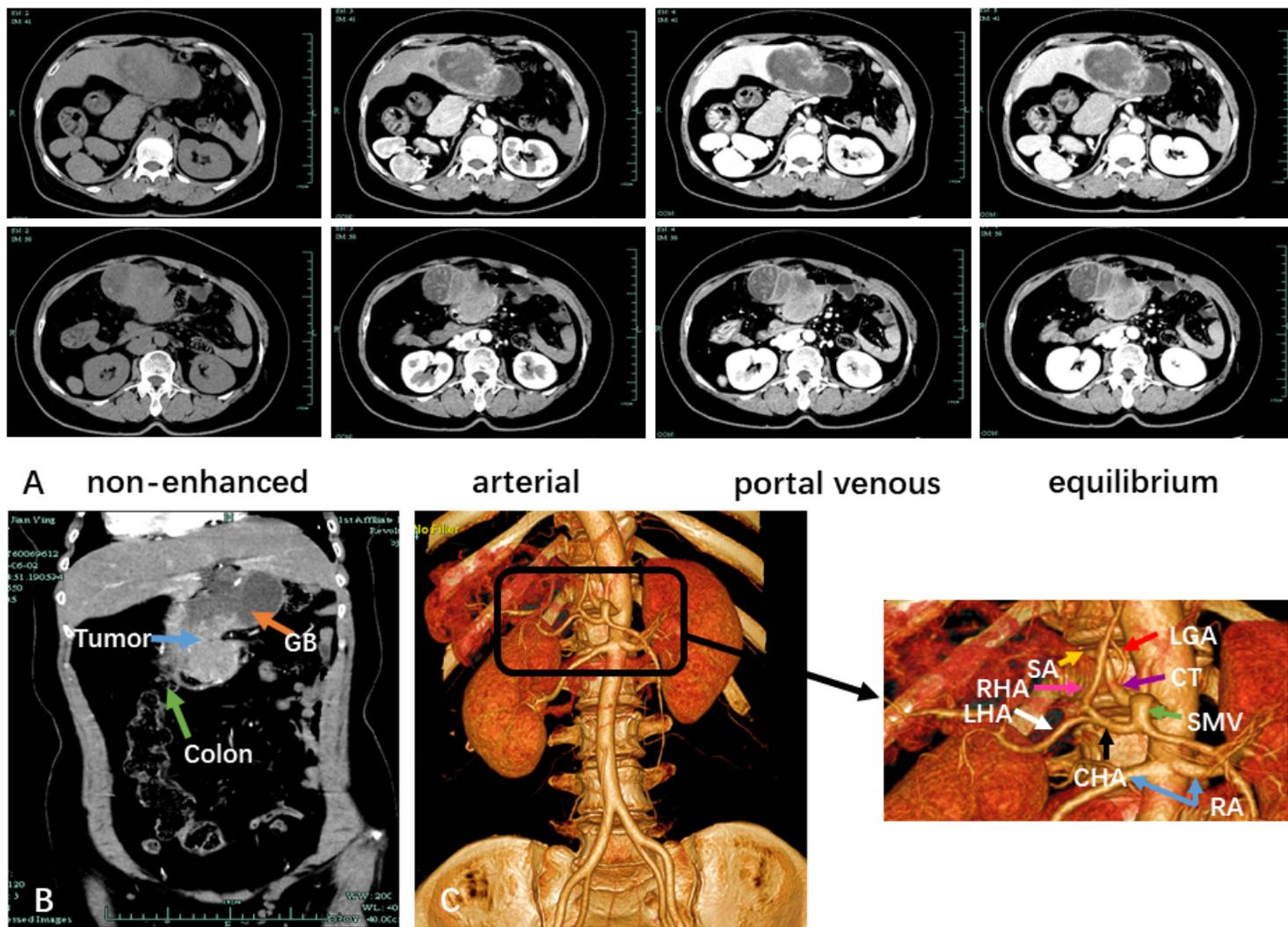


Figure 2

Preoperative CT scan indicated the diagnosis of gallbladder cancer in the SIT setting. (A) The CT images in the non-enhanced, arterial, portal venous, and equilibrium phases; (B) The coronal view showing tumor's involvement of transverse colon; GB, gallbladder (C) The CT angiography demonstrating significant vascular abnormalities. SMA, superior mesenteric artery; CT, celiac trunk; CHA, common hepatic artery; LGA, left gastric artery; SA, splenic artery; RHA, right hepatic artery; LHA, left hepatic artery; RA, renal artery.

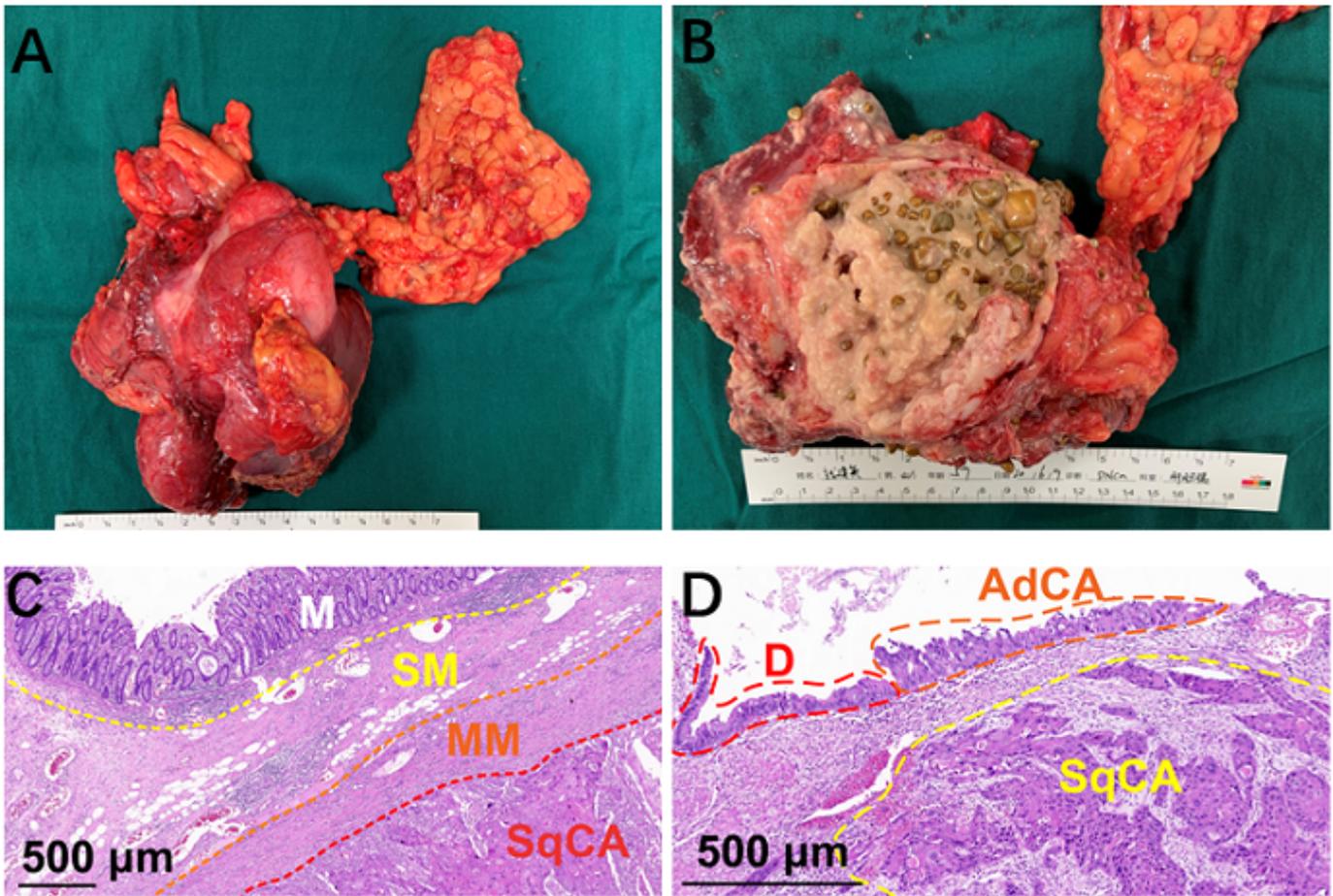


Figure 3

Pathology studies confirmed the diagnosis of gallbladder cancer. (A) The resected sample with adjacent colon and liver tissues; (B) Cross-sectional profile showing huge gallbladder mass and multiple gallstones; (C) H & E staining showing tumor's involvement of colon. M, mucosa layer; SM, submucosa layer; MM, muscular layer; SqCA, squamous carcinoma. (D) H & E staining of gallbladder adenosquamous carcinoma. D, dysplasia in gallbladder glandular epithelium; AdCA, adenocarcinoma; SqCA, squamous carcinoma.

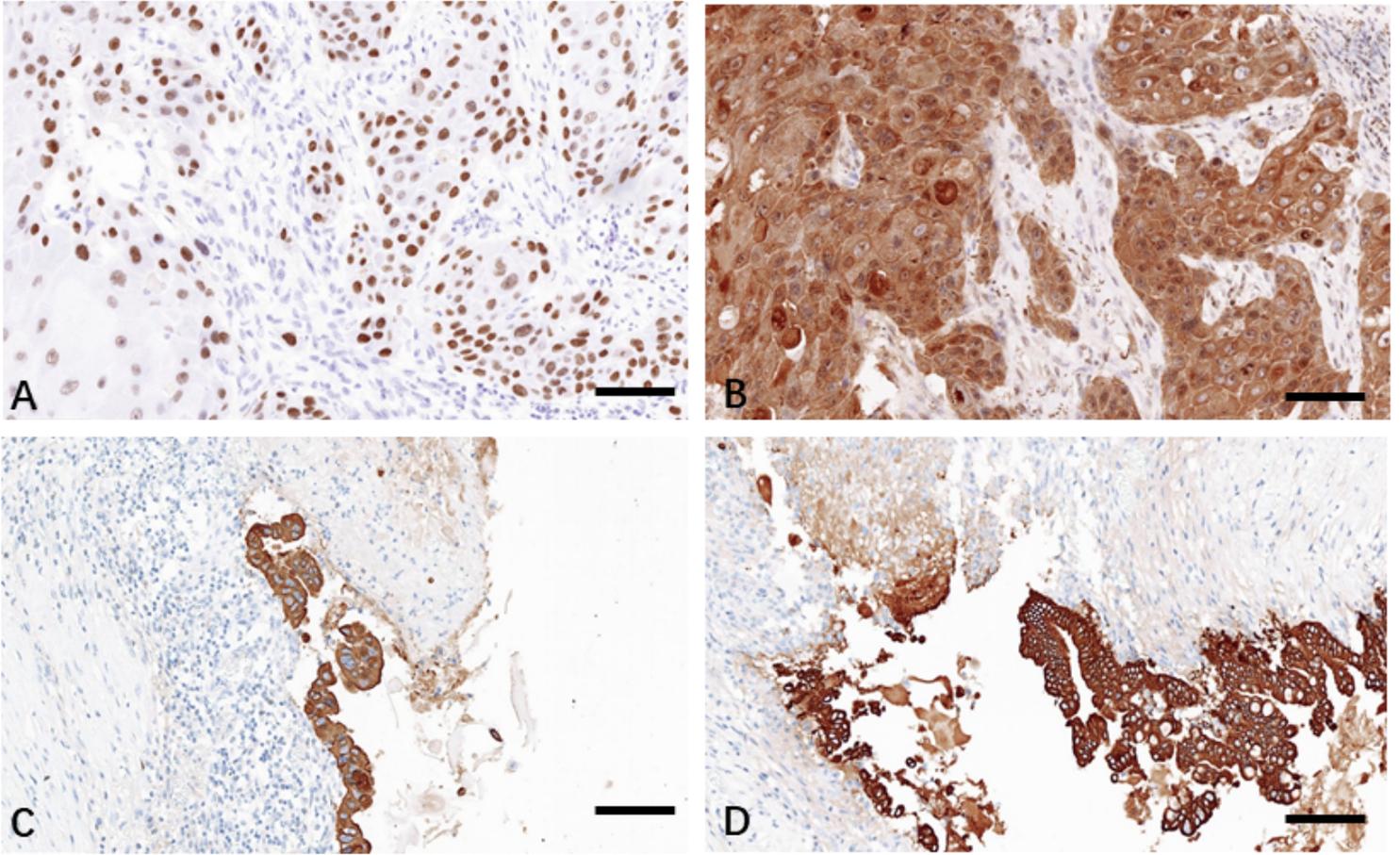


Figure 4

Immunohistochemistry assays suggested (A) positive P63, (B) positive CK5/6, (C) positive CK7, and (D) positive CK19 expression. The scale bars indicate 100 μ m.